General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and 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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (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) Gilbert J. Burckart at 301-796-2065.

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

December 2014
Clinical Pharmacology

General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and 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
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
http://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)

December 2014
Clinical Pharmacology

TABLE OF CONTENTS

General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products

Guidance for Industry[1]

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This draft guidance is intended to assist those sponsors of new drug applications (NDAs), biologics license applications (BLAs) for therapeutic biologics, and supplements to such applications who are planning to conduct clinical studies in pediatric populations. Effectiveness, safety, or dose-finding studies in pediatric patients involve gathering clinical pharmacology information, such as information regarding a product's pharmacokinetics and pharmacodynamics pertaining to dose selection and individualization. This guidance addresses general clinical pharmacology considerations for conducting studies so that the dosing and safety information for drugs and biologic products in pediatric populations can be sufficiently characterized, leading to well-designed trials to evaluate effectiveness.[2]

In general, this draft 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 the use of quantitative approaches (i.e., pharmacometrics) to employ disease and exposure-response knowledge from relevant prior clinical studies to design and evaluate future pediatric studies. The guidance does not describe: (1) standards for approval of drug and biological products in the pediatric population, (2) criteria to allow a determination that the course of a disease and the effects of a drug or a biologic are the same in adults and pediatric populations, or (3) clinical pharmacology studies for vaccine therapy, blood products, or other products not

[1] This draft 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 (MPCC) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

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

regulated by the Center for Drug Evaluation and Research.

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

II. BACKGROUND

During the past two decades, the Food and Drug Administration (FDA) has worked to address the problem of inadequate pediatric testing and inadequate pediatric use information in drug and biological product labeling. The Food and Drug Administration Modernization Act of 1997 (the Modernization Act) addressed the need for improved information about drug use in the pediatric population by establishing incentives for conducting pediatric studies on drugs for which exclusivity or patent protection exists.[3] Congress subsequently passed the Best Pharmaceuticals for Children Act (BPCA)[4] in 2002 and the Pediatric Research Equity Act (PREA) in 2003.[5] Both BCPA and PREA were reauthorized in 2007.[6] In 2012, BPCA and PREA were made permanent under Title V of the Food and Drug Administration Safety and Innovation Act (FDASIA).[7]

Under BPCA, sponsors of certain applications and supplements filed under section 505 of the FD&C Act and under section 351 of the Public Health Service 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.[8] Under PREA, sponsors of certain applications and supplements filed under section 505 of the FD&C Act or section 351 of the Public Health Service Act are required to submit pediatric assessments, unless they receive an applicable waiver or deferral of this requirement.[9] If applicable, sponsors must submit a request for a deferral or waiver as part of an initial pediatric study plan (section 505B(e) of the FD&C Act) (see section V of this guidance).

The FD&C Act requires a description of pediatric study data in labeling arising from study data

[3] Public Law No. 105-115, 111 Stat. 2296 (Nov. 21, 1997).
[4] Public Law No. 107-109, 115 Stat. 1408 (Jan. 4, 2002).
[5] Public Law No. 108-155, 117 Stat. 1936 (Dec. 3, 2003).
[6] Food and Drug Administration Amendments Act of 2007 (FDAAA), Public Law No. 110-85, 121 Stat. 823 (Sept. 27, 2007).
[7] Public Law No. 112-144, 126 Stat. 993 (July 9, 2012).
[8] Section 505A of the FD&C Act; 21 U.S.C. 355a.
[9] Section 505B of the FD&C Act; 21 U.S.C. 355c.

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.[10] The PREA requirements are triggered by the submission of an application or supplement for a drug for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration under Section 505 of the FD&C Act or Section 351 of the PHS Act.[11] If a full or partial waiver is granted under PREA because there is evidence that the drug would be ineffective or unsafe in pediatric populations, the information must be included in the product's labeling.[12]

This guidance deals with the clinical pharmacology considerations of any planned pediatric study, whether or not it is conducted pursuant to BPCA or PREA.

III. CLINICAL PHARMACOLOGY CONSIDERATIONS

There are several recognized approaches to providing substantial evidence to support the safe and effective use of drugs in pediatric populations, 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 pediatric populations to support the same indication(s) approved for adults; or (3) evidence from adequate and well-controlled studies in adults and additional information in the specific pediatric population.[13] The first approach generally requires a full pediatric development program. The second approach above generally involves the use of prior disease and exposure-response knowledge from studies in adults and relevant pediatric information to design and, in some cases, analyze new pediatric studies. For the third approach, the assumption is that the course of the disease and the effects of the drug are sufficiently similar in the pediatric and adult populations to permit extrapolation of the adult efficacy data to pediatric patients (Dunne, Rodriguez et al. 2011). If the third approach is taken, there would ordinarily be a pediatric study to determine a dose in the pediatric population that provides a drug exposure similar to the exposure that is effective in adults. If there is a concern that exposure-response relationships might be different in pediatric patients, studies relating blood levels of drug to pertinent pharmacodynamic effects other than the desired clinical outcome (exposure-response data for both desired and undesired effects) for the drug in the pediatric population might also be important. For all three

[10] Section 505A of the FD&C Act; 21 U.S.C. 355a; Section 505B of the FD&C Act; 21 U.S.C. 355c.
[11] Section 505B(a)(1) of the FD&C Act; 21 U.S.C. 355c(e)(1).
[12] Section 505B(a)(4)(D) of the FD&C Act; 21 U.S.C. 355c(A)(4)(D).
[13] See *Guidance for Industry*: *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, May 1998, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078749.pdf.

approaches, the extent of the required pediatric safety studies may take into consideration prior experience with similar drugs in pediatric populations, the seriousness of the adverse events in adults or in pediatric populations, when this information is available, and the feasibility of conducting studies in pediatric patients.

Clinical pharmacology studies in the pediatric population should be conducted in patients receiving therapy for a particular indication, or in rare instances, in those who are at risk for the condition of interest. The identification of the appropriate ages to study and decisions on how to stratify data by age are drug-specific and require scientific justification, taking into consideration developmental biology and pharmacology.

The Center for Drug Evaluation and Research generally divides the pediatric population into the following groups:[14]

- Neonates: birth up to 1 month;
- Infants: 1 month up to 2 years;
- Children: 2 up to 12 years; and
- Adolescents: 12 years up to 16 years.[15]

The measurement or prediction of a drug or biologic'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 or biologic in the pediatric population. In some instances, knowledge of pharmacogenetic differences, which can affect a product's exposure, may also be required.

A. Pharmacokinetics

Pharmacokinetic 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 or biologic from the body. Drugs may be eliminated in the unchanged (parent) form, or undergo metabolism (M) to one or more active and inactive metabolites. The overall set of processes is often referred to as ADME, which ultimately determines systemic exposure to a drug and its metabolites after drug

[14] 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 this final rule, which revised the *Pediatric Use* subsection of the labeling for human prescription drugs to provide for the inclusion of more complete information about the use of a drug or biological product in pediatric populations.

[15] Sponsors should address the entire age range but need not use these specific age categories. If physiologic categories or groupings based upon systems ontogeny are used, they should be supported with scientific and developmental data.

administration. This systemic exposure, reflected in plasma drug or metabolite concentrations, or both, is generally correlated with both beneficial and adverse drug effects. All drugs and biologics show inter- and intra-individual variability in PK measures and parameters. In the pediatric population, growth and developmental changes in factors influencing ADME can also lead to changes in PK parameters. The PK of a drug or biologic is typically evaluated over the entire pediatric age range in which the agents will be used (Kauffman and Kearns 1992; Kearns 2000). Special areas of importance in planning pediatric PK 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 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 (Yaffe and Aranda 2010).

- Distribution

Distribution of a drug or biologic 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 may also influence distribution. Differences between pediatric patients and adults in blood flow to an organ, such as the brain, can also affect the distribution of a drug or biologic in the body.

- Metabolism

Drug metabolism commonly 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 bioavailability and elimination, depending on the degree to which intestinal and hepatic metabolic processes are involved (Leeder 2004). Although developmental changes are recognized, information on drug metabolism of specific drugs in newborns, infants, and children is limited. Both rates of metabolite formation and the principal metabolic pathway can be different in pediatric patients compared to adults and within the pediatric population. In vitro studies performed early in drug development may be useful in focusing attention on

metabolic pathways in both adults and pediatric patients.[16]

- 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.

- Protein Binding

Protein binding to a drug or its metabolites 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 (Kearns, Abdel-Rahman et al. 2003). 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.

- Clearance

Clearance of drugs or biologic products as a function of age is generally a valuable parameter for determining the dose for each age group in the pediatric population, and drug clearance has provided a valuable tool in the assessment of pediatric clinical pharmacology studies (Rodriguez, Selen et al., 2008). Plasma clearance can be defined as the volume of plasma which is completely cleared of drug in a given time period.

- Additional Factors

Growth and developmental changes in the pediatric population will create substantial changes in ADME. PK measures and parameters for a drug or biologic may need to 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) (Kearns, Abdel-Rahman et al. 2003). The maturational changes in systems affecting ADME, such as membrane transporters and metabolizing enzymes, should be taken into consideration in choosing age groups and doses to study in the pediatric population.

[16] See the draft *Guidance for Industry*: *Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*, Feb. 2012, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm292362.pdf.

B. Pharmacodynamics

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

If the clinical endpoint cannot be measured directly because the effect is delayed or rare, then the selection of an appropriate biomarker to substitute for the clinical efficacy or toxicity endpoint is essential. In many cases, biomarkers are first evaluated in an adult population, in which case the support for the use of the biomarker in a pediatric population depends on evidence that the disease pathophysiology and pharmacologic response in pediatric patients is sufficiently similar to adults.

C. Pharmacogenetics

Genetic differences that clinically affect both exposure and response are increasingly documented,[17] but the relationship between genomic profiles and developmentally regulated gene expression has not been extensively studied in pediatric populations. Some of the difficulties in obtaining specific pharmacogenetic information in pediatric patients have been reviewed (Leeder 2004). Nevertheless, if drug exposure in a pediatric clinical pharmacology study is dependent on a well-known pharmacogenomic biomarker (e.g., cytochrome P4502D6),[18] obtaining patient DNA may provide additional information for the interpretation of the PK and PD results.

IV. ETHICAL CONSIDERATIONS

FDA-regulated clinical investigations are governed, in part, by the institutional review board (IRB) regulations at 21 CFR Part 56 and the human subject protections at 21 CFR Part 50. Pediatric subjects who are enrolled in FDA-regulated clinical pharmacology studies must be afforded the additional safeguards found at 21 CFR Part 50, Subpart D. These safeguards restrict the allowable risk to which a pediatric subject may be exposed in a clinical investigation based

[17] Food and Drug Administration: Table of Pharmacogenomic Biomarkers in Drug Labeling (2008), available at *http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm*.

[18] See *Guidance for Industry*: *Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations* (Footnote 16).

on whether the proposed intervention or procedure offers a prospect of direct clinical benefit to the individual child. Clinical pharmacology studies generally do not provide a direct clinical benefit to individual pediatric subjects, and must therefore present no more than minimal risk (21 CFR 50.51) or a minor increase over minimal risk (21 CFR 50.53). Exceptions to this general rule may include, for example, dose-monitoring studies that directly benefit individual pediatric subjects by ensuring that serum levels of a drug remain within a therapeutic range. Under such circumstances, a clinical pharmacology study may be approvable by an IRB under 21 CFR 50.52. Before initiation of the clinical trial, an IRB must approve the proposed trial under the requirements of 21 CFR 50 subpart D.[19] However, FDA has an independent responsibility to assess the compliance of the proposed clinical trial under 21 CFR 50 subpart D. Failure of a proposed clinical trial to be in compliance with 21 CFR Part 50, Subpart D, may be sufficient grounds for FDA to impose a clinical hold because the investigation could present an unreasonable and significant risk of illness or injury (21 CFR 312.42(b)).

The assessment under 21 CFR Part 50, Subpart D of a clinical pharmacology protocol depends on whether the experimental drug or biologic is being administered (1) solely for the purposes of obtaining pharmacokinetic data or (2) in such a way that it offers the enrolled child a prospect of direct clinical benefit. The following two paragraphs discuss these two cases, respectively. In both cases, administration of an experimental drug or biological product is always considered to represent more than minimal risk and thus is not approvable by an IRB under 21 CFR 50.51. For IRB approval under 21 CFR 50.53, an enrolled child must have a disorder or condition that is the focus of the clinical investigation. For IRB approval of a clinical investigation under 21 CFR 50.52, an enrolled child must have a prospect of direct clinical benefit from administration of the investigational product. Thus, only patients with a therapeutic need for the investigational drug product can be enrolled in such trials. Consequently, healthy pediatric subjects (i.e., without a disorder or condition which is the focus of the research) cannot be enrolled in clinical pharmacology studies absent a determination by the Commissioner, 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 (which allows clinical investigations to proceed that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children) are met.[20]

Case 1: IRB review of a clinical pharmacology study using pediatric human subjects under 21 CFR 50.53.

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

[20] See *Guidance for Clinical investigators, Institutional Review Boards, and Sponsors Process for Handling Referrals to FDA Under 21 CFR 50.54*, December 2006, available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127605.pdf.

When the experimental drug or biologic is being administered solely for the purpose of obtaining pharmacokinetic data, both the experimental drug administration and the pharmacokinetic sampling must present no more than a minor increase over minimal risk (21 CFR 50.53(a)). In addition, pediatric subjects may be exposed to such risks 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 subject must have a disorder or condition. A condition may include being "at risk" for the disease. In addition, sufficient empirical data regarding the risks of the proposed interventions or procedures need to be available to ascertain that the risks are no more than a minor increase over minimal risk (21 CFR 50.53(a)). The available adult data including dose-response data may be considered for this purpose. Even if the risk is thought to be low, if there are not enough data to adequately characterize the risk, then the intervention or procedure cannot 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. In addition, the risks of the blood and/or fluid sampling procedures need to be no more than a minor increase over minimal risk. An example of a clinical pharmacology study that may be conducted under 21 CFR 50.53 is the pharmacokinetics of a *single dose* of an over-the-counter cough and cold product. To be enrolled in such a study, a child may either be symptomatic from an upper 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.

Case 2: IRB review of a clinical pharmacology study using pediatric human subjects under 21 CFR 50.52.

The experimental drug administration may present more than a minor increase over minimal risk as long as this level of risk exposure is justified by a sufficient prospect of direct clinical benefit to the subjects (21 CFR 50.52(a)). For example, dose-monitoring studies that directly benefit individual pediatric subjects by ensuring that serum levels of a drug remain within a therapeutic range would fall under 21 CFR 50.52. In this case, pharmacokinetic studies of investigational products must be done in children who have a therapeutic need for the drug or biologic, and the drug or biologic must be administered using a dosing regimen that offers a sufficient prospect of direct clinical benefit to justify the risks (21 CFR 50.52(a)). In such studies, the limited venipunctures that may be required to obtain specimens for pharmacokinetic analyses are generally considered either minimal risk or a minor increase over minimal risk, and therefore may be approvable absent a prospect of direct benefit (21 CFR 50.51 and 50.53). This approach to the analysis of clinical pharmacology trials is called a component analysis of risk, whereby the interventions that do and do not offer a prospect of direct benefit in any given protocol must be

analyzed separately.[21]

Adequate information from clinical pharmacology studies to support pediatric dosing is critical to the development of ethically sound confirmatory trials. For example, pivotal trials of antihypertensive agents may have failed to demonstrate efficacy in the pediatric population as a result of inadequate pediatric dosing (Benjamin, Smith et al., 2008; Rodriguez, Selen et al., 2008). FDA considers the public health need for adequate pediatric dosing in its assessment of the ethical propriety of proposed studies. For further information, investigators and IRBs may refer to the American Academy of Pediatrics Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations (Shaddy and Denne, 2010) or the International Conference on Harmonization (ICH) Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance (ICH E6), which contains a section on nontherapeutic studies in special populations.[22]

V. THE PEDIATRIC STUDY PLAN DESIGN AND POINTS TO CONSIDER

Under Section 505B(e)(1) of the FD&C Act, a sponsor who will be submitting an application for a drug or biological product that includes a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration is required to submit an initial pediatric study plan (PSP). A pediatric study plan (PSP) outlines the pediatric study or studies that the applicant plans to conduct.[23]

The submission of the initial PSP is intended to encourage sponsors to consider pediatric studies early in product development and, when appropriate, begin planning for these studies. The

[21] See 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 (Jan. 13, 1978)); *Guidance for Industry: Acute Bacterial Otitis Media: Developing Drugs for Treatment*, September 2012, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070947.pdf; and Preamble to the Final Rule on the Additional Safeguards for Children in Clinical Investigations of Food and Drug Administration-Regulated Products, 78 FR12937, 12937-12950 (Feb. 26, 2013).

[22] See section 4.8.14., ICH *Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance*, Apr. 1996, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf. See also the ICH *Guidance for Industry: E11 Clinical Investigation of Medicinal Products in the Pediatric Population*, Dec. 2000, available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129477.pdf.

[23] See section 505B(e)(2)(B) of the FD&C Act; 21 U.S.C. 355c(e)(2)(B) and the draft *Guidance for Industry-Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf.

initial PSP must include "(i) an outline of the pediatric study or studies that the applicant plans to conduct (including, to the extent practicable, study objectives and design, age groups, relevant endpoints, and statistical approach); (ii) any request for a deferral, partial waiver, or waiver…if applicable, along with any supporting information; and (iii) other information specified in the regulations" promulgated by the FDA.[24,25] When designing the 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 using all of the information available should therefore be an integral part of all pediatric development programs. The following sections are critically important when developing the clinical pharmacology components of a pediatric study plan.

A. Approaches to Pediatric Studies

In addition to the usual considerations of PK (i.e., drug exposure), PD (i.e., effect on biomarker or clinical endpoint), and exposure-response relationships that may be different from those of adults, a pediatric drug development program should consider the time course of development of the drug metabolizing enzyme(s), drug excretory systems, and transporters specific to the drug being studied. This is probably best achieved by characterizing the PK of the drug across the appropriate pediatric age range. Based on the availability and reliability of the information about such factors, the pediatric study planning and extrapolation algorithm[26] in the Appendix of this guidance illustrates the different approaches in conducting pediatric clinical studies.

PK Only Approach (i.e., full extrapolation[27]): This approach is appropriate when it is reasonable to assume that children, when compared to adults, have (1) a similar progression of disease; (2) a similar response of the disease to treatment; (3) a similar exposure-response or concentration-response relationship; and (4) the drug (or active metabolite) concentration is measureable and predictive of the clinical response. Evidence that could support a conclusion of similar disease course and similar drug effect in adult and pediatric populations includes evidence of common pathophysiology and natural history of the disease in the adult and pediatric populations, evidence of common drug metabolism and similar concentration-response relationships in each

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

[25] Further information about the content of the initial PSP can be found in the draft *Guidance for Industry- Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* (Footnote 23).

[26] This algorithm is an updated version of the Pediatric Study Decision Tree that was appended to the *Guidance for Industry: Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications*, Apr. 2003, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf.

[27] For a discussion of the different approaches to extrapolation, see Dunne J, Rodriguez WJ, Murphy MD, et al., "Extrapolation of adult data and other data in pediatric drug-development programs." Pediatrics. 2011 Nov;128(5):e1242-1249.

population, and experience with the drug, or other drugs in its therapeutic class, in the disease or condition or related diseases or conditions.[28]

If there is no currently used pediatric dose, if there is insufficient PK information about a currently used pediatric dose, or if the currently used pediatric dose in the same clinical context would not be expected to match adult exposure, then a PK study should be performed to identify the pediatric dose that will provide similar exposure to adults. This PK study should be conducted before any additional pediatric clinical studies are initiated to ensure the optimal dose for these studies. Before conducting a PK study, simulations should be performed to identify the dose expected to achieve an appropriate target exposure (e.g., the observed adult drug exposure) in the same clinical context. The antibacterial therapeutic area is a good example of this approach, where the organism is expected to respond to similar plasma concentrations in adults and pediatric patients. In this case, the study can focus on identifying the doses in the pediatric setting that would result in exposures similar to those attained in adults.

PK and PD Approach (i.e., partial extrapolation): This approach is applicable when the disease and intervention are believed to behave similarly in pediatric patients and adults, but the exposure-response relationship in pediatric patients is either inadequately defined or thought not to be sufficiently similar. To use this approach, the exposure-response relationship in adults should be well-characterized The goal of such an approach is to characterize and compare the exposure-response relationship in adults and in the pediatric population with the appropriate pediatric doses based on the exposure-response relationships seen in pediatric patients. Clinical measures (e.g., symptoms, signs, outcomes) can be used to select doses, but an appropriate biomarker considered to be related to such an endpoint can also be used, which is usually a biomarker based on adult experience. If there is uncertainty about whether extrapolation of efficacy is appropriate, a single adequate and well-controlled study using a clinical endpoint may be necessary. Additional studies powered to demonstrate efficacy may not be required.

The antiarrhythmic therapeutic area is one example of this approach, where mortality and morbidity studies cannot be ethically conducted in pediatric patients. In the case of antiarrhythmic therapy, the Agency accepted a clinical study assessing the beta adrenergic blocking effects of sotalol on heart rate and the effect on QTc, both of which are acceptable biomarkers in pediatrics, as the basis for labeling information on use of the drug in pediatric patients.

PK and Efficacy Approach (i.e., no extrapolation): If the 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 provide substantial evidence of the

[28] See *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (Footnote 13).

effectiveness and safety of the drug product in pediatric subjects in one or more clinical studies, usually evaluating more than one dose.[29] The study objectives are to provide evidence of effectiveness and safety and to characterize the PK and exposure-response relationships to aid in optimizing pediatric dosing strategies. A population PK analysis can be conducted concurrently using PK data from the efficacy study to confirm PK estimates in the age subgroups.[30]

For the "PK and PD" and "PK and Efficacy" approaches, response data in pediatric studies should be collected and analyzed. Response or PD data may include biomarkers or clinical endpoints for both safety and effectiveness. The specific endpoints for an exposure-response evaluation for each drug or biologic product should be discussed with the Agency.

A dedicated PK study is not always required in every age group. For example, prior experience with dosing in adolescent patients has demonstrated that knowledge of adult dosing and appropriate dose scaling may be sufficient for some drugs with adequate justification. Confirmatory population PK studies may be used to supplement such a program in which a dedicated PK study is not considered essential.

B. Alternative Approaches

In addition to conventional PK studies with intensive blood sampling in pediatric patients, other approaches can be used to obtain useful drug exposure information. Urine and saliva collection are noninvasive, but the interpretation of drug analysis of either is complicated and requires careful consideration before use. Likewise, tissue or cerebrospinal fluid that is being collected for clinical purposes present both an opportunity and a challenge for the appropriate interpretation of these results in understanding the PK of the drug.

When clinical PK studies in pediatric patients are not feasible, there are situations in which interpolation or extrapolation of PK data may be sufficient. PK information in certain pediatric age groups may be gained by interpolating or extrapolating from existing data in adults, data in pediatric patients in other age groups, or both. However, extrapolation of data to very young pediatric patients, particularly neonates, is rarely credible. Significant metabolic differences may exist between neonates and older pediatric patients or adults that can give rise to considerable variability in metabolism and drug disposition. This variability can lead to an altered dose-response relationship. Modeling and simulation can provide another method for reducing residual uncertainty about drug dosing in special pediatric populations.

[29] See *Guidance for Industry*: *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (Footnote 13).

[30] See the *Guidance for Industry: Population Pharmacokinetics*, Feb. 1999, available at http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/WomensHealthResearch/UCM133184.pdf.

C. Pediatric Dose Selection

Selection of an appropriate dose range to be studied is critical in deriving rational dosing recommendations for the pediatric population. Because there may be limited information on the safety of the dose to be administered to a neonate or infant, the dose range in initial studies requires careful consideration. Factors for consideration include (1) similarity of the disease and exposure-response in other studied pediatric groups; (2) the relative bioavailability of the new formulation compared to the previous formulations; (3) the age and developmental stage of the population; (4) the pharmacogenetic characteristics of the drug or biologic; (5) the toxicity of the drug or biologic; and (6) PK data from other pediatric populations. Initial doses are typically normalized to body size (mg/kg) or BSA (mg/m^2).

When separate efficacy studies in pediatrics are not conducted (i.e., for the PK 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 as defined above. Differences in interpatient variability in these PK measures and/or parameters between age groups or between pediatric and adult patients should be interpreted with regard to their impact on dosing, safety, and/or efficacy. In these instances, the sponsor should specify the criteria by which exposure matching would be acceptable. For example, one approach would be to select the appropriate dosing strategy through simulations that ensure the pediatric exposures are within the range of exposures (e.g., 5^{th} to 95^{th} percentile) shown to be safe and effective in adults.

As science and technology continue to advance, *in silico* and other alternative modeling study methods may be developed that 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 physiologically-based PK (PBPK) *in silico* model that integrates drug-dependent parameters (e.g., renal clearance, metabolic pathways) and system-dependent parameters (e.g., non-drug parameters such as blood flow rate, protein binding, and enzyme and transporter activities) is one possible approach. PBPK has been used in pediatric drug development programs for (a) planning for a first-in-pediatric PK study, (b) optimizing the study design, (c) verifying the model in specific age groups, (d) recommending starting doses, (e) informing enzyme ontogeny using a benchmark drug, and (f) facilitating covariate analysis for the effects of organ dysfunction or drug interactions in pediatric patients (Leong, Vieira et al. 2012). The model selected should incorporate *in vivo* PK/PD data obtained in other groups of pediatric and adult patients as well as human volunteer studies, as appropriate.

Reference to the Centers for Disease Control and Prevention (CDC) growth charts provides a preliminary assessment of the weight ranges that can be anticipated within specific age groups.[31] 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 6 years and the 90th percentile at 12 years (17.7 kg to 54 kg in males).

An estimate of the exposure-response relationship across a range of body-size doses (dose/kg or dose/m^2) may be important. For the "PK and PD" and "PK and efficacy" approaches discussed in section V.A above, investigation of a range of doses and exposures should allow assessment of those relationships and development of rational dosing instructions.

Where PK/PD data are developed, the dose range should account for observed differences in response between adults and the pediatric population (Benjamin, Smith et al. 2008), 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. Therefore, pediatric studies may 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 (i.e., dosing regimen, palatability) are an important part of pediatric clinical pharmacology studies.[32] If there is a pediatric indication, an age-appropriate dosage formulation must be made available for pediatric patients.[33] One way to fulfill this requirement is to develop and test a pediatric formulation and seek approval for that formulation.

If the sponsor demonstrates that reasonable attempts to develop a pediatric formulation have failed, the sponsor should develop and test an age-appropriate formulation that can be prepared by a pharmacist in a licensed pharmacy using an FDA-approved drug product and commercially available ingredients.[34] If the sponsor conducts the pediatric studies using such a formulation,

---

[31] 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.

[32] See also the ICH *Guidance for Industry: E11 Clinical Investigation of Medicinal Products in the Pediatric Population* (Footnote 22).

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

[34] Pediatric Written Request Template. http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM207644.pdf.

the following information should be provided in the study report:

- A statement on how the selected final concentration was optimized to help ensure that the doses can be accurately measured with commercially available dosing devices;
- A statement that the volume to be prepared is appropriate to be dispensed for a course of therapy for one patient, unless there are safety factors that necessitate decreasing the volume to be prepared;
- A listing of all excipients, including diluents, suspending agents, sweeteners and flavoring agents, and coloring agents;
- Information on containers (designated containers should be readily and commercially available to retail pharmacies) and storage requirements (if possible the most user friendly storage condition [room temperature] should be evaluated and or studied); and
- Testing results on formulation stability, not to exceed the expiration date of the original drug product lot from which the pediatric formulation is derived.

The bioavailability of any formulation used in pediatric studies should be characterized in relation to the adult formulation. If needed, a relative bioavailability study comparing the age-appropriate formulation to the approved drug should be conducted in adults. Potential drug-food or vehicle interactions should be considered, such as those that have been reported with apple juice (Abdel-Rahman, Reed et al. 2007), in these study designs.

Extended-release dosage forms or combination products produced for adults should be made available for pediatric patients as an age-appropriate formulation when it is appropriate to do so.

E. Sample Size

1. Number of Patients

The precision of PK and exposure-response parameters in the sample size calculation is critical for pediatric studies. 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 sample size for ensuring precise parameter estimation. The sponsor should account for all potential sources of variability, including inter-subject and intra-subject variability, and differences between the adult and pediatric populations in 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 the development of the drug-metabolizing enzymes and excretory mechanisms, and safety considerations. An example of age groups to be studied is provided in the table below. If the drug is intended to be used in newborn infants, the pediatric study plan should specify whether

premature or small for gestational age infants will be included in the study population.

Example of age groups to be studied for the drug or biologic product
≥1 month to <6 months
6 months to <24 months
2 years to <6 years
6 years to <12 years
12 years to <17 years

The sponsor should discuss the distribution of the number of patients across each age range and the appropriateness of these age ranges with the Agency, because this will be drug product-specific. Justification should be provided for the sample size selected. For example, one approach would be to prospectively target a 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for the drug in each pediatric subgroup with at least 80% 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 to achieve this precision standard (Wang, Jadhav et al. 2012). Conceivably, certain disease states might not allow recruitment of an adequate number of participants to meet the standard, but practical considerations should be taken into account in determining the sample size.

2. Number of Samples Per Patient

In addition to the number of patients, the number of blood samples collected in the clinical pharmacology study to estimate PK measures and parameters for each patient in the study should be carefully considered. The number of samples may be very limited in some pediatric patients such as neonates (for more on collection of blood or plasma samples, see section F below). Clinical study simulations or optimal sampling techniques may be recommended to justify the proposed sampling scheme. Additional sampling for drug or metabolite concentrations is also recommended when an adverse event occurs.

F. Sample Collection

Blood or plasma concentrations of drug or metabolite have been used as supporting evidence of effectiveness or dose selection through exposure-response analyses in pediatric patients. However, the volume and frequency of blood sampling are often of concern in pediatric studies. Blood samples can be obtained by direct venipuncture or through the use of an indwelling intravascular catheter. Because repeated venipuncture may cause discomfort and bruising at the puncture site, an indwelling intravascular catheter should be used when possible. The volume

and frequency of blood sampling can be minimized by using micro-volume drug assays, dried blood spots, and sparse-sampling techniques. These types of assays and analysis are especially relevant when studying neonates (Long, Koren et al. 1987). Modern assay techniques allow small sample volumes to be used to determine drug concentration (Kauffman and Kearns 1992), but data quality may 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 may be beneficial when samples are being obtained for clinical purposes. Noninvasive sampling procedures, such as urine and saliva collection, may suffice if correlated with outcomes or if the correlation with blood or plasma levels has been documented.

Given the difficulty in collecting blood samples in the pediatric population, special approaches to allow optimal times of sample collection may be useful. The sampling scheme should be planned carefully to obtain the maximum information using the minimum number of samples. If possible, collect additional PK samples when adverse events are observed to understand the relationship between drug exposure and toxicity. Samples for DNA should be collected when appropriate, as discussed in section III of this guidance.[35]

G. Covariates and Phenotype Data

The sponsor should obtain the following covariates for each pediatric patient: age, body weight, BSA, gestational age and birth weight for neonates, race or ethnicity, sex, and relevant laboratory tests that reflect the function of the organs responsible for drug elimination. Concomitant and recent drug therapy should also be recorded. Sponsors are encouraged to collect DNA samples in pediatric PK studies under the circumstances described in section II, along with appropriate phenotype information to optimize the interpretation of pharmacogenetic findings. For example, when genotype information is obtained for a cytochrome P450 enzyme, the sponsor should look at the influence of genetic mutations on PK, PD, and/or dose-response to determine whether genetically defined subsets of patients may need special dosing considerations.

The sponsor should examine the relationship between the covariates and the PK of the drug or biologic agent of interest. The contribution of weight or BSA and age to the PK variability should be assessed. The following practice for assessing effect of age on pediatric PK, which

[35] See also the draft *Guidance for Industry*: *Clinical Pharmacogenomics: Premarketing Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling*, Jan. 2013, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM337169.pdf.

is applicable in most cases, is recommended:

- Identify the accurate relationship between PK and body weight or BSA using allometric scaling (Mahmood 2006; Mahmood 2007).

- Analyze the residuals versus age visually, after accounting for the body weight or BSA effect on CL, followed by a more formal analysis exploiting the physiological understanding underlying the CL, if appropriate. Residual is referring to the difference between individual value (treated as predicted value) and the population mean (treated as actual value). Testing for other biologically relevant predictive factors for PK in pediatric patients may be important.

In pediatric PK studies, an estimation of creatinine clearance is recommended because of the challenge with using exogenous markers such as iohexol as an estimate of the glomerular filtration rate (GFR). The modified Schwartz equation, with adjustments for premature infants (Brion, Fleischman et al. 1986), neonates and infants (Schwartz, Feld et al. 1984), and children (Schwartz, Haycock et al. 1976) can be used. The older Schwartz equations may require correction for enzymatic creatinine assays. The Cockcroft-Gault formula should be used to estimate creatinine clearance in adolescents. This formula has been shown to be the best prediction of GFR, as measured by inulin clearance, when compared with the Schwartz and MDRD formulas in adolescents older than 12 years of age (Pierrat, Gravier et al. 2003).

a. Modified Schwartz equation (pediatric patients < 12 years of age):

CrCl (ml/min/1.73 m^2) = (K * Ht) / Scr

height (Ht) in cm; serum creatinine (Scr) in mg/dl

K (proportionality constant):

Infant (LBW < 1year): K=0.33

Infant (Term <1year): K=0.45

Female Child (<12 years): K=0.55

Male Child (<12 years): K=0.70

b. Cockcroft-Gault equation (pediatric patients $\geq$ 12 years of age):

ClCr (ml/min) = [(140 - age) x weight in kg] / [Scr x 72] (x 0.85 if female)

When studying pediatric patients with impaired renal function, the sponsor should refer to the draft Guidance for Industry *Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling*, March 2010, for the general concepts of study design.[36] Newer formulas incorporating cystatin C may be used to estimate GFR in pediatric patients with impaired renal function (Schwartz, Munoz et al. 2009).

If factors affecting the PK of the drug are to be studied (e.g., the effect of a concomitant medication or the presence or absence of a disease), a justification for the numbers of patients with and without those factors in the study should be included.

H. Sample Analysis

An accurate, precise, sensitive, specific, and reproducible analytical method to quantify the drug and metabolites in the biologic fluids of interest is essential.[37] A method that is readily adaptable and that uses only minimum sample volumes should be chosen.

I. Data Analysis

Two basic approaches for performing the PK analysis in pediatric patients can be used; a standard noncompartmental PK approach and a population PK approach.

1. Noncompartmental Analysis

The noncompartmental analysis PK approach involves administering either single or multiple doses of a drug to a relatively small group of patients with relatively frequent blood and urine sample collection. 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 can be used to establish PK 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 interindividual variances. In this approach, including a sufficient number of patients 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 patient in the PK study, some understanding of intra-individual variability in PK parameters can be obtained.

[36] When final, this guidance will represent FDA's current thinking on the topic. Available at http://www.fda.gov/downloads/Drugs/Guidances/UCM204959.pdf.

[37] See the *Guidance for Industry: Bioanalytical Method Validation*, May 2001, available at http://www.fda.gov/downloads/Drugs/Guidances/ucm070107.pdf.

2. Population Analysis

An alternative approach for analysis in pediatric clinical pharmacology studies is the population approach to PK analysis. Population PK accommodates infrequent (sparse) sampling of blood or plasma from a larger patient population than would be used in a compartmental or noncompartmental analysis PK approach to determine PK parameters. Sparse sampling of blood or plasma is considered more acceptable for pediatric studies, because the total volume of blood sampled can be minimized. Sampling can often be performed concurrently with clinically necessary blood or urine sampling. Because relatively large numbers of patients are studied and samples can be collected at various times of the day and repeatedly over time in a given patient, 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.[38]

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 patient are available. Simultaneous modeling of data across all patients provides the best opportunity to describe the exposure-response relationship.[39]

J. Clinical Study Report

The clinical study report should follow the ICH E3 guidance on the *Structure and Content of Clinical Study Reports* 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 Exposure-Response Guidance[40] and the Population PK Guidance,[41] respectively. In submitting PK information, the sponsor should submit the data illustrating 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 noncompartmental analysis results.

K. 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

[38] For more information on population PK, see the *Guidance for Industry: Population Pharmacokinetics* (Footnote 30).

[39] See the *Guidance for Industry: Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications* (Footnote 26).

[40] See the *Guidance for Industry: Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications* (Footnote 26).

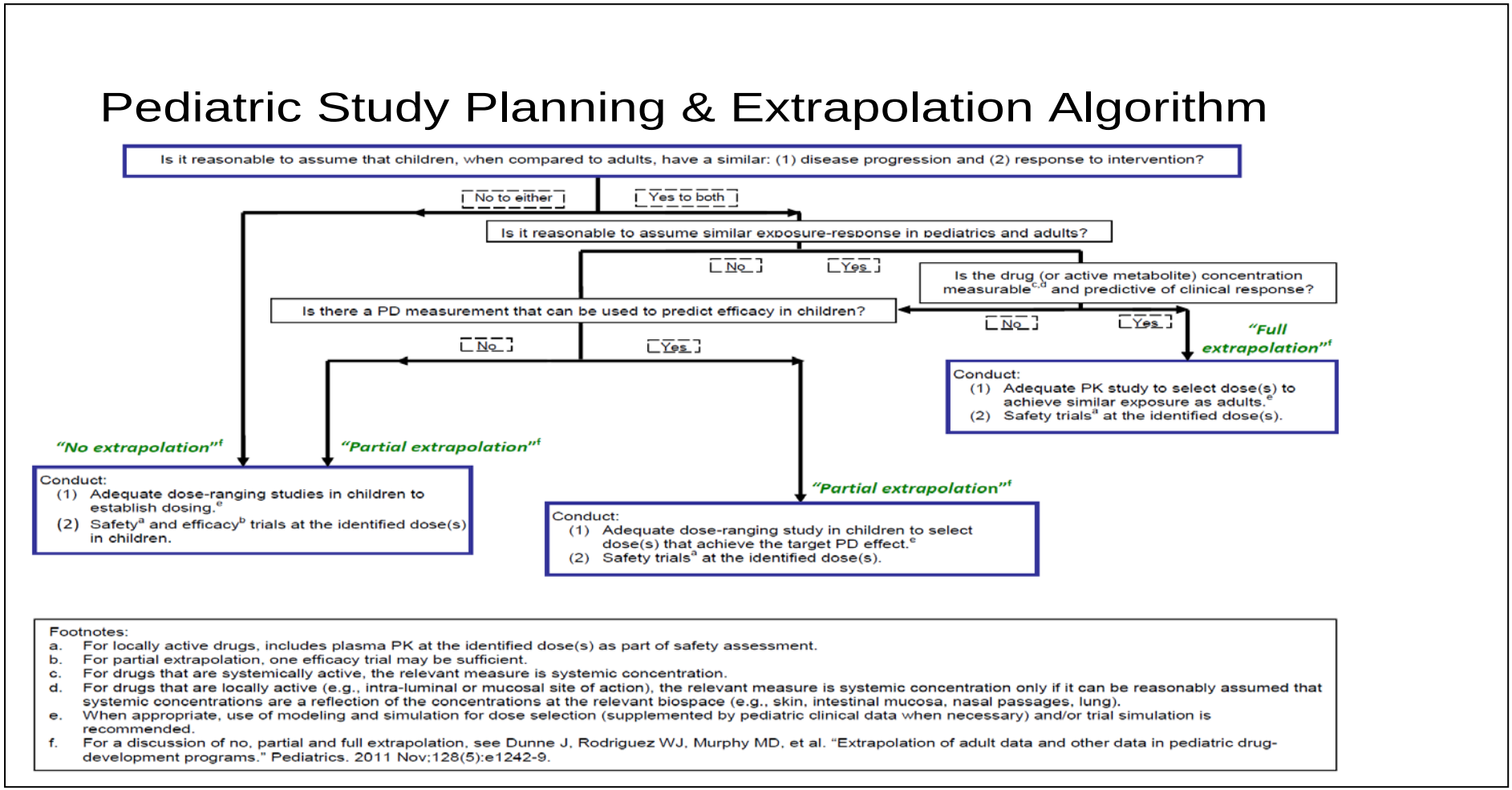
[41] See the *Guidance for Industry: Population Pharmacokinetics* (Footnote 30).

738 Standards Council [42] and the CDER Study Data Standards web sites for more information.[43] The
739 sponsor should also submit PK and exposure-response data used for modeling and simulation in
740 an SAS.XPT-compatible format.

[42] FDA Resources for Data Standards, available at http://www.fda.gov/ForIndustry/DataStandards/default.htm.
[43] Study Data Standards for Submission to CDER, available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

741 **APPENDIX**[44]

742



[44] See the Guidance for Industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (Footnote 13).

REFERENCES

Abdel-Rahman, S. M., M. D. Reed, et al. (2007). "Considerations in the rational design and conduct of phase I/II pediatric clinical trials: avoiding the problems and pitfalls." Clinical Pharmacology & Therapeutics **81**(4): 483-494.

Benjamin, D. K., Jr., P. B. Smith, et al. (2008). "Pediatric antihypertensive trial failures: analysis of end points and dose range." Hypertension **51**(4): 834-840.

Booth, B. P., A. Rahman, et al. (2007). "Population pharmacokinetic-based dosing of intravenous busulfan in pediatric patients." Journal of Clinical Pharmacology **47**(1): 101-111.

Brion, L. P., A. R. Fleischman, et al. (1986). "A simple estimate of glomerular filtration rate in low birth weight infants during the first year of life: noninvasive assessment of body composition and growth." Journal of Pediatrics **109**(4): 698-707.

Dunne, J., W. J. Rodriguez, et al. (2011). "Extrapolation of adult data and other data in pediatric drug-development programs." Pediatrics **128**: e1242-1249.

Kauffman, R. E. and G. L. Kearns (1992). "Pharmacokinetic studies in paediatric patients. Clinical and ethical considerations.[see comment]." Clinical Pharmacokinetics **23**(1): 10-29.

Kearns, G. L. (2000). "Impact of developmental pharmacology on pediatric study design: overcoming the challenges." Journal of Allergy & Clinical Immunology **106**(3 Suppl): S128-138.

Kearns, G. L., S. M. Abdel-Rahman, et al. (2003). "Developmental pharmacology--drug disposition, action, and therapy in infants and children." New England Journal of Medicine **349**(12): 1157-1167.

Leeder, J. S. (2004). "Translating pharmacogenetics and pharmacogenomics into drug development for clinical pediatrics and beyond." Drug Discovery Today **9**(13): 567-573.

Leong, R., M. L. T. Vieira, et al. (2012). "Regulatory experience with physiologically based pharmacokinetic modeling for pediatric drug trials." Clinical Pharmacology & Therapeutics **91**(5): 926-931.

Li, F., P. Nandy, et al. (2009). "Pharmacometrics-based dose selection of levofloxacin as a treatment for post-exposure inhalational anthrax in children." Antimicrobial Agents and Chemotherapy **doi:10.1128/AAC.00667-09**: 1-21.

Long, D., G. Koren, et al. (1987). "Ethics of drug studies in infants: how many samples are required for accurate estimation of pharmacokinetic parameters in neonates?" Journal of Pediatrics **111**(6 Pt 1): 918-921.

Mahmood, I. (2006). "Prediction of drug clearance in children from adults: a comparison of several allometric methods." British Journal of Clinical Pharmacology **61**(5): 545-557.

Mahmood, I. (2007). "Prediction of drug clearance in children: impact of allometric exponents, body weight, and age." Therapeutic Drug Monitoring **29**(3): 271-278.

Pierrat, A., E. Gravier, et al. (2003). "Predicting GFR in children and adults: a comparison of the Cockcroft-Gault, Schwartz, and modification of diet in renal disease formulas.[see comment]." Kidney International **64**(4): 1425-1436.

Rodriguez, W., A. Selen, et al. (2008). "Improving pediatric dosing through pediatric initiatives: what we have learned." Pediatrics **121**(3): 530-539.

Schwartz, G. J., L. G. Feld, et al. (1984). "A simple estimate of glomerular filtration rate in full-term infants during the first year of life." Journal of Pediatrics **104**(6): 849-854.

Schwartz, G. J., G. B. Haycock, et al. (1976). "A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine." Pediatrics **58**(2): 259-263.

Schwartz, G. J., A. Munoz, et al. (2009). "New equations to estimate GFR in children with CKD." Journal of the American Society of Nephrology **20**(3): 629-637.

Shaddy, R. E. and S. C. Denne (2010). "Clinical report--guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations." Pediatrics **125**(4): 850-860.

Tornoe, C. W., J. J. Tworzyanski, et al. (2007). "Optimising piperacillin/tazobactam dosing in paediatrics." International Journal of Antimicrobial Agents **30**(4): 320-324.

Wang, Y., P. R. Jadhav, et al. (2012). "Clarification on Precision Criteria to Derive Sample Size When Designing Pediatric Pharmacokinetic Studies " J Clin Pharmacol **52**: 1601-1606.