Pediatric Drug Development Under the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act: Scientific Considerations

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Division of Pediatric and Maternal Health at 301-796-2200 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
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TABLE OF CONTENTS

Pediatric Drug Development Under the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act: Scientific Considerations Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to assist industry in developing data and obtaining information needed to support approval of drug products in pediatric populations.[2] This guidance addresses selected clinical, scientific, and ethical issues regarding the development of drugs for pediatric use when such drugs are subject to the Pediatric Research Equity Act (PREA)[3] and/or the Best Pharmaceuticals for Children Act (BPCA).[4] In 2010, the Biologics Price Competition and Innovation Act of 2009 extended provisions of the BPCA to biological products.[5]

This guidance does not address the clinical development of drugs that are not subject to either PREA or the BPCA. This guidance, along with the draft guidance for industry *Pediatric Drug Development: Regulatory Considerations — Complying With the Pediatric Research Equity Act*

[1] This guidance has been prepared by the Division of Pediatrics and Maternal Health in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

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

[3] Public Law 108-155 (2003), codified at section 505B of the FD&C Act (21 U.S.C. 355c). Although section 505B has been amended since the passage of PREA, by convention, that section of the FD&C Act is often referred to by the acronym for the Act that created it, PREA. We adopt that convention in this guidance.

[4] Public Law 107-109 (2002), codified at section 505A of the FD&C Act (21 U.S.C. 355a). Although section 505A has been amended since the passage of the BPCA, by convention, that section of the FD&C Act is often referred to by the acronym for the Act that created it, the BPCA. We adopt that convention in this guidance..

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

and Qualifying for Pediatric Exclusivity Under the Best Pharmaceuticals for Children Act (May 2023) (draft Regulatory Considerations guidance),[6] revises and replaces the draft guidance for industry *How to Comply With the Pediatric Research Equity Act*.[7] This guidance also addresses certain additional topics that FDA has not previously addressed in guidance.

This guidance only addresses briefly the Food and Drug Administration Reauthorization Act of 2017's (FDARA's) amendments to PREA[8] relating to requirements that sponsors of certain adult oncology drugs with molecular targets that are determined to be substantially relevant to the growth or progression of a pediatric cancer submit reports on molecularly targeted pediatric cancer investigations.[9]

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

II. BACKGROUND

Many diseases that occur in adults also occur in children, and children are often treated with the same drugs as adults. The effects of many drugs may vary considerably for adults and children or for different pediatric subgroups. Labeling for many drugs marketed in the United States lacks information on the safe and effective use in all or certain pediatric age groups. Indeed, labeling for many of the drugs that are widely used in pediatric patients specify that safety and effectiveness in pediatric patients have not been established.

The absence of adequate pediatric use information in labeling poses significant risks for children. Inadequate pediatric dosing information in labeling may lead to inappropriate dosing that can increase the risk of adverse reactions and/or lead to ineffective treatments. The lack of pediatric safety data may lead to inappropriate use in pediatric patients and expose such patients to the potential risk of age-specific adverse reactions that are unexpected based on data gathered from the use of the drug in adults. The absence of adequate pediatric labeling also may deny pediatric

[6] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[7] This guidance also addresses certain topics previously addressed in the guidance for industry *Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act*. That guidance was withdrawn August 7, 2013 (78 FR 48175).

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

[9] For additional information on FDA's implementation of these amendments to section 505B of the FD&C Act, see the guidance for industry *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act* (May 2021). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

patients therapeutic advances because physicians choose to prescribe drugs that are potentially less effective in pediatric populations due to the lack of information regarding use. Failure to develop an age-appropriate pediatric formulation of a drug may also deny pediatric patients access to important new therapies or may result in pediatric patients taking extemporaneous formulations where bioavailability may be poor or inconsistent.

III. LEGISLATIVE AND REGULATORY CONTEXT

This section contains a brief summary of PREA and the BPCA and a description of the Pediatric Review Committee (PeRC). A more complete discussion of the requirements under PREA and the BPCA, as well as recommendations regarding how to comply with them, is available in the draft Regulatory Considerations guidance.[10]

A. PREA

1. Pediatric Assessments: Section 505B(a)(1)(A) of the Federal Food, Drug, and Cosmetic Act

PREA requires that any applications (or supplements to an application)[11] falling within the requirements of section 505B(a)(1) of the Federal Food, Drug, and Cosmetic (FD&C) Act for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration must either include a pediatric assessment[12] or reports on the molecularly targeted pediatric cancer investigation (as appropriate),[13] or a request for waiver and/or deferral of the pediatric assessments or reports on the molecularly targeted pediatric cancer investigation.[14] There are certain exceptions; for example, PREA requirements generally do not apply to a drug for an indication for which orphan designation has been granted.[15]

[10] When finalized, the draft Regulatory Considerations guidance will represent FDA's current thinking on the topics therein.

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

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

[13] See section 505B(a)(3) of the FD&C Act (21 U.S.C. 355c(a)(3)). For additional information, see the guidance for industry *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act*.

[14] See sections 505B(a)(1), 505B(a)(4), and 505B(a)(5) of the FD&C Act (21 U.S.C. 355c(a)(1); 21 U.S.C. 355c(a)(4); and 21 U.S.C. 355c(a)(5)).

[15] See section 505B(k)(1) of the FD&C Act (21 U.S.C. 355c(k)(1)). Under section 505B(k)(2) of the FD&C Act, this "orphan exemption" does not apply to products that trigger PREA under section 505B(a)(1)(B) of the FD&C Act. For additional information, see the draft Regulatory Considerations guidance. When final, this guidance will represent the FDA's current thinking on this topic.

The FD&C Act requires sponsors planning to submit applications subject to PREA to submit an initial Pediatric Study Plan (iPSP);[16] these are typically submitted during the investigational phase of development, which helps to ensure that sponsors thoroughly consider a pediatric clinical development program earlier in their overall clinical development program. Section 505B(b) of the FD&C Act also requires holders of approved new drug applications and biologics license applications for marketed drugs to conduct pediatric assessments under certain circumstances.[17] Drugs developed for use only in pediatric populations may be subject to the pediatric assessment requirements of PREA.[18] The appropriate pediatric age ranges to be studied may vary, depending on, for example, the pharmacology of the drug, the incidence and the manifestations of the disease in various age groups, and the ability to measure the response to therapy.

Under PREA, a pediatric assessment must contain data, gathered using appropriate formulations for each age group for which the assessment is required, that are adequate to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations, and that support dosing and administration for each pediatric subpopulation for which the drug is safe and effective.[19] If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, FDA may determine that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adult subjects.[20]

In general, PREA requirements do not apply to a drug for an indication for which orphan designation has been granted.[21] Thus, submission of pediatric assessments is not required for an application to market a drug for an indication for which orphan designation has been granted.[22]

For more detailed information regarding waivers or deferrals of the requirement to submit pediatric assessments, see the draft Regulatory Considerations guidance.[23]

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

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

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

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

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

[21] See section 505B(k) of the FD&C Act (21 U.S.C. 355c(k)). We note that section 505B(k)(1) of the FD&C Act states, "Unless the Secretary requires otherwise by regulation…this section does not apply to any drug or biological product for an indication for which orphan designation has been granted under section 526." The Secretary has delegated this authority to FDA on these issues, and, as of the date of publication of this guidance, FDA has not issued any such regulations. We also note that under section 505B(k)(2) of the FD&C Act, the orphan exemption does not apply to drugs that trigger PREA under section 505B(a)(1)(B) of the FD&C Act.

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

[23] When final, this guidance will represent the FDA's current thinking on this topic.

2. Molecularly Targeted Pediatric Cancer Investigation: Section 505B(a)(1)(B) of the FD&C Act

Pursuant to section 505B(a)(1)(B) of the FD&C Act, a person who submits an original application on or after August 18, 2020, for a new active ingredient, where the drug that is the subject of the application is intended for the treatment of an adult cancer and directed at a molecular target that FDA determines to be substantially relevant to the growth or progression of a pediatric cancer, must submit reports on the molecularly targeted pediatric cancer investigation, unless submission of the reports is waived or deferred.[24]

A molecularly targeted pediatric cancer investigation "shall be designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling."[25] For a drug that is the subject of a molecularly targeted pediatric cancer investigation, if the course of the disease and the effects of the drug are sufficiently similar in adult and pediatric patients, FDA may determine that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adult subjects.[26]

PREA requirements generally do not apply to a drug for an indication for which orphan designation has been granted; however, this *orphan exemption* does not apply to drugs that trigger PREA under section 505B(a)(1)(B) of the FD&C Act.[27] Accordingly, for such drugs meeting the criteria in section 505B(a)(1)(B), the requirement to submit reports on the molecularly targeted pediatric cancer investigation applies even if the drug is for an adult indication for which orphan designation has been granted.[28]

B. BPCA

The BPCA provides for additional marketing exclusivity if FDA issues a written request (WR), the applicant agrees to the request, the applicant completes the requested studies using appropriate formulations for each age group for which the studies were requested and within the requested time frame, and the reports of the studies are submitted and accepted by FDA.[29] When accepting or rejecting the reports, FDA determines whether the studies fairly respond to the WR, have been conducted in accordance with commonly accepted scientific principles and protocols, and have been reported in accordance with filing requirements.[30]

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[24] Sections 505B(a)(1)(B), 505B(a)(3), 505B(a)(4), and 505B(a)(5) of the FD&C Act (21 U.S.C. 355c(a)(1)(B), 21 U.S.C. 355c(a)(3), 21 U.S.C. 355c(a)(4), and 21 U.S.C. 355c(a)(5)).

[25] Section 505B(a)(3)(A) of the FD&C Act (21 U.S.C. 355c(a)(3)(A)).

[26] Section 505B(a)(2)(B) and 505B(a)(3)(B) of the FD&C Act (21 U.S.C. 355c(a)(2)(B) and 355c(a)(3)(B)).

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

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

[29] See sections 505A(b)(1) and 505A(c)(1) of the FD&C Act (21 U.S.C. 355a(b)(1) and 21 U.S.C. 355a(c)(1)).

[30] See section 505A(d)(4) of the FD&C Act (21 U.S.C. 355a(d)(4)).

FDA may issue a WR for pediatric studies either in response to a proposed pediatric study request (PPSR) ***or*** at the initiative of FDA. A PPSR describes the studies the applicant proposes to conduct. The procedures for qualifying for exclusivity and the protections to which that exclusivity attaches are described in more detail in the draft Regulatory Considerations guidance.[31]

It is important to note the distinction between the scope of the studies requested under the BPCA and those required under PREA. FDA's authority to issue a WR extends to the use of an active moiety for indications that may produce health benefits in the pediatric population, regardless of whether the indications have been previously approved in adults.[32] Under PREA, pediatric assessments are required only for those indications included in the pending (or approved) application.[33] To qualify for pediatric exclusivity, the pediatric studies conducted to satisfy the requirements of PREA must be the subject of a WR and satisfy all other requirements for pediatric exclusivity under the BPCA.[34] As discussed in the draft regulatory considerations guidance, FDA does not expect to issue WRs solely for studies or planned studies that are required under PREA. For more detailed information regarding WRs for pediatric studies and PPSRs, see the draft Regulatory Considerations guidance.[35]

C. The PeRC

FDA's internal pediatric review committee (i.e., the PeRC) is consulted on all iPSPs, waivers, deferrals, assessments, deferral extensions, and WRs.[36] The PeRC is also provided all responses to PPSRs, not just WRs that result from those requests.[37] Members of this committee include employees of FDA with expertise in pediatrics (including representation from the Office of Pediatric Therapeutics), neonatology, biopharmacology (i.e., pharmacology/toxicology),

[31] When final, the draft Regulatory Considerations guidance will represent FDA's current thinking on the topics therein.

[32] See sections 505A(a), 505A(b)(1), 505A(c)(1), and 505A(d)(1)(B) of the FD&C Act (21 U.S.C. 355a(a), 21 U.S.C. 355a(b)(1), 21 U.S.C. 355a(c)(1), and 21 U.S.C. 355a(d)(1)(B)).

[33] See sections 505B(a)(1)(A) and 505B(a)(2) of the FD&C Act (21 U.S.C. 355c(a)(1)(A) and 21 U.S.C. 355c(a)(2)). Note, however, that molecularly targeted pediatric cancer investigations are based on molecular mechanism of action rather than clinical indication. See sections 505B(a)(1)(B) and 505B(a)(3) of the FD&C Act (21 U.S.C. 355c(a)(1)(B) and 21 U.S.C. 355c(a)(3)). For additional information see the guidance for industry *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act*.

[34] See sections 505A(b)(1), 505A(c)(1), 505A(d), and 505A(h) of the FD&C Act (21 U.S.C. 355a(b)(1), 21 U.S.C. 355a(c)(1), 21 U.S.C. 355a(d), and 21 U.S.C. 355a(h)).

[35] When final, the draft Regulatory Considerations guidance will represent FDA's current thinking on the topics therein.

[36] See sections 505C, 505B(f)(1), and 505A(f)(1) of the FD&C Act (21 U.S.C. 355d, 21 U.S.C. 355c(f)(1), and 21 U.S.C. 355a(f)(1)).

[37] See section 505A(f)(7) of the FD&C Act (21 U.S.C. 355a(f)(7)).

statistics, chemistry, legal issues, pediatric ethics, the appropriate expertise pertaining to the pediatric drug under review, and other individuals as needed.[38] As a general matter, members of the relevant drug review division provide background information to the PeRC and are present during the discussion of the application to provide insight on their reviews and to answer questions.

IV. SCIENTIFIC CONSIDERATIONS FOR PEDIATRIC DRUG DEVELOPMENT[39]

In general, principles that guide pediatric drug development do not differ greatly from the principles that apply to drugs developed for adults. Before initiating a development program in pediatric populations, applicants should consider the condition(s) to be investigated, the drug under study, and the pediatric subpopulation(s) for whom such a drug would represent a meaningful therapeutic option.

The information needed to approve a drug for pediatric use includes data from nonclinical studies, and clinical dosing, safety, and effectiveness information.[40] Applicants should consider whether efficacy could be partially or fully extrapolated from studies in adults or other pediatric populations (see section IV.B., Pediatric Extrapolation). Finally, applicants should determine whether existing data from adult human studies or animal disease models can be used to support both the safety and preliminary effectiveness of the drug sufficiently to initiate pediatric studies. If such information does not exist, applicants should plan and initiate necessary studies to obtain this information.

The intent of the pediatric study plan (PSP), as required under PREA,[41] is to identify needed pediatric studies early in drug development and begin planning for these studies. An iPSP must be submitted to FDA before submission of the required assessments or investigation, and no later than either 60 calendar days after the date of the end-of-phase 2 meeting or such other time as agreed upon between FDA and the applicant.[42] However, FDA encourages applicants to consult with FDA or submit iPSPs to FDA earlier in development than is required by section 505B(e) of the FD&C Act, when appropriate. More information on the timing of iPSPs, the contents of an

[38] See section 505C of the FD&C Act (21 U.S.C. 355d).

[39] This section generally does not pertain to biological products licensed under section 351(k) of the PHS Act (42 U.S.C. 262(k)). For more information regarding biosimilar products and PREA, see the guidance for industry *Questions and Answers on Biosimilar Development and the BPCI Act* (September 2021) and the draft guidance for industry *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 3)* (September 2021). The draft guidance is available on the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[40] For purposes of section 505A of the FD&C Act, the term *pediatric studies* or *studies* is defined as at least one clinical investigation (that, at the Secretary's discretion, may include pharmacokinetic studies) in pediatric age groups (including neonates in appropriate cases) in which a drug is anticipated to be used, and, at the discretion of the Secretary, may include preclinical studies (21 U.S.C. 355a(a)).

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

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

iPSP, the process for reaching agreement with FDA, and the process for amending an agreed iPSP can be found in guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (July 2020).

A. Considerations Regarding Data in Pediatric Populations

The following considerations may be relevant to the overall development strategy of a pediatric development program. Considerations applicable to both PREA and the BPCA have been incorporated.

1. Formulation Development

PREA requires pediatric assessments to be conducted "using appropriate formulations for each age group for which the assessment is required."[43] PREA also requires that a molecularly targeted pediatric cancer investigation gather data "using appropriate formulations for each age group for which the study is required."[44] A marketing application that includes a pediatric indication may need a new dosage form (e.g., a liquid rather than a tablet), addition of a new strength (e.g., tablet containing a lower dose), or several different dosage forms (e.g., drops, orally disintegrating tablets, pellets). The intent of PREA is to require sponsors to develop and study formulations that allow for use in all relevant pediatric populations, in situations where the existing dosage form or strength may be unsuitable for use in all or part of the relevant pediatric populations.

When developing formulations for pediatric populations, applicants should consider the following, where applicable.

- With respect to age appropriateness of the dosage form:
  - The proposed dosage form in relation to the targeted age group(s). If adult dosage form is to be used, the volume and size of the dosage form.
  - The proposed drug product composition for the pediatric formulation(s) planned to be used in pediatric studies and how the planned formulations will be dosed (e.g., for an oral dosage form, whether it will be swallowed, chewed, and/or mixed in soft foods and/or liquids).
  - For orally administered dosage forms, the palatability of the dosage form.
  - If a device is to be used for administration, the type of device and how it will be used by pediatric populations in all age groups studied (e.g., dropper, syringe, measuring cup, inhalers).
- With respect to toxicity (safety):

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

[44] See section 505B(a)(3)(A) of the FD&C Act (21 U.S.C. 355c(a)(3)(A)).

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253 — The use of excipients, including certain dyes, alcohols, flavoring agents, or
254 preservatives, considering any potential interactions.
255
256 — The use of a delivery device (e.g., dropper, syringe, measuring cup) copackaged with
257 the formulation. Applicants should consider how the device will be calibrated for
258 accuracy during the proposed in-use period. Applicants should plan studies to assess
259 the presence of leachable/extractable components that may be toxic to younger
260 children or neonates.
261
262 • With respect to stability of the drug product:
263
264 — The compatibility and stability assessments of the drug substance with the proposed
265 excipients under storage conditions during marketing and in-use conditions.
266
267 — The stability of the formulation, as well as maintenance of intended drug
268 dissolution/release characteristics when drug products (e.g., disintegrating tablet,
269 sprinkles, pellets, films, liquids) are given in aqueous solutions, juice, human (breast)
270 milk, formula, and soft foods such as apple sauce.
271
272 • With respect to characterizing oral drug products' dissolution/release characteristics in
273 media simulating gastric fluids and environment:
274
275 — The performing of dissolution/release testing using standard dissolution media as well
276 as media mimicking in vivo gastric fluids and environment (such as media containing
277 milk for neonate and infant studies).
278
279 Early consultation with FDA is strongly recommended when embarking on pediatric formulation
280 development.
281
282 *2. Nonclinical Information*
283
284 Nonclinical data, specific to the pediatric population, may be needed to support the initiation of
285 clinical studies in different pediatric age groups, in addition to traditional toxicology studies
286 and/or data from adult clinical development programs. In certain cases, data from clinical
287 studies in adult subjects, supported by nonclinical studies in adult animals, have been used to
288 support the initiation of studies in pediatric populations. However, such studies may not always
289 assess possible drug effects on developmental processes that occur at specific ages in pediatric
290 populations. Developmental processes in pediatric populations may also differentially affect
291 drug pharmacokinetics and pharmacodynamics, compared to these parameters in adult
292 therapeutic use. Juvenile animal studies may assist in identifying postnatal developmental
293 toxicities that are not assessed in reproductive toxicity testing and that may not be safely

evaluated in pediatric clinical studies. The adequacy of nonclinical data to support initiation of clinical studies in different pediatric age groups should be discussed with FDA.[45]

If human safety data and previous animal studies are insufficient to inform adequately the likely safety profile of the drug in the intended pediatric age group, or if the drug's mechanism of action or its pharmacokinetic (PK) profile suggests that it may affect growth or developmental processes, juvenile animal studies should be considered to address these concerns. This section contains a brief summary of considerations for nonclinical information to support pediatric drug development. Additional discussion of juvenile animal studies is available in other guidance.[46]

When appropriately designed, juvenile animal studies (in vitro and in vivo) can provide a hazard assessment that specifically addresses identified safety concerns in immature, developing organ systems; for example:

- Specific toxicity studies in juvenile animals can include an assessment of exposure (toxicokinetics) to address specific developmental endpoints (e.g., neurotoxicity, immunotoxicity, effects on growth or sexual maturation, nephrotoxicity) at particular developmental phases consistent with the intended clinical use

- Studies in specific animal disease models may be useful when studies in healthy juvenile animals may not adequately inform the safety in pediatric populations (e.g., inborn errors of metabolism)

Many investigational cellular and gene therapy drug products are intended to treat severely debilitating illnesses that exist predominantly in children (e.g., neurodegenerative diseases, metabolic disorders, lysosomal storage disorders). These drug products are usually administered via an invasive route (e.g., intracranial, intraspinal, subretinal, intravenous), can distribute to nontarget tissues, and can remain in the body for prolonged periods. Therefore, safety data, as well as data regarding the prospect of direct clinical benefit, to support an appropriate starting dose is sometimes obtained from nonclinical studies. Many of these studies are conducted in animal disease models that are juveniles or young adults. Additional information on cellular and gene therapy drug products can be found in other guidance.[47]

[45] We support the principles of the 3Rs (reduce/refine/replace) for animal use in testing when feasible. The FDA encourages sponsors to consult with review divisions when considering a nonanimal testing method believed to be suitable, adequate, validated, and feasible. The FDA will consider if the alternative method could be assessed for equivalency to an animal test method.

[46] Additional information can be found in the guidance for industry *Nonclinical Safety Evaluation of Pediatric Drug Products* (February 2006) and the International Council for Harmonisation (ICH) guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010).

[47] For example, see the guidance for industry *Preclinical Assessment of Investigational Cellular and Gene Therapy Products* (November 2013).

3. Clinical Pharmacology[48]

Well-designed early phase dosing studies are critical to a successful pediatric development program. Inadequate dosing studies in the past have contributed to failed efficacy studies and have delayed or prevented approval in pediatric age groups. Modeling and simulation, when appropriate, should be used to inform dose selection and/or trial design. Confirmatory PK studies may be critical, particularly in younger children, in whom dosing is not necessarily predictable based on the experience in adult or adolescents.

Depending on the approach, PK and/or pharmacodynamic (PD) studies may be needed to establish dosing recommendations when extrapolating efficacy from adult to pediatric populations, between different pediatric age groups, or between formulations.

Regarding PK studies, applicants should consider the following:

- The sample size for PK studies should be justified, taking into account the expected variability in PK parameters for that age group.

- Matching exposure using pharmacokinetics relies on a reasonable assumption that exposure-response is similar in adults and the pediatric age group being studied; therefore, it is most appropriate when pediatric extrapolation is being used.

- A dedicated PK study may not be needed in every age group. For example, prior experience with dosing in adolescents has demonstrated that knowledge of adult dosing and appropriate dose scaling may be sufficient for some drugs, with adequate justification.[49]

- Minimizing blood sampling may be possible using sparse PK sampling techniques and population pharmacokinetics, when such studies are properly designed.

- There is limited information regarding the effect of maturational changes on pharmacogenetic effects in neonates and infants. Consideration should be given to the potential for differences of pharmacogenetic effects in this age group from observed effects in older children and adults.[50]

- When administration of the investigational drug presents more than a minor increase over minimal risk, applicants should also consider combining PK studies with safety or

[48] Additional information can be found in the draft guidance for industry *General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products* (September 2022). When final, this guidance will represent FDA's current thinking on this topic.

[49] See Momper JD, Mulugeta Y, Green DJ, et al., 2013, Adolescent Dosing and Labeling Since the Food and Drug Administration Amendments Act of 2007, JAMA Pediatr, 167(10):926–932.

[50] Additional information can be found in the guidance for industry *General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products* (July 2022).

efficacy studies that provide the prospect of direct clinical benefit to the enrolled children (see section IV.C., Timing of Pediatric Studies).[51]

PD studies are particularly important when drug concentrations cannot be measured in a pertinent bodily fluid (e.g., plasma, cerebrospinal fluid, urine). In all cases, however, applicants should consider the following:

- PD differences between adult and pediatric populations (e.g., influence of maturation of receptors and/or organ systems), especially as related to drug dosing and study endpoints
- The use of bridging studies from one population to another (e.g., from adult and older pediatric age groups to younger children) including, where appropriate, the use of PD modeling
- The potential for changes in PD response between age groups in the pediatric population

4. Safety Information

Safety information from adult human studies and animal models may provide preliminary information regarding the expected safety profile of a drug in pediatric populations, but safety information from administration of the drug to children is almost always needed to establish safety in the pediatric populations. Adverse effects of a drug in pediatric populations may not be predictable based on the adult experience, particularly adverse effects related to behavior, cognition, or growth. Nonetheless, pediatric safety information that is available from different formulations of a drug, or from other closely related drugs within the same class, as appropriate, should be reviewed. In addition, because some effects may be measurable only in children of a certain age or maturity level, long-term follow-up studies, particularly for drugs tested in neonates, infants or young children, may be needed to assess the effects of the drug.[52] If appropriate, potential risks of the drug should be assessed by age group. If there is an approved risk evaluation and mitigation strategy for a drug that is already marketed for use in the adult population, sponsors should assess what steps should be taken to mitigate risk in the pediatric population. Pharmacovigilance programs developed to assess known or potential safety signals in adult subjects should also include pediatric subjects, when appropriate.

B. Pediatric Extrapolation

To obtain approval of a new drug application, manufacturers must provide substantial evidence

[51] See 21 CFR 50.52 and 50.53. Additional information can be found in the draft guidance for industry, sponsors, and institutional review boards *Ethical Considerations for Clinical Investigations of Medical Products Involving Children* (September 2022). When final, this guidance will represent the FDA's current thinking on this topic.

[52] Additional information can be found in the draft guidance for industry *Considerations for Long-Term Clinical Neurodevelopmental Safety Studies in Neonatal Product Development* (February 2023). When final, this guidance will represent the FDA's current thinking on this topic.

of effectiveness.[53] FDA's thinking regarding the quantity and quality of evidence that may be necessary to support effectiveness is described in other guidance.[54]

FDA recognizes that in some cases conducting clinical studies in pediatric populations may be challenging, and study approaches commonly used to generate data in adult populations may not be feasible. Pediatric ethical issues, vulnerabilities particular to the study population, limited number of children available for participation in a study, difficulty in developing age-appropriate endpoints, limited availability of validated patient-reported outcome measurements, the potential need to use surrogate endpoints, the potential need for alternative study designs, and other factors may pose unique challenges in the development of protocols for clinical studies in pediatric populations.

One approach that can increase the efficiency of pediatric drug development, where appropriate, is the use of pediatric extrapolation. The use of pediatric extrapolation in drug development is discussed in other guidance.[55]

C. Timing of Pediatric Studies

From a scientific and ethical perspective, the timing of pediatric trials is grounded in 21 CFR part 50, subpart D, Additional Safeguards for Children in Clinical Investigations.[56] FDA-regulated clinical investigations that involve children as subjects generally may be initiated when, among other things, sufficient data from animal disease models and/or adult human subjects are available to support either (1) a sufficiently low risk of the intervention or procedure

[53] See section 505(d) of the FD&C Act (21 U.S.C. 355(d)). We note that under section 351 of the PHS Act, licenses for biological products have been issued only upon a showing that the products are "safe, pure, and potent." Potency has long been interpreted to include effectiveness (21 CFR 600.3(s)). FDA has also generally considered *substantial evidence* of effectiveness to be necessary to support licensure of a biological product under section 351 of the PHS Act. For additional information, see the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). When final, this guidance will represent FDA's current thinking on this topic.

[54] Additional information can be found in the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998).

[55] Additional information can be found in the draft ICH guidance for industry *E11A Pediatric Extrapolation* (April 2022). When final, this guidance will represent the FDA's current thinking on this topic.

[56] See the draft guidance for industry, sponsors, and institutional review boards *Ethical Considerations for Clinical Investigations of Medical Products Involving Children*. When final, this guidance will represent the FDA's current thinking on this topic.

absent any prospect of direct benefit;[57] or (2) a sufficient prospect of direct benefit to justify the risks.[58]

Applicants should consider initiation of pediatric studies during the adult development program if sufficient data on the safety and potential benefit of a drug already exist (e.g., from a previously approved indication, or a different formulation). For many drugs with little previous human exposure, the initial phase of pediatric development (i.e., phase 1) might begin after the adult phase 2 and/or 3 studies have established evidence of a sufficient prospect of direct benefit to justify exposing pediatric populations to the risks of the drug. Dosing, safety, and effectiveness studies may then be conducted in pediatric populations concurrently with the effectiveness trial in adult subjects.[59]

Pediatric studies of drugs for life-threatening diseases for which approved treatment is not available also should be considered earlier in development than might occur for less serious diseases.[60] For example, pediatric studies of some oncology drugs have begun as early as adult phase 1 or phase 2 studies, after initial safety data in adult subjects were available. Even when no approved therapies are available, initiation of pediatric studies still generally requires, among other things, either a sufficiently low risk of the intervention or procedure or that the prospect of direct benefit to the enrolled pediatric populations is sufficient to justify the risks.[61] Absent sufficient adult human data, the nonclinical evidence of benefit and risk from an appropriate in vitro and/or animal model may be particularly important. FDA encourages applicants to discuss with the Agency the plan for the development of such drugs as early as possible (e.g., pre-investigational new drug application, end-of-phase 1 meetings).

FDA recognizes that in certain cases, scientific and ethical considerations dictate that pediatric studies should not begin until after adequate safety and efficacy data are available in adult subjects; for example, where a drug has not shown any advantage over other approved drugs in the class, the therapeutic gain is likely to be low, and the risks of exposing pediatric subjects to the new drug may not be justified until the drug's safety profile is better established in adult subjects. In these cases, the applicant can request a deferral of required pediatric studies (see section III. A., PREA). However, if substantial pediatric use may be anticipated after the drug is approved for use in adults, early initiation of pediatric studies should be considered.

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[57] See 21 CFR 50.53 (regarding clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition). Additionally, approval by an institutional review board of studies presenting no greater than minimal risk to children and not offering a prospect of direct benefit also may be considered under 21 CFR 50.51; however, FDA generally views the administration of an FDA-regulated drug as presenting more than minimal risk.

[58] See 21 CFR 50.52.

[59] For discussion on the timing of pediatric studies relative to adult studies in the context of antiretroviral drugs for the treatment of human immunodeficiency virus (HIV), see the guidance for industry *Pediatric HIV Infection: Drug Product Development for Treatment* (March 2019).

[60] Additional information can be found in the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics* (May 2014).

[61] See 21 part 50, subpart D.

D. Drug Development for the Neonatal Population[62]

FDA also recognizes that clinical development of drugs for use in the neonatal population poses additional challenges. The ability to apply information about the safety and effectiveness of drugs from older pediatric populations and adult subjects to neonates is extremely limited. Neonatal physiology may differ considerably from that of older populations. Moreover, some disorders occur only in neonates and other disorders that affect older populations may not be apparent in the neonatal period.

In addition, the neonatal period (generally considered to include birth through 27 days corrected gestational age) represents an extremely brief window for study enrollment. Furthermore, although there may be reluctance to enroll children from all pediatric populations, parents may be especially reluctant to expose newborns to investigational therapies and invasive tests. The relationship among some surrogate endpoints (e.g., need for supplemental oxygen at 30 days) and longer term outcomes that are meaningful to patients (e.g., improvement in neurodevelopmental outcome) have not been established. Clinical or laboratory tests that are routine in older children may not be standardized or validated in neonates, making the results of such studies difficult to interpret. Necessary limits on the volume of blood that may be withdrawn make testing more difficult. Data may be lacking to fully elucidate the short- and long-term risks of a drug because clinical studies in neonates that are not specifically conducted to provide substantial evidence of efficacy and safety of a drug often have small sample sizes and are of limited duration. Finally, neonatal clinical trials face substantial hurdles from within the practice of neonatology, including the use of unproven therapies that often become standard of care in the absence of data establishing dosing, safety, and effectiveness.

As a result of increasing attention to the lack of high-quality data for the use of drugs in neonates, several provisions in the BPCA and PREA address clinical development in neonates. For example, if FDA issues a WR that does *not* include a request to study a drug in neonates, the BPCA requires that FDA "include a statement describing the rationale for not requesting studies in neonates."[63] In addition, when pediatric assessments are required under PREA, applicants are required to submit assessments that are adequate to assess safety and effectiveness for the claimed indications in all relevant pediatric age groups, which may include neonates.[64]

When drugs may be appropriate for use in the neonatal population, special consideration should be given to the timing of neonatal clinical studies relative to studies in older populations. The failure to study neonates before approval in older children and/or adults has meant that drugs are often used in neonates without adequate information about dosing, safety, or effectiveness. Unless previous animal or human data exist to suggest that use of a drug should not be studied in the neonatal population because of safety concerns, FDA recommends that applicants consider

[62] Additional information can be found in the guidance for industry *General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products*.

[63] See section 505A(d)(1)(A) of the FD&C Act (21 U.S.C. 355a(d)(1)(A)).

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

dosing, safety, and efficacy studies, as appropriate, of any drug that may be used in the neonatal population. In general, such studies should be undertaken at the same time as studies in older pediatric populations, unless efficacy or safety data from older pediatric populations are necessary before initiation of studies in the neonatal population. Uncertainties regarding potential developmental or neurocognitive effects of a drug on the neonatal population generally are not adequate justification for failing to study such effects concurrently with other pediatric populations. Long-term safety studies in drugs developed for neonates may be needed to assess these effects.[65]

[65] Additional information can be found in the draft guidance for industry *Considerations for Long-Term Clinical Neurodevelopmental Safety Studies in Neonatal Product Development*.