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

Guidance for Industry

DRAFT GUIDANCE

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

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Contains Nonbinding Recommendations

Draft – Not for Implementation

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3 ## Guidance for Industry[1]

4

5
6 This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current
7 thinking on this topic. It does not create or confer any rights for or on any person and does not operate to
8 bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of
9 the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA
10 staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call
11 the appropriate number listed on the title page of this guidance.
12

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14
15 ## I. INTRODUCTION
16
17 This draft guidance is intended to assist those sponsors of new drug applications (NDAs),
18 biologics license applications (BLAs) for therapeutic biologics, and supplements to such
19 applications who are planning to conduct clinical studies in pediatric populations.
20 Effectiveness, safety, or dose-finding studies in pediatric patients involve gathering clinical
21 pharmacology information, such as information regarding a product's pharmacokinetics and
22 pharmacodynamics pertaining to dose selection and individualization. This guidance addresses
23 general clinical pharmacology considerations for conducting studies so that the dosing and safety
24 information for drugs and biologic products in pediatric populations can be sufficiently
25 characterized, leading to well-designed trials to evaluate effectiveness.[2]
26
27 In general, this draft guidance focuses on the clinical pharmacology information (e.g., exposure-
28 response, pharmacokinetics, and pharmacodynamics) that supports findings of effectiveness and
29 safety and helps identify appropriate doses in pediatric populations. This guidance also describes
30 the use of quantitative approaches (i.e., pharmacometrics) to employ disease and exposure-
31 response knowledge from relevant prior clinical studies to design and evaluate future pediatric
32 studies. The guidance does not describe: (1) standards for approval of drug and biological
33 products in the pediatric population, (2) criteria to allow a determination that the course of a
34 disease and the effects of a drug or a biologic are the same in adults and pediatric populations, or
35 (3) clinical pharmacology studies for vaccine therapy, blood products, or other products not

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[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.

36 regulated by the Center for Drug Evaluation and Research.
37
38 FDA's guidance documents, including this guidance, do not establish legally enforceable
39 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should
40 be viewed only as recommendations, unless specific regulatory or statutory requirements are
41 cited. The use of the word *should* in Agency guidances means that something is suggested or
42 recommended, but not required.
43
44
45 **II. BACKGROUND**
46
47 During the past two decades, the Food and Drug Administration (FDA) has worked to address
48 the problem of inadequate pediatric testing and inadequate pediatric use information in drug and
49 biological product labeling. The Food and Drug Administration Modernization Act of 1997 (the
50 Modernization Act) addressed the need for improved information about drug use in the pediatric
51 population by establishing incentives for conducting pediatric studies on drugs for which
52 exclusivity or patent protection exists.[3] Congress subsequently passed the Best Pharmaceuticals
53 for Children Act (BPCA)[4] in 2002 and the Pediatric Research Equity Act (PREA) in 2003.[5]
54 Both BCPA and PREA were reauthorized in 2007.[6] In 2012, BPCA and PREA were made
55 permanent under Title V of the Food and Drug Administration Safety and Innovation Act
56 (FDASIA).[7]
57
58 Under BPCA, sponsors of certain applications and supplements filed under section 505 of the
59 FD&C Act and under section 351 of the Public Health Service Act can obtain an additional six
60 months of exclusivity if, in accordance with the requirements of the statute, the sponsor submits
61 information responding to a Written Request from the Secretary relating to the use of a drug in
62 the pediatric population.[8] Under PREA, sponsors of certain applications and supplements filed
63 under section 505 of the FD&C Act or section 351 of the Public Health Service Act are required
64 to submit pediatric assessments, unless they receive an applicable waiver or deferral of this
65 requirement.[9] If applicable, sponsors must submit a request for a deferral or waiver as part of an
66 initial pediatric study plan (section 505B(e) of the FD&C Act) (see section V of this guidance).
67
68 The FD&C Act requires a description of pediatric study data in labeling arising from study data

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[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.

69   submitted in response to a Written Request under BPCA and/or data from studies required under
70   PREA, whether the findings are positive, negative, or inconclusive.[10] The PREA requirements
71   are triggered by the submission of an application or supplement for a drug for a new active
72   ingredient, new indication, new dosage form, new dosing regimen, or new route of
73   administration under Section 505 of the FD&C Act or Section 351 of the PHS Act.[11] If a full or
74   partial waiver is granted under PREA because there is evidence that the drug would be
75   ineffective or unsafe in pediatric populations, the information must be included in the product's
76   labeling.[12]
77
78   This guidance deals with the clinical pharmacology considerations of any planned pediatric
79   study, whether or not it is conducted pursuant to BPCA or PREA.
80
81

82   **III. CLINICAL PHARMACOLOGY CONSIDERATIONS**

83
84   There are several recognized approaches to providing substantial evidence to support the safe
85   and effective use of drugs in pediatric populations, including (1) evidence from adequate and
86   well-controlled investigations of a specific pediatric indication different from the indication(s)
87   approved for adults; (2) evidence from adequate and well-controlled investigations in pediatric
88   populations to support the same indication(s) approved for adults; or (3) evidence from adequate
89   and well-controlled studies in adults and additional information in the specific pediatric
90   population.[13] The first approach generally requires a full pediatric development program. The
91   second approach above generally involves the use of prior disease and exposure-response
92   knowledge from studies in adults and relevant pediatric information to design and, in some cases,
93   analyze new pediatric studies. For the third approach, the assumption is that the course of the
94   disease and the effects of the drug are sufficiently similar in the pediatric and adult populations
95   to permit extrapolation of the adult efficacy data to pediatric patients (Dunne, Rodriguez et al.
96   2011). If the third approach is taken, there would ordinarily be a pediatric study to determine a
97   dose in the pediatric population that provides a drug exposure similar to the exposure that is
98   effective in adults. If there is a concern that exposure-response relationships might be different
99   in pediatric patients, studies relating blood levels of drug to pertinent pharmacodynamic effects
100   other than the desired clinical outcome (exposure-response data for both desired and undesired
101   effects) for the drug in the pediatric population might also be important. For all three

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[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.

102 approaches, the extent of the required pediatric safety studies may take into consideration prior
103 experience with similar drugs in pediatric populations, the seriousness of the adverse events in
104 adults or in pediatric populations, when this information is available, and the feasibility of
105 conducting studies in pediatric patients.
106
107 Clinical pharmacology studies in the pediatric population should be conducted in patients
108 receiving therapy for a particular indication, or in rare instances, in those who are at risk for the
109 condition of interest. The identification of the appropriate ages to study and decisions on how to
110 stratify data by age are drug-specific and require scientific justification, taking into consideration
111 developmental biology and pharmacology.
112
113 The Center for Drug Evaluation and Research generally divides the pediatric population into the
114 following groups:[14]
115
116 • Neonates: birth up to 1 month;
117 • Infants: 1 month up to 2 years;
118 • Children: 2 up to 12 years; and
119 • Adolescents: 12 years up to 16 years.[15]
120
121 The measurement or prediction of a drug or biologic's pharmacokinetics (exposure) and
122 pharmacodynamics (response) is essential to the clinical pharmacology assessment. It is
123 important to describe the exposure-response relationship of a drug or biologic in the pediatric
124 population. In some instances, knowledge of pharmacogenetic differences, which can affect a
125 product's exposure, may also be required.
126
127 **A. Pharmacokinetics**
128
129 Pharmacokinetic measures, such as area under the curve (AUC) and maximum concentration
130 (C_{max}) and parameters such as clearance (CL), half-life, and volume of distribution, reflect the
131 absorption (A), distribution (D), and excretion (E) of a drug or biologic from the body. Drugs
132 may be eliminated in the unchanged (parent) form, or undergo metabolism (M) to one or more
133 active and inactive metabolites. The overall set of processes is often referred to as ADME,
134 which ultimately determines systemic exposure to a drug and its metabolites after drug

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[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.

135   administration. This systemic exposure, reflected in plasma drug or metabolite concentrations,
136   or both, is generally correlated with both beneficial and adverse drug effects. All drugs and
137   biologics show inter- and intra-individual variability in PK measures and parameters. In the
138   pediatric population, growth and developmental changes in factors influencing ADME can also
139   lead to changes in PK parameters. The PK of a drug or biologic is typically evaluated over the
140   entire pediatric age range in which the agents will be used (Kauffman and Kearns 1992; Kearns
141   2000). Special areas of importance in planning pediatric PK studies are discussed in the
142   following paragraphs.
143
144   •   Absorption
145
146   Developmental changes in the pediatric population that can affect absorption include effects on
147   gastric acidity, rates of gastric and intestinal emptying, surface area of the absorption site,
148   gastrointestinal drug-metabolizing enzyme systems, gastrointestinal permeability, biliary
149   function, and transporter expression. Similarly, developmental changes in skin, muscle, and fat,
150   including changes in water content and degree of vascularization, can affect absorption patterns
151   of drugs delivered by intramuscular, subcutaneous, or percutaneous absorption (Yaffe and
152   Aranda 2010).
153
154   •   Distribution
155
156   Distribution of a drug or biologic can be affected by changes in body composition, such as
157   changes in total body water and adipose tissue, which are not necessarily proportional to changes
158   in total body weight. Plasma protein binding and tissue binding changes arising from changes in
159   body composition with growth and development may also influence distribution. Differences
160   between pediatric patients and adults in blood flow to an organ, such as the brain, can also affect
161   the distribution of a drug or biologic in the body.
162
163   •   Metabolism
164
165   Drug metabolism commonly occurs in the liver, but may also occur in the blood,
166   gastrointestinal wall, kidney, lung, and skin. Developmental changes in metabolizing capacity
167   can affect both bioavailability and elimination, depending on the degree to which intestinal and
168   hepatic metabolic processes are involved (Leeder 2004). Although developmental changes are
169   recognized, information on drug metabolism of specific drugs in newborns, infants, and
170   children is limited. Both rates of metabolite formation and the principal metabolic pathway
171   can be different in pediatric patients compared to adults and within the pediatric population. In
172   vitro studies performed early in drug development may be useful in focusing attention on

173 metabolic pathways in both adults and pediatric patients.[16]
174
175 •   Excretion
176
177 Drug excretion by the kidney is the net result of glomerular filtration, tubular secretion, and
178 tubular reabsorption. Because these processes mature at different rates in the pediatric
179 population, age can affect the systemic exposure of drugs when renal excretion is a dominant
180 pathway of elimination. The maturation of other excretory pathways, including biliary and
181 pulmonary routes of excretion, is also important.
182
183 •   Protein Binding
184
185 Protein binding to a drug or its metabolites may change with age and concomitant illness. In
186 certain circumstances, an understanding of protein binding may be needed to interpret the data
187 from a blood level measurement and to determine appropriate dose adjustments (Kearns, Abdel-
188 Rahman et al. 2003). In vitro plasma protein binding studies can determine the extent of binding
189 of the parent and the major active metabolite(s) and identify specific binding proteins, such as
190 albumin and alpha-1 acid glycoprotein.
191
192 •   Clearance
193
194 Clearance of drugs or biologic products as a function of age is generally a valuable parameter for
195 determining the dose for each age group in the pediatric population, and drug clearance has
196 provided a valuable tool in the assessment of pediatric clinical pharmacology studies (Rodriguez,
197 Selen et al., 2008). Plasma clearance can be defined as the volume of plasma which is
198 completely cleared of drug in a given time period.
199
200 •   Additional Factors
201
202 Growth and developmental changes in the pediatric population will create substantial changes in
203 ADME. PK measures and parameters for a drug or biologic may need to be described as a
204 function of age and be related to some measure of body size, such as height, weight, or body
205 surface area (BSA) (Kearns, Abdel-Rahman et al. 2003). The maturational changes in systems
206 affecting ADME, such as membrane transporters and metabolizing enzymes, should be taken
207 into consideration in choosing age groups and doses to study in the pediatric population.
208

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[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.

209 **B. Pharmacodynamics**
210
211   Sponsors should collect and analyze both PK and, whenever possible, pharmacodynamics (PD)
212   data in pediatric studies to determine how the two are linked (i.e., the PK-PD or exposure-
213   response relationship). Pharmacodynamics may include the effect of the drug on biomarkers or
214   clinical endpoints for both effectiveness and safety. These measurements may allow a better
215   understanding of whether the PK-PD relationships of the drug or biologic in pediatric patients
216   are similar to those observed in adults, and may aid in deriving rational dosing strategies in
217   pediatrics.
218
219   If the clinical endpoint cannot be measured directly because the effect is delayed or rare, then the
220   selection of an appropriate biomarker to substitute for the clinical efficacy or toxicity endpoint is
221   essential. In many cases, biomarkers are first evaluated in an adult population, in which case the
222   support for the use of the biomarker in a pediatric population depends on evidence that the
223   disease pathophysiology and pharmacologic response in pediatric patients is sufficiently similar
224   to adults.
225
226   **C. Pharmacogenetics**
227
228   Genetic differences that clinically affect both exposure and response are increasingly
229   documented,[17] but the relationship between genomic profiles and developmentally regulated
230   gene expression has not been extensively studied in pediatric populations. Some of the
231   difficulties in obtaining specific pharmacogenetic information in pediatric patients have been
232   reviewed (Leeder 2004). Nevertheless, if drug exposure in a pediatric clinical pharmacology
233   study is dependent on a well-known pharmacogenomic biomarker (e.g., cytochrome P4502D6),[18]
234   obtaining patient DNA may provide additional information for the interpretation of the PK and
235   PD results.
236
237
238   **IV. ETHICAL CONSIDERATIONS**
239
240   FDA-regulated clinical investigations are governed, in part, by the institutional review board
241   (IRB) regulations at 21 CFR Part 56 and the human subject protections at 21 CFR Part 50.
242   Pediatric subjects who are enrolled in FDA-regulated clinical pharmacology studies must be
243   afforded the additional safeguards found at 21 CFR Part 50, Subpart D. These safeguards restrict
244   the allowable risk to which a pediatric subject may be exposed in a clinical investigation based

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[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).

245 on whether the proposed intervention or procedure offers a prospect of direct clinical benefit to
246 the individual child. Clinical pharmacology studies generally do not provide a direct clinical
247 benefit to individual pediatric subjects, and must therefore present no more than minimal risk (21
248 CFR 50.51) or a minor increase over minimal risk (21 CFR 50.53). Exceptions to this general
249 rule may include, for example, dose-monitoring studies that directly benefit individual pediatric
250 subjects by ensuring that serum levels of a drug remain within a therapeutic range. Under such
251 circumstances, a clinical pharmacology study may be approvable by an IRB under 21 CFR
252 50.52. Before initiation of the clinical trial, an IRB must approve the proposed trial under the
253 requirements of 21 CFR 50 subpart D.[19] However, FDA has an independent responsibility to
254 assess the compliance of the proposed clinical trial under 21 CFR 50 subpart D. Failure of a
255 proposed clinical trial to be in compliance with 21 CFR Part 50, Subpart D, may be sufficient
256 grounds for FDA to impose a clinical hold because the investigation could present an
257 unreasonable and significant risk of illness or injury (21 CFR 312.42(b)).
258
259 The assessment under 21 CFR Part 50, Subpart D of a clinical pharmacology protocol depends
260 on whether the experimental drug or biologic is being administered (1) solely for the purposes of
261 obtaining pharmacokinetic data or (2) in such a way that it offers the enrolled child a prospect of
262 direct clinical benefit. The following two paragraphs discuss these two cases, respectively. In
263 both cases, administration of an experimental drug or biological product is always considered to
264 represent more than minimal risk and thus is not approvable by an IRB under 21 CFR 50.51. For
265 IRB approval under 21 CFR 50.53, an enrolled child must have a disorder or condition that is the
266 focus of the clinical investigation. For IRB approval of a clinical investigation under 21 CFR
267 50.52, an enrolled child must have a prospect of direct clinical benefit from administration of the
268 investigational product. Thus, only patients with a therapeutic need for the investigational drug
269 product can be enrolled in such trials. Consequently, healthy pediatric subjects (i.e., without a
270 disorder or condition which is the focus of the research) cannot be enrolled in clinical
271 pharmacology studies absent a determination by the Commissioner, after consultation with a
272 panel of experts in pertinent disciplines and opportunity for public review and comment, that the
273 conditions in 21 CFR 50.54 (which allows clinical investigations to proceed that present an
274 opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare
275 of children) are met.[20]
276
277 *Case 1: IRB review of a clinical pharmacology study using pediatric human subjects under 21*
278 *CFR 50.53.*
279

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[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.

280   When the experimental drug or biologic is being administered solely for the purpose of obtaining
281   pharmacokinetic data, both the experimental drug administration and the pharmacokinetic
282   sampling must present no more than a minor increase over minimal risk (21 CFR 50.53(a)). In
283   addition, pediatric subjects may be exposed to such risks if, among other criteria, the intervention
284   or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition
285   that is of vital importance for the understanding or amelioration of that disorder or condition (21
286   CFR 50.53(c)). Thus, for a clinical investigation to be approved by an IRB under this category,
287   the enrolled pediatric subject must have a disorder or condition. A condition may include being
288   "at risk" for the disease. In addition, sufficient empirical data regarding the risks of the proposed
289   interventions or procedures need to be available to ascertain that the risks are no more than a
290   minor increase over minimal risk (21 CFR 50.53(a)). The available adult data including dose-
291   response data may be considered for this purpose. Even if the risk is thought to be low, if there
292   are not enough data to adequately characterize the risk, then the intervention or procedure cannot
293   be considered to present no more than a minor increase over minimal risk because the risks of
294   the intervention or procedure would not be known with sufficient accuracy. In addition, the risks
295   of the blood and/or fluid sampling procedures need to be no more than a minor increase over
296   minimal risk. An example of a clinical pharmacology study that may be conducted under 21 CFR
297   50.53 is the pharmacokinetics of a *single dose* of an over-the-counter cough and cold product.
298   To be enrolled in such a study, a child may either be symptomatic from an upper respiratory
299   infection (URI) or be at risk for a future URI based on the presence of criteria such as the
300   frequency of past infections, number of people living in the home, or exposure to others in a
301   preschool or school setting.
302
303   *Case 2: IRB review of a clinical pharmacology study using pediatric human subjects under 21*
304   *CFR 50.52.*
305
306   The experimental drug administration may present more than a minor increase over minimal risk
307   as long as this level of risk exposure is justified by a sufficient prospect of direct clinical benefit
308   to the subjects (21 CFR 50.52(a)). For example, dose-monitoring studies that directly benefit
309   individual pediatric subjects by ensuring that serum levels of a drug remain within a therapeutic
310   range would fall under 21 CFR 50.52. In this case, pharmacokinetic studies of investigational
311   products must be done in children who have a therapeutic need for the drug or biologic, and the
312   drug or biologic must be administered using a dosing regimen that offers a sufficient prospect of
313   direct clinical benefit to justify the risks (21 CFR 50.52(a)). In such studies, the limited
314   venipunctures that may be required to obtain specimens for pharmacokinetic analyses are
315   generally considered either minimal risk or a minor increase over minimal risk, and therefore
316   may be approvable absent a prospect of direct benefit (21 CFR 50.51 and 50.53). This approach
317   to the analysis of clinical pharmacology trials is called a component analysis of risk, whereby the
318   interventions that do and do not offer a prospect of direct benefit in any given protocol must be

319 analyzed separately.[21]
320
321 Adequate information from clinical pharmacology studies to support pediatric dosing is critical
322 to the development of ethically sound confirmatory trials. For example, pivotal trials of
323 antihypertensive agents may have failed to demonstrate efficacy in the pediatric population as a
324 result of inadequate pediatric dosing (Benjamin, Smith et al., 2008; Rodriguez, Selen et al.,
325 2008). FDA considers the public health need for adequate pediatric dosing in its assessment of
326 the ethical propriety of proposed studies. For further information, investigators and IRBs may
327 refer to the American Academy of Pediatrics Guidelines for the Ethical Conduct of Studies to
328 Evaluate Drugs in Pediatric Populations (Shaddy and Denne, 2010) or the International
329 Conference on Harmonization (ICH) Guidance for Industry E6 Good Clinical Practice:
330 Consolidated Guidance (ICH E6), which contains a section on nontherapeutic studies in special
331 populations.[22]
332
333
334 **V. THE PEDIATRIC STUDY PLAN DESIGN AND POINTS TO CONSIDER**
335
336 Under Section 505B(e)(1) of the FD&C Act, a sponsor who will be submitting an application for
337 a drug or biological product that includes a new active ingredient, new indication, new dosage
338 form, new dosing regimen, or new route of administration is required to submit an initial
339 pediatric study plan (PSP). A pediatric study plan (PSP) outlines the pediatric study or studies
340 that the applicant plans to conduct.[23]
341
342 The submission of the initial PSP is intended to encourage sponsors to consider pediatric studies
343 early in product development and, when appropriate, begin planning for these studies. The

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[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.

344 initial PSP must include "(i) an outline of the pediatric study or studies that the applicant plans to
345 conduct (including, to the extent practicable, study objectives and design, age groups, relevant
346 endpoints, and statistical approach); (ii) any request for a deferral, partial waiver, or waiver…if
347 applicable, along with any supporting information; and (iii) other information specified in the
348 regulations" promulgated by the FDA.[24,25] When designing the pediatric clinical studies,
349 sponsors should be mindful that modeling and simulation, and pharmacologic considerations, are
350 often critical for the successful completion of a study. Modeling and simulation using all of the
351 information available should therefore be an integral part of all pediatric development programs.
352 The following sections are critically important when developing the clinical pharmacology
353 components of a pediatric study plan.
354
355 **A. Approaches to Pediatric Studies**
356
357 In addition to the usual considerations of PK (i.e., drug exposure), PD (i.e., effect on biomarker
358 or clinical endpoint), and exposure-response relationships that may be different from those of
359 adults, a pediatric drug development program should consider the time course of development of
360 the drug metabolizing enzyme(s), drug excretory systems, and transporters specific to the drug
361 being studied. This is probably best achieved by characterizing the PK of the drug across the
362 appropriate pediatric age range. Based on the availability and reliability of the information about
363 such factors, the pediatric study planning and extrapolation algorithm[26] in the Appendix of this
364 guidance illustrates the different approaches in conducting pediatric clinical studies.
365
366 PK Only Approach (i.e., full extrapolation[27]): This approach is appropriate when it is reasonable
367 to assume that children, when compared to adults, have (1) a similar progression of disease; (2) a
368 similar response of the disease to treatment; (3) a similar exposure-response or concentration-
369 response relationship; and (4) the drug (or active metabolite) concentration is measureable and
370 predictive of the clinical response. Evidence that could support a conclusion of similar disease
371 course and similar drug effect in adult and pediatric populations includes evidence of common
372 pathophysiology and natural history of the disease in the adult and pediatric populations,
373 evidence of common drug metabolism and similar concentration-response relationships in each

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[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.

374 population, and experience with the drug, or other drugs in its therapeutic class, in the disease or
375 condition or related diseases or conditions.[28]
376
377 If there is no currently used pediatric dose, if there is insufficient PK information about a
378 currently used pediatric dose, or if the currently used pediatric dose in the same clinical context
379 would not be expected to match adult exposure, then a PK study should be performed to identify
380 the pediatric dose that will provide similar exposure to adults. This PK study should be
381 conducted before any additional pediatric clinical studies are initiated to ensure the optimal dose
382 for these studies. Before conducting a PK study, simulations should be performed to identify the
383 dose expected to achieve an appropriate target exposure (e.g., the observed adult drug exposure)
384 in the same clinical context. The antibacterial therapeutic area is a good example of this
385 approach, where the organism is expected to respond to similar plasma concentrations in adults
386 and pediatric patients. In this case, the study can focus on identifying the doses in the pediatric
387 setting that would result in exposures similar to those attained in adults.
388
389 PK and PD Approach (i.e., partial extrapolation): This approach is applicable when the disease
390 and intervention are believed to behave similarly in pediatric patients and adults, but the
391 exposure-response relationship in pediatric patients is either inadequately defined or thought not
392 to be sufficiently similar. To use this approach, the exposure-response relationship in adults
393 should be well-characterized The goal of such an approach is to characterize and compare the
394 exposure-response relationship in adults and in the pediatric population with the appropriate
395 pediatric doses based on the exposure-response relationships seen in pediatric patients. Clinical
396 measures (e.g., symptoms, signs, outcomes) can be used to select doses, but an appropriate
397 biomarker considered to be related to such an endpoint can also be used, which is usually a
398 biomarker based on adult experience. If there is uncertainty about whether extrapolation of
399 efficacy is appropriate, a single adequate and well-controlled study using a clinical endpoint may
400 be necessary. Additional studies powered to demonstrate efficacy may not be required.
401
402 The antiarrhythmic therapeutic area is one example of this approach, where mortality and
403 morbidity studies cannot be ethically conducted in pediatric patients. In the case of
404 antiarrhythmic therapy, the Agency accepted a clinical study assessing the beta adrenergic
405 blocking effects of sotalol on heart rate and the effect on QTc, both of which are acceptable
406 biomarkers in pediatrics, as the basis for labeling information on use of the drug in pediatric
407 patients.
408
409 PK and Efficacy Approach (i.e., no extrapolation): If the disease progression is unique to
410 pediatric patients or its progression and/or response to intervention is undefined or dissimilar to
411 that in adults, then the pediatric development program should provide substantial evidence of the

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

412 effectiveness and safety of the drug product in pediatric subjects in one or more clinical studies,
413 usually evaluating more than one dose.[29] The study objectives are to provide evidence of
414 effectiveness and safety and to characterize the PK and exposure-response relationships to aid in
415 optimizing pediatric dosing strategies. A population PK analysis can be conducted concurrently
416 using PK data from the efficacy study to confirm PK estimates in the age subgroups.[30]
417
418 For the "PK and PD" and "PK and Efficacy" approaches, response data in pediatric studies
419 should be collected and analyzed. Response or PD data may include biomarkers or clinical
420 endpoints for both safety and effectiveness. The specific endpoints for an exposure-response
421 evaluation for each drug or biologic product should be discussed with the Agency.
422
423 A dedicated PK study is not always required in every age group. For example, prior experience
424 with dosing in adolescent patients has demonstrated that knowledge of adult dosing and
425 appropriate dose scaling may be sufficient for some drugs with adequate justification.
426 Confirmatory population PK studies may be used to supplement such a program in which a
427 dedicated PK study is not considered essential.
428
429 **B. Alternative Approaches**
430
431 In addition to conventional PK studies with intensive blood sampling in pediatric patients, other
432 approaches can be used to obtain useful drug exposure information. Urine and saliva collection
433 are noninvasive, but the interpretation of drug analysis of either is complicated and requires
434 careful consideration before use. Likewise, tissue or cerebrospinal fluid that is being collected
435 for clinical purposes present both an opportunity and a challenge for the appropriate
436 interpretation of these results in understanding the PK of the drug.
437
438 When clinical PK studies in pediatric patients are not feasible, there are situations in which
439 interpolation or extrapolation of PK data may be sufficient. PK information in certain pediatric
440 age groups may be gained by interpolating or extrapolating from existing data in adults, data in
441 pediatric patients in other age groups, or both. However, extrapolation of data to very young
442 pediatric patients, particularly neonates, is rarely credible. Significant metabolic differences may
443 exist between neonates and older pediatric patients or adults that can give rise to considerable
444 variability in metabolism and drug disposition. This variability can lead to an altered dose-
445 response relationship. Modeling and simulation can provide another method for reducing
446 residual uncertainty about drug dosing in special pediatric populations.
447

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[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.

448 **C. Pediatric Dose Selection**
449
450 Selection of an appropriate dose range to be studied is critical in deriving rational dosing
451 recommendations for the pediatric population. Because there may be limited information on
452 the safety of the dose to be administered to a neonate or infant, the dose range in initial studies
453 requires careful consideration. Factors for consideration include (1) similarity of the disease
454 and exposure-response in other studied pediatric groups; (2) the relative bioavailability of the
455 new formulation compared to the previous formulations; (3) the age and developmental stage
456 of the population; (4) the pharmacogenetic characteristics of the drug or biologic; (5) the
457 toxicity of the drug or biologic; and (6) PK data from other pediatric populations. Initial doses
458 are typically normalized to body size (mg/kg) or BSA (mg/m^2).
459
460 When separate efficacy studies in pediatrics are not conducted (i.e., for the PK only approach
461 described in section V.A above), in general, PK studies in the pediatric population should
462 determine how the dosage regimen should be adjusted to achieve the same level of systemic
463 exposure in adults as defined above. Differences in interpatient variability in these PK measures
464 and/or parameters between age groups or between pediatric and adult patients should be
465 interpreted with regard to their impact on dosing, safety, and/or efficacy. In these instances, the
466 sponsor should specify the criteria by which exposure matching would be acceptable. For
467 example, one approach would be to select the appropriate dosing strategy through simulations
468 that ensure the pediatric exposures are within the range of exposures (e.g., 5th to 95th percentile)
469 shown to be safe and effective in adults.
470
471 As science and technology continue to advance, *in silico* and other alternative modeling study
472 methods may be developed that can provide preliminary data to inform the design and conduct of
473 PK/PD studies for investigational drugs in pediatric populations. For example, the development
474 of a physiologically-based PK (PBPK) *in silico* model that integrates drug-dependent parameters
475 (e.g., renal clearance, metabolic pathways) and system-dependent parameters (e.g., non-drug
476 parameters such as blood flow rate, protein binding, and enzyme and transporter activities) is one
477 possible approach. PBPK has been used in pediatric drug development programs for (a)
478 planning for a first-in-pediatric PK study, (b) optimizing the study design, (c) verifying the
479 model in specific age groups, (d) recommending starting doses, (e) informing enzyme ontogeny
480 using a benchmark drug, and (f) facilitating covariate analysis for the effects of organ
481 dysfunction or drug interactions in pediatric patients (Leong, Vieira et al. 2012). The model
482 selected should incorporate *in vivo* PK/PD data obtained in other groups of pediatric and adult
483 patients as well as human volunteer studies, as appropriate.
484

485 Reference to the Centers for Disease Control and Prevention (CDC) growth charts provides a
486 preliminary assessment of the weight ranges that can be anticipated within specific age groups.[31]
487 For example, weights can vary 2.5- to 3-fold in healthy children between the 10th percentile at 2
488 years and 90th percentile at age 6 (10.6 kg to 25.3 kg for males) and between the 10th percentile at
489 6 years and the 90th percentile at 12 years (17.7 kg to 54 kg in males).
490
491 An estimate of the exposure-response relationship across a range of body-size doses (dose/kg or
492 dose/m^2) may be important. For the "PK and PD" and "PK and efficacy" approaches discussed
493 in section V.A above, investigation of a range of doses and exposures should allow assessment
494 of those relationships and development of rational dosing instructions.
495
496 Where PK/PD data are developed, the dose range should account for observed differences in
497 response between adults and the pediatric population (Benjamin, Smith et al. 2008), both in
498 terms of exposure and response. For example, there is evidence that pediatric populations are on
499 average less sensitive to antihypertensive drugs than the adult population. Therefore, pediatric
500 studies may include exposures greater than the highest drug exposure associated with the
501 approved adult dose, provided that prior data about the exposure-response relationship and safety
502 information justify such an exposure. Studies of distinctly different ranges of exposure are
503 desirable to provide sufficient information for the calculation of an optimal dose.
504
505 **D. Pediatric Dosage Formulation**
506
507 Pediatric formulations that permit accurate dosing and enhance adherence (i.e., dosing regimen,
508 palatability) are an important part of pediatric clinical pharmacology studies.[32] If there is a
509 pediatric indication, an age-appropriate dosage formulation must be made available for pediatric
510 patients.[33] One way to fulfill this requirement is to develop and test a pediatric formulation and
511 seek approval for that formulation.
512
513 If the sponsor demonstrates that reasonable attempts to develop a pediatric formulation have
514 failed, the sponsor should develop and test an age-appropriate formulation that can be prepared
515 by a pharmacist in a licensed pharmacy using an FDA-approved drug product and commercially
516 available ingredients.[34] If the sponsor conducts the pediatric studies using such a formulation,

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[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.

517 the following information should be provided in the study report:
518

- 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

16

557 premature or small for gestational age infants will be included in the study population.
558

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

559
560 The sponsor should discuss the distribution of the number of patients across each age range and
561 the appropriateness of these age ranges with the Agency, because this will be drug product-
562 specific. Justification should be provided for the sample size selected. For example, one
563 approach would be to prospectively target a 95% confidence interval within 60% and 140% of the
564 geometric mean estimates of clearance and volume of distribution for the drug in each pediatric
565 subgroup with at least 80% power. Noncompartmental analysis (NCA) based on rich PK
566 sampling, population PK modeling analysis based on sparse PK sampling, or other scientifically
567 justified methods can be applied to achieve this precision standard (Wang, Jadhav et al. 2012).
568 Conceivably, certain disease states might not allow recruitment of an adequate number of
569 participants to meet the standard, but practical considerations should be taken into account in
570 determining the sample size.
571
572 *2. Number of Samples Per Patient*
573
574 In addition to the number of patients, the number of blood samples collected in the clinical
575 pharmacology study to estimate PK measures and parameters for each patient in the study should
576 be carefully considered. The number of samples may be very limited in some pediatric patients
577 such as neonates (for more on collection of blood or plasma samples, see section F below).
578 Clinical study simulations or optimal sampling techniques may be recommended to justify the
579 proposed sampling scheme. Additional sampling for drug or metabolite concentrations is also
580 recommended when an adverse event occurs.
581
582 **F. Sample Collection**
583
584 Blood or plasma concentrations of drug or metabolite have been used as supporting evidence of
585 effectiveness or dose selection through exposure-response analyses in pediatric patients.
586 However, the volume and frequency of blood sampling are often of concern in pediatric studies.
587 Blood samples can be obtained by direct venipuncture or through the use of an indwelling
588 intravascular catheter. Because repeated venipuncture may cause discomfort and bruising at the
589 puncture site, an indwelling intravascular catheter should be used when possible. The volume

590 and frequency of blood sampling can be minimized by using micro-volume drug assays, dried
591 blood spots, and sparse-sampling techniques. These types of assays and analysis are especially
592 relevant when studying neonates (Long, Koren et al. 1987). Modern assay techniques allow
593 small sample volumes to be used to determine drug concentration (Kauffman and Kearns 1992),
594 but data quality may be affected if the sample volume is insufficient to allow for reanalysis when
595 necessary. Blood samples for analysis should be collected from the circulating blood volume
596 and not from reservoir dead space created by catheters or other devices. Sampling technique is
597 critical when using the available pediatric indwelling intravenous catheters. The time of sample
598 collection, proper sample transportation and storage, and sample handling techniques should be
599 documented. The collection of fluids such as cerebral spinal fluid (CSF) or bronchial fluids may
600 be beneficial when samples are being obtained for clinical purposes. Noninvasive sampling
601 procedures, such as urine and saliva collection, may suffice if correlated with outcomes or if the
602 correlation with blood or plasma levels has been documented.
603
604 Given the difficulty in collecting blood samples in the pediatric population, special approaches to
605 allow optimal times of sample collection may be useful. The sampling scheme should be
606 planned carefully to obtain the maximum information using the minimum number of samples. If
607 possible, collect additional PK samples when adverse events are observed to understand the
608 relationship between drug exposure and toxicity. Samples for DNA should be collected when
609 appropriate, as discussed in section III of this guidance.[35]
610
611 **G. Covariates and Phenotype Data**
612
613 The sponsor should obtain the following covariates for each pediatric patient: age, body weight,
614 BSA, gestational age and birth weight for neonates, race or ethnicity, sex, and relevant
615 laboratory tests that reflect the function of the organs responsible for drug elimination.
616 Concomitant and recent drug therapy should also be recorded. Sponsors are encouraged to
617 collect DNA samples in pediatric PK studies under the circumstances described in section
618 II, along with appropriate phenotype information to optimize the interpretation of
619 pharmacogenetic findings. For example, when genotype information is obtained for a
620 cytochrome P450 enzyme, the sponsor should look at the influence of genetic mutations on PK,
621 PD, and/or dose-response to determine whether genetically defined subsets of patients may need
622 special dosing considerations.
623
624 The sponsor should examine the relationship between the covariates and the PK of the drug or
625 biologic agent of interest. The contribution of weight or BSA and age to the PK variability
626 should be assessed. The following practice for assessing effect of age on pediatric PK, which

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[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.

627 is applicable in most cases, is recommended:
628
629 · Identify the accurate relationship between PK and body weight or BSA using
630 allometric scaling (Mahmood 2006; Mahmood 2007).
631
632 · Analyze the residuals versus age visually, after accounting for the body weight or BSA
633 effect on CL, followed by a more formal analysis exploiting the physiological
634 understanding underlying the CL, if appropriate. Residual is referring to the difference
635 between individual value (treated as predicted value) and the population mean (treated
636 as actual value). Testing for other biologically relevant predictive factors for PK in
637 pediatric patients may be important.
638
639 In pediatric PK studies, an estimation of creatinine clearance is recommended because of
640 the challenge with using exogenous markers such as iohexol as an estimate of the
641 glomerular filtration rate (GFR). The modified Schwartz equation, with adjustments for
642 premature infants (Brion, Fleischman et al. 1986), neonates and infants (Schwartz, Feld et
643 al. 1984), and children (Schwartz, Haycock et al. 1976) can be used. The older Schwartz
644 equations may require correction for enzymatic creatinine assays. The Cockcroft-Gault
645 formula should be used to estimate creatinine clearance in adolescents. This formula has been
646 shown to be the best prediction of GFR, as measured by inulin clearance, when compared with
647 the Schwartz and MDRD formulas in adolescents older than 12 years of age (Pierrat, Gravier et
648 al. 2003).
649
650   a. Modified Schwartz equation (pediatric patients < 12 years of age):
651
652       $\text{CrCl (ml/min/1.73 m}^2) = (K * Ht) / Scr$
653
654   height (Ht) in cm; serum creatinine (Scr) in mg/dl
655
656   K (proportionality constant):
657
658   Infant (LBW < 1year): K=0.33
659
660   Infant (Term <1year): K=0.45
661
662   Female Child (<12 years): K=0.55
663
664   Male Child (<12 years): K=0.70
665
666   b. Cockcroft-Gault equation (pediatric patients ≥ 12 years of age):
667
668   ClCr (ml/min) = [(140 - age) x weight in kg] / [Scr x 72] (x 0.85 if female)
669

670   When studying pediatric patients with impaired renal function, the sponsor should refer to the
671   draft Guidance for Industry *Pharmacokinetics in Patients with Impaired Renal Function — Study*
672   *Design, Data Analysis, and Impact on Dosing and Labeling*, March 2010, for the general
673   concepts of study design.[36] Newer formulas incorporating cystatin C may be used to estimate
674   GFR in pediatric patients with impaired renal function (Schwartz, Munoz et al. 2009).
675
676   If factors affecting the PK of the drug are to be studied (e.g., the effect of a concomitant medication or
677   the presence or absence of a disease), a justification for the numbers of patients with and without those
678   factors in the study should be included.
679

680   **H. Sample Analysis**

681
682   An accurate, precise, sensitive, specific, and reproducible analytical method to quantify the drug
683   and metabolites in the biologic fluids of interest is essential.[37] A method that is readily
684   adaptable and that uses only minimum sample volumes should be chosen.
685

686   **I. Data Analysis**

687
688   Two basic approaches for performing the PK analysis in pediatric patients can be used; a
689   standard noncompartmental PK approach and a population PK approach.
690

691   *1.   Noncompartmental Analysis*

692
693   The noncompartmental analysis PK approach involves administering either single or multiple
694   doses of a drug to a relatively small group of patients with relatively frequent blood and urine
695   sample collection. Samples are collected over specified time intervals chosen on the basis of
696   absorption and disposition half-lives, and subsequently assayed for either total or unbound
697   concentrations of drug and relevant metabolites. Noncompartmental analysis can be used to
698   establish PK parameters such as AUC, C_{max}, CL, volume of distribution, and half-life, which are
699   descriptive of the concentration of drug or metabolite over time. Data are usually expressed as
700   the means of the relevant measure or parameter and interindividual variances. In this approach,
701   including a sufficient number of patients to give a precise estimate of the mean is essential, as
702   discussed in section V.E. If drug administration and sampling are repeated in a patient in the
703   PK study, some understanding of intra-individual variability in PK parameters can be obtained.
704

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[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.

705   *2.*   *Population Analysis*
706
707   An alternative approach for analysis in pediatric clinical pharmacology studies is the population
708   approach to PK analysis. Population PK accommodates infrequent (sparse) sampling of blood or
709   plasma from a larger patient population than would be used in a compartmental or
710   noncompartmental analysis PK approach to determine PK parameters. Sparse sampling of blood
711   or plasma is considered more acceptable for pediatric studies, because the total volume of blood
712   sampled can be minimized. Sampling can often be performed concurrently with clinically
713   necessary blood or urine sampling. Because relatively large numbers of patients are studied and
714   samples can be collected at various times of the day and repeatedly over time in a given patient,
715   estimates of both population and individual means, as well as estimates of intra- and inter-subject
716   variability, can be obtained if the population PK study is properly designed.[38]
717
718   Exposure-response analyses predominantly employ a population analysis approach. Individual
719   analysis is generally not recommended unless responses from a wide range of doses from each
720   patient are available. Simultaneous modeling of data across all patients provides the best
721   opportunity to describe the exposure-response relationship.[39]
722
723   **J. Clinical Study Report**
724
725   The clinical study report should follow the ICH E3 guidance on the *Structure and Content of*
726   *Clinical Study Reports* for the general content and the format of the pediatric clinical study
727   report. The evaluation of exposure-response relationships and the population PK analyses
728   should be included as stipulated in the Exposure-Response Guidance[40] and the Population PK
729   Guidance,[41] respectively. In submitting PK information, the sponsor should submit the data
730   illustrating the relationship between the relevant PK parameters (e.g., CL unadjusted and
731   adjusted for body size in the manner described in section VI.G) and important covariates (e.g.,
732   age, renal function) in addition to the noncompartmental analysis results.
733
734   **K. Data Submission**
735
736   The preferred *submission standard* for clinical data is the Clinical Data Interchanges Standards
737   Consortium (CDISC) Study Data Tabulation Model (SDTM) standard. Please see the FDA Data

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[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.

741
APPENDIX[44]

742

Pediatric Study Planning & Extrapolation Algorithm

Is it reasonable to assume that children, when compared to adults, have a similar: (1) disease progression and (2) response to intervention?

No to either — Yes to both

Is it reasonable to assume similar exposure-response in pediatrics and adults?

No — Yes

Is the drug (or active metabolite) concentration measurable[c,d] and predictive of clinical response?

Is there a PD measurement that can be used to predict efficacy in children?

No — Yes

No — Yes

"Full extrapolation"[f]

"No extrapolation"[f]

"Partial extrapolation"[f]

Conduct:
(1) Adequate PK study to select dose(s) to achieve similar exposure as adults.[e]
(2) Safety trials[a] at the identified dose(s).

Conduct:
(1) Adequate dose-ranging studies in children to establish dosing.[e]
(2) Safety[a] and efficacy[b] trials at the identified dose(s) in children.

"Partial extrapolation"[f]

Conduct:
(1) Adequate dose-ranging study in children to select dose(s) that achieve the target PD effect.[e]
(2) Safety trials[a] at the identified dose(s).

Footnotes:
a. For locally active drugs, includes plasma PK at the identified dose(s) as part of safety assessment.
b. For partial extrapolation, one efficacy trial may be sufficient.
c. For drugs that are systemically active, the relevant measure is systemic concentration.
d. For drugs that are locally active (e.g., intra-luminal or mucosal site of action), the relevant measure is systemic concentration only if it can be reasonably assumed that systemic concentrations are a reflection of the concentrations at the relevant biospace (e.g., skin, intestinal mucosa, nasal passages, lung).
e. When appropriate, use of modeling and simulation for dose selection (supplemented by pediatric clinical data when necessary) and/or trial simulation is recommended.
f. For a discussion of no, partial and full 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):e1242-9.

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

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