Pediatric Study Plans:
Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans
Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Rosemary Addy 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
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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Revision 1

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Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 provide information to sponsors regarding the submission of an initial pediatric study plan (iPSP) and any amendments to the iPSP. Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding implementation of the requirement for sponsors to submit an iPSP as described in section 505B(e) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Food and Drug Administration Safety and Innovation Act (FDASIA).[2]

This guidance addresses the following:

- Who must submit an iPSP
- When an iPSP must be submitted
- What should be included in an iPSP
- What should be included in a requested amendment to an agreed iPSP
- A template that should be used for an iPSP submission[3]

[1] This guidance has been prepared by the Pediatric Study Plan Working Group, composed of members from the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Office of the Commissioner (OC) at the Food and Drug Administration.

[2] Public Law 112-144, 126 Stat. 993 (July 9, 2012)

[3] In addition to consulting guidance, sponsors are encouraged to contact the specific CDER/CBER review division to discuss specific issues that arise during preparation of the iPSP. Sponsors can request that the review division consult with the Division of Pediatric and Maternal Health in the CDER Office of New Drugs and, if appropriate, the Office of Pediatric Therapeutics in the OC Office of Special Medical Programs.

This guidance does not contain a discussion of general requirements for development of drugs for pediatric use under the Pediatric Research Equity Act (PREA) or the Best Pharmaceuticals for Children Act (BPCA).[4]

This guidance revises the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* issued in July 2013. This revision includes additional clarifications regarding sections previously included in the 2013 guidance as well as new sections that have been added, including: section V.A., Materially Incomplete iPSPs, section VI., Relationship of Agreed iPSP to the Requirement to Submit a Pediatric Plan With an Application, section VII., Contents and Timing of Requested Amendment to an Initial PSP, section VIII., Non-Agreed Initial Pediatric Study Plans, and section IX., Reaching Agreement on the Non-Agreed Initial Pediatric Study Plan. Additionally, Appendix 1, Initial Pediatric Study Plan Template, has been updated.

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

Over the last 2 decades, the FDA has worked to address the problem of inadequate testing of drugs in pediatric populations and inadequate pediatric use information in drug and biological product labeling. In 1994, the FDA published a final rule that required manufacturers of marketed drugs to survey existing data and determine whether those data were sufficient to support adding pediatric use information to the drug's labeling.[5] However, the 1994 rule did not impose a general requirement that manufacturers carry out studies when existing information was not sufficient to support adding pediatric use information. This initial attempt to encourage sponsors to submit pediatric studies and plans to sufficiently inform use of drugs in pediatric patients was not successful in achieving adequate labeling for most drugs and biological products regarding use in the pediatric subpopulation, and product labeling frequently failed to provide directions for safe and effective use in pediatric patients.

[4] For purposes of this guidance, references to *drugs* and *drug and biological products* include drugs approved under section 505 of the FD&C Act (21 U.S.C. 355) and biological drug products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262).

[5] See "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of 'Pediatric Use' Subsection in the Labeling" (59 FR 64240, December 13, 1994).

To address this continued problem, the Food and Drug Administration Modernization Act of 1997[6] was signed into law and contained provisions that established incentives for conducting pediatric studies on drugs for which exclusivity or patent protection exists. Also, on December 2, 1998, the FDA published a regulation known as the pediatric rule.[7] This rule partially addressed the lack of pediatric use information by requiring manufacturers of certain new and marketed drugs and biologics to conduct studies to provide sufficient data and information to support directions for pediatric use for the claimed indications. The pediatric rule also stated that the FDA would provide sponsors with its best judgment on whether pediatric studies will be required and whether their submission will be deferred until after approval. This input was given by the FDA at the end-of-phase 1 meeting, for drugs and biologics for life-threatening diseases,[8] and at the end-of-phase 2 meeting, for other drugs, as described in other FDA regulations.[9]

The pediatric rule also stated that sponsors should submit, at least 1 month in advance of the end-of-phase 2 meeting, certain background information, including a proposed timeline for protocol finalization, enrollment, completion, and data analysis, or, in the alternative, information to support a planned request for waiver or deferral. However, on October 17, 2002, the U.S. District Court for the District of Columbia held that the FDA had exceeded its statutory authority when issuing the pediatric rule and the court suspended the rule's implementation and enjoined its enforcement.[10]

Congress subsequently passed PREA, which was signed into law on December 3, 2003.[11] Many of the provisions described under the pediatric rule were adopted under PREA. Under PREA as originally enacted and under its reauthorization under the Food and Drug Administration Amendments Act of 2007, a proposed timeline and plan for the submission of pediatric studies were not required to be submitted during the investigational new drug application (IND) phase of drug development.[12] Under FDASIA, signed into law on July 9, 2012, for the first time PREA includes a provision that requires sponsors planning to submit an application for a drug subject to PREA to submit an iPSP early in the development process. The intent of the iPSP is to identify needed pediatric studies early in development and begin planning for these studies. The timing and content of the submission of an iPSP are described below. FDASIA requires the FDA to promulgate regulations and issue guidance to implement these and other provisions.[13] The FDA is issuing this guidance and intends to publish a proposed regulation consistent with FDASIA.

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[6] Public Law 105-115, 111 Stat. 2296 (Nov. 21, 1997)

[7] See "Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients" (63 FR 66632, December 2, 1998).

[8] See 21 CFR 312.81(a).

[9] See 21 CFR 312.47 and 312.82.

[10] *Association of Am. Physicians & Surgeons, Inc. v. FDA*, 226 F. Supp. 2d 204, 222 (D.D.C. 2002)

[11] Public Law 108-155, 117 Stat. 1936 (Dec. 3, 2003)

[12] Public Law 110-85, 121 Stat. 823 (Sept. 27, 2007)

[13] See section 505B(e)(7) of the FD&C Act; 21 U.S.C. 355c(e)(7).

III. APPLICATIONS THAT REQUIRE SUBMISSION OF AN INITIAL PSP[14]

A sponsor who is planning to submit a marketing application for a drug that includes a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration (i.e., that is subject to PREA) is required to submit an iPSP,[15] unless the drug has been granted orphan designation for the proposed indication at the time the iPSP is required.[16] By statute, a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a *new active ingredient* for purposes of PREA.[17] The sponsor should submit the iPSP to the relevant drug's IND for review by the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research as appropriate.[18] A sponsor should submit an iPSP according to the time frame outlined in section IV., Timing of an Initial PSP Submission. Additionally, for drugs that are being developed specifically for use in pediatric populations, an iPSP should be submitted.

If a drug has been previously approved and granted waivers or deferrals under PREA, and the sponsor plans to submit a new application for the same drug that will be subject to PREA, an iPSP must be submitted as described in section IV.[19]

IV. TIMING OF AN INITIAL PSP SUBMISSION

A sponsor must submit the iPSP before the date on which the sponsor submits the required assessments and not later than 60 calendar days after the date of the end-of-phase 2 meeting.[20] In the absence of an end-of-phase 2 meeting, the sponsor should submit the iPSP as early as

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

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

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

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

[18] See the guidance for industry *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009* and the draft guidance for industry *Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009* (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 Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

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

[20] See section 505B(e)(2)(A) of the FD&C Act; 21 U.S.C. 355c(e)(2)(A). Section 505B(e)(2)(A) specifies the time frame for submission of an iPSP if there is an end-of-phase 2 meeting or such other time as may be agreed upon between the FDA and the sponsor. The FDA expects to agree to time frames other than those specified in this guidance only if there are exceptional circumstances. Sponsors should contact the appropriate component of CDER or CBER if they believe exceptional circumstances exist.

practicable but before the initiation of any phase 3 studies, or any combined phase 2 and phase 3 studies, of the drug that is the subject of the iPSP. If a phase 3 study, or a combined phase 2 and phase 3 study, will not be conducted, the sponsor should submit the iPSP no later than 210 calendar days before it submits a marketing application or supplement. A sponsor should submit the iPSP to its IND for the drug. In cases when there is no active IND for the drug, but the sponsor expects upon submission of the IND that the initial studies would include a phase 3 study, the iPSP should be submitted as a pre-IND submission. In this situation, the FDA encourages sponsors to schedule a pre-IND meeting before submission of the iPSP, and, as stated above, the sponsor should submit the iPSP before the initiation of any phase 3 studies or combined phase 2 and phase 3 studies.[21]

A sponsor should not submit a marketing application or supplement until agreement has been reached on the iPSP. Although a formal decision by the FDA about granting a waiver and/or deferral of required pediatric assessments will not be made until approval of the marketing application, the sponsor will receive feedback at the time of the review of the iPSP on the plan to request a waiver and/or deferral upon submission of the marketing application. For example, this feedback may include recommendations on the timing of pediatric drug development with the aim of including pediatric data in the initial marketing application, rather than needing a deferral.

After an iPSP is submitted by the sponsor, the FDA has 90 days to review the iPSP and provide comments to the sponsor.[22] A second 90-day review period is initiated after the sponsor has received these comments. By the end of this second 90-day review period, the sponsor must submit an agreed iPSP.[23] The FDA then has 30 days to review and issue correspondence confirming agreement, or issue correspondence stating that the FDA does not agree. If the FDA does not agree, the iPSP is considered a *non-agreed iPSP* (see section VIII., Non-Agreed Initial Pediatric Study Plans). The total length for review of an iPSP is 210 days.

V. CONTENTS OF THE INITIAL PSP

The FD&C Act requires that an iPSP include "(i) an outline of the pediatric study or studies that the sponsor plans to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); (ii) any request for a deferral, partial waiver, or waiver . . . if applicable, along with any supporting information; and (iii) other information specified in the regulations" promulgated by the FDA.[24] This section of the

[21] Information on the timing of submission of an iPSP for biosimilar products can be found in the draft guidance for industry *Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*.

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

[23] See section 505B(e)(3) of the FD&C Act; 21 U.S.C. 355c(e)(3).

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

guidance describes information sponsors must or should submit in the iPSP submission.[25] In certain situations, it may be premature to include a detailed outline of a planned pediatric study (or studies) because additional data are needed (e.g., efficacy, safety, potential endpoints). In such cases, the outline of the pediatric studies should include a brief explanation for not including more detailed information.

Appendix 1 provides a template that sponsors should complete with all information available at the time of the iPSP submission.[26] The FDA acknowledges that the development program for a drug may change based on data collected from nonclinical studies, clinical trials, and/or other clinical development programs. Therefore, sponsors should consider the current stage of the clinical development program for their specific drug at the time they complete the iPSP template. Additionally, sponsors can submit amendments to an agreed-upon iPSP at any time[27] if changes to the pediatric plan need to be considered based on additional data described above. Submission of amendments to an agreed iPSP are discussed in section VII., Contents and Timing of Requested Amendment to an Initial PSP.

Earlier dialogue on a comprehensive pediatric development plan, including both required pediatric studies under PREA and potential pediatric uses under the BPCA, is intended to result in a more efficient pediatric drug development program. Toward this end, sponsors can include information in the iPSP (see section 2 in section V.B., Recommendations for the Contents of Each Section of the iPSP) about plans for submission of a concurrent or future proposed pediatric study request (PPSR), as appropriate. However, the iPSP and PPSR should be submitted as separate documents to facilitate appropriate review and comment by the FDA.

As stated above, although a formal decision by the FDA about granting a waiver and/or deferral of required pediatric assessments will not be made until approval of the marketing application, the information contained in an agreed iPSP will be considered in any requests for waiver and/or deferral at the time of the application review.

A. Materially Incomplete iPSPs

Failure to include required information as described above may result in an iPSP that is considered *materially incomplete*. For example, if a sponsor fails to address all pediatric age groups and all indications, the FDA would consider the iPSP to be materially incomplete. If the iPSP is considered materially incomplete, the sponsor will be contacted and a complete iPSP should be submitted within 30 days to address the identified deficiencies. A new 210-day review period will be started when a complete iPSP is submitted.

[25] The iPSP submission itself should be marked with the words "**INITIAL PEDIATRIC STUDY PLAN**" in large font, bolded type at the beginning of the title page.

[26] This template also is available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM338453.pdf.

[27] See section 505B(e)(5) of the FD&C Act; 21 U.S.C. 355c(e)(5).

However, if the sponsor has included sufficient information for the FDA to evaluate the plan, even if the FDA disagrees with the proposed plan, the FDA in general will consider the iPSP to be complete. For example, if a sponsor has included a plan to request full waivers as part of the iPSP, and the FDA disagrees with this plan, then the FDA would not consider this iPSP materially incomplete and would proceed with the usual timeline for internal review.

B. Recommendations for the Contents of Each Section of the iPSP

This section provides specific recommendations for the contents of each section of the iPSP.

TITLE PAGE

Sponsors should include relevant administrative information on the title page (e.g., drug name, IND number, indication(s) that apply) (see Appendix 1).

1. Overview of the Disease Condition in the Pediatric Population

This section should briefly summarize (1 to 3 pages)[28] available information on the pathophysiology of the disease, methods of diagnosis, and currently available treatments and/or prevention strategies in the pediatric population, including neonates. The sponsor should also include available information on the incidence and prevalence of the disease in the overall population and the incidence and prevalence in the pediatric population. Additionally, the sponsor should provide evidence and assumptions on key differences between the disease in adults and in the pediatric population.

2. Overview of the Drug or Biological Product

This section should briefly summarize (1 to 3 pages) the proposed mechanism of action of the drug (to the extent understood). A broad consideration of any possible therapeutic uses of the drug in children beyond the disease or indication being sought in adults may serve as the basis for a Written Request under section 505A of the FD&C Act (21 U.S.C. 355a). The FDA encourages sponsors to discuss the potential therapeutic benefits and/or fulfillment of therapeutic needs in the pediatric population, including neonates, beyond the indication(s) for which pediatric assessments will be required under PREA. Any changes to this discussion of the use of the drug, including any clinical studies that may be proposed other than those required under PREA, will not require an amendment to an agreed iPSP. If a sponsor plans to submit a PPSR asking the FDA to issue a Written Request in the future, that information should be included in the overview as appropriate.[29] Sponsors seeking FDA review and comments on proposed pediatric studies that could be conducted under a pediatric Written Request, in addition to those required under PREA and included in the iPSP, should submit a separate PPSR.

[28] The recommended page counts for each section of the iPSP applies to the overall iPSP and not to the individual active ingredients in the case of a fixed-dose combination product.

[29] For additional information regarding Written Requests, see section 505A of the FD&C Act; 21 U.S.C. 355a.

3. Overview of Planned Extrapolation of Effectiveness to Specific Pediatric Populations

The iPSP should address whether extrapolation of effectiveness to pediatric populations is planned for the proposed product. Extrapolation of effectiveness from adult populations to pediatric populations may be appropriate if the course of the disease and the effects of the drug are sufficiently similar in adult and pediatric patients.[30] Extrapolation of effectiveness from one pediatric age group to another pediatric age group also may be appropriate.[31] Extrapolation of effectiveness assumes that an appropriate pediatric dose can be established either through achieving a similar exposure in children as in adults, or by using an appropriate pharmacodynamic or clinical endpoint to achieve the targeted effect.[32] This section should address any plans to extrapolate effectiveness from adult to pediatric patients or from one pediatric age group to another (1 to 5 pages). The sponsor should consider all age ranges of pediatric patients, including neonates. The sponsor should provide justification for the extrapolation, including any available supporting data for all age groups for which the sponsor intends to extrapolate effectiveness. This justification should include supportive data from all available sources (e.g., sponsor data, published literature, expert panels, and workshops). Extrapolation of effectiveness for other drugs in the same class, if previously accepted by the FDA, also may be considered supportive information.

However, if an understanding of exposure-response in adults that can be applied to pediatrics (or from one pediatric age group to another) has not yet been established, the ability to extrapolate effectiveness may not be known at the time of the iPSP submission. If the ability to extrapolate effectiveness from adults to children is not known at the time of the iPSP submission, the sponsor must include a plan for studies to establish pediatric effectiveness in the iPSP.[33] Subsequently, if information becomes available to support pediatric extrapolation, a proposed amendment to the agreed iPSP can then be submitted that addresses any modifications based on extrapolation in the marketing application or supplement.

When determining whether the data are sufficient or will be used to support extrapolation of effectiveness, sponsors should include information in the iPSP on the similarities (and differences) between, for example, adults and children (or between one pediatric age group and another) in disease pathogenesis, criteria for disease definition, clinical classification, and measures of disease progression, as well as pathophysiologic, histopathologic, and pathobiological characteristics of the disease. In addition, if appropriate, the sponsor should include discussion on similarity in exposure-response relationship for effectiveness between adults and pediatrics based on experience with drugs in the same class or other drugs approved for use in the same disease/disorder. Extrapolation of effectiveness from one pediatric age group

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

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

[32] For further discussion, see the draft guidance for industry *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products* and the Pediatric Study Planning & Extrapolation Algorithm in its Appendix. When final, this guidance will represent the FDA's current thinking on this topic.

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

to another, often from older to younger patients, and from one formulation to another should be discussed when applicable. The use of modeling and simulation to optimize studies to support extrapolation should be discussed when applicable.

In certain circumstances one may be able to leverage existing safety information in adults or other pediatric populations to draw inferences about the safety of the drug in one or more pediatric populations. For example, for a drug that is approved for another pediatric indication that has similar dosing as the new indication, it may be possible to use the existing safety data to support safety for the new indication. For other drugs that may have disparate pediatric and adult safety profiles, such as drugs that act in the central nervous system, the adult safety data may not be relevant to the pediatric safety population. Similarly, a dedicated pharmacokinetic (PK) study is not always needed in every age group. For example, prior experience with dosing in adolescent patients has demonstrated that knowledge of adult dosing and appropriate dose scaling may be sufficient for some drugs with adequate justification.[34,35] Confirmatory population PK studies can be used to supplement such a program in which a dedicated PK study is not considered essential.

4. Request for Drug-Specific Waiver(s)

Under PREA, sponsors may request waiver of pediatric assessments at the time of the submission of the new drug application (NDA), biologics license application (BLA), or supplement.[36] PREA authorizes the FDA to grant a full waiver of required assessments if it finds that: (1) necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed); (2) there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups; or (3) the drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients.[37]

In addition, PREA authorizes the FDA to grant a partial (i.e., with respect to a specific pediatric age group) waiver of required pediatric assessments if it finds that: (1) necessary studies are impossible or highly impracticable (because, for example, the number of patients in that age group is so small or the patients in that age group are geographically dispersed); (2) there is

[34] Momper JD, Mulugeta Y, Green DJ, et al., 2013, Adolescent Dosing and Labeling Since the Food and Drug Administration Amendments Act of 2007, JAMA pediatrics, Oct;167(10):926-932.

[35] Edginton AN, Shah B, Sevestre M, Momper JD, 2013, The Integration of Allometry and Virtual Populations to Predict Clearance and Clearance Variability in Pediatric Populations Over the Age of 6 Years, Clinical Pharmacokinetics, Aug;52(8):693-703.

[36] Under PREA, a pediatric assessment "shall contain data, gathered using appropriate formulations for each age group for which the assessment is required, that are adequate (i) to assess the safety and effectiveness of the drug or the biological product for the claimed indications in all relevant pediatric subpopulations; and (ii) to support dosing and administration for each pediatric subpopulation for which the drug or the biological product is safe and effective." See section 505B(a)(2)(A) of the FD&C Act; 21 U.S.C. 355c(a)(2)(A). Also, see section 505B(a)(4) of the FD&C Act regarding waivers of pediatric assessments.

[37] See section 505B(a)(4)(A) of the FD&C Act; 21 U.S.C. 355c(a)(4)(A).

evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in that age group; (3) the drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group and is not likely to be used in a substantial number of pediatric patients in that age group; or (4) the sponsor can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.[38]

This section should discuss the plans to request a waiver (either full or partial) of the requirement to provide data from pediatric studies (1 to 3 pages). Because an agreed iPSP that may contain plans for requests for waivers must be submitted with the NDA/BLA along with the formal waiver request, the information in this section should be as complete as possible and updated as needed.[39] The sponsor should provide justification with a summary of supporting data, for all age groups for which the waiver will be sought. Supportive data should include data from all relevant sources, including sponsor data, published literature, expert panels and workshops, and consensus documents. Full or partial waivers previously granted for other drugs in the same class can be considered supportive information.

If the FDA agrees that a plan for a waiver is reasonable early in the preapproval development period (e.g., end-of-phase 1 or end-of-phase 2 meetings), such agreement would reflect the FDA's best judgment at that time. If, before approval of an application, the FDA or the sponsor become aware of new or additional information that affects the decision to plan for a waiver (or partial waiver) of pediatric assessments, the sponsor should reconsider the plan to request the waiver/partial waiver. If the sponsor becomes aware of new information, the sponsor should submit an amended iPSP at the earliest possible time. If the FDA becomes aware of new information, it will notify the sponsor at the earliest possible time and request that the sponsor amend the iPSP to reflect the new information (see section VI., Relationship of Agreed iPSP to the Requirement to Submit a Pediatric Plan With an Application). Such agreement could include a plan for deferral of pediatric studies if necessary. The FDA formally grants or denies a waiver request when it issues an approval letter for an NDA, BLA, or supplement.

Sponsors seeking a full waiver of pediatric studies should complete only sections 1, 2, 4, and 12 of the iPSP template (see Appendix 1).

If studies will be waived because there is evidence that the drug would be ineffective or unsafe in any pediatric age group, this information must be included in the product labeling.[40] Generally, this information would be included in the *Pediatric Use* subsection of labeling and also can be included in the CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS sections, depending on the seriousness of any safety concern that would be the grounds for waiver of pediatric studies.

[38] See section 505B(a)(4)(B) of the FD&C Act; 21 U.S.C. 355c(a)(4)(B).

[39] See 21 CFR 314.101(d)(3).

[40] See section 505B(a)(4)(D) of the FD&C Act; 21 U.S.C. 355c(a)(4)(D).

5. Plan to Request Deferral of Pediatric Studies

Under PREA, sponsors may request deferral of pediatric assessments at the time of the submission of the NDA, BLA, or supplement.[41] Because an agreed iPSP that may contain plans for requests for deferral of pediatric assessments must be submitted with the NDA/BLA along with the formal deferral request,[42] the information in this section should be as complete as possible and updated as needed. The iPSP should include any plans to request deferral of pediatric assessments in some or all pediatric groups until after approval of a future application (or supplement) in other age groups. If new information, such as data from ongoing or planned studies, indicates that a criterion for a waiver (or partial waiver) is met, planned requests for deferral of pediatric assessments in the iPSP can be changed to planned requests for waiver (or partial waiver). These changes should be submitted as an amendment to an agreed or amended iPSP.

For any studies listed in the sample table in section 6 of planned nonclinical and pediatric clinical studies that will not be submitted as part of a planned application (i.e., NDA, BLA, or efficacy supplement), sponsors must include their plan to submit a request for a deferral.[43] PREA also states that at the time of approval of an application, the FDA may grant a deferral of required pediatric assessments if it finds that: (1) the drug or biological product is ready for approval for use in adults before pediatric studies are complete; (2) pediatric studies should be delayed until additional safety or effectiveness data have been collected; or (3) there is another appropriate reason for deferral.[44] The planned request for a deferral should be listed in the order of the proposed studies in the sample table in section 6, and should include adequate justification and any currently available evidence justifying the request for a deferral (1 to 2 pages). If the FDA agrees that a plan for a deferral is reasonable early in the preapproval development period (e.g., end-of-phase 1 or end-of-phase 2 meetings), such agreement would reflect its best judgment at that time.

If, before approval of an application, the FDA or the sponsor becomes aware of new or additional information that affects the decision to plan for a deferral of pediatric assessments, the sponsor should reconsider the plan to request a deferral. If the sponsor becomes aware of new information, it should submit an amended iPSP at the earliest possible time. If the FDA becomes aware of new information, it will notify the sponsor at the earliest possible time and request that

[41] Under PREA, a pediatric assessment "shall contain data, gathered using appropriate formulations for each age group for which the assessment is required, that are adequate (i) to assess the safety and effectiveness of the drug or the biological product for the claimed indications in all relevant pediatric subpopulations; and (ii) to support dosing and administration for each pediatric subpopulation for which the drug or the biological product is safe and effective." See section 505B(a)(2)(A) of the FD&C Act; 21 U.S.C. 355c(a)(2)(A). Also, see section 505(B)(a)(3) of the FD&C Act regarding deferrals of pediatric assessments.

[42] See sections 505B(a)(1), 505B(a)(3)(A)(ii), and 505B(e) of the FD&C Act; see also 21 CFR 314.101(d).

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

[44] See section 505B(a)(3)(A)(i) of the FD&C Act; 21 U.S.C. 355c(a)(3)(A)(i). In addition, the sponsor must submit: (1) a certification of the grounds for deferring the assessments; (2) a iPSP; (3) evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time; and (4) a timeline for the completion of the studies. See section 505B(a)(3)(A)(ii) of the FD&C Act; 21 U.S.C. 355c(a)(3)(A)(ii).

the sponsor amend the iPSP to reflect the new information (see section VI., Relationship of Agreed iPSP to the Requirement to Submit a Pediatric Plan With an Application). In addition, new information may become available that could support changing the plans for a deferred study to a waiver (e.g., new safety information). The FDA would review this information and consider whether a plan for a deferred study should be converted to a waiver. It should be noted that the FDA does not formally grant or deny a request for a deferral in the iPSP. The FDA formally grants or denies a deferral when it issues an approval letter for an NDA, BLA, or supplement.

6. Tabular Summary of Planned Nonclinical and Clinical Studies

This section should include a summary in tabular form of all planned: (1) nonclinical studies to be conducted in support of the proposed clinical trials (see also section 7); and (2) clinical pediatric studies (categorized by age). The table should include a column to identify whether the sponsor will request a deferral of the study (i.e., the data are not planned to be submitted until after the application is approved). The table should also include any age groups for which the sponsor will request waivers. A sample table is included below. It should be noted that the table is provided as an example only. The specific studies planned for a specific drug (e.g., the type of studies and the age groups studied) may differ from those studies listed in the sample table.

SAMPLE TABLE: Table of Nonclinical and Clinical Studies for Drug X

PLANNED NONCLINICAL STUDIES*			
Species	Type of Study	Comments	Deferral Request Planned for the Study (Y/N)**
Rat (or appropriate animal species)	Toxicology study in juvenile animals	To support initiation of clinical studies in children ages x – xx	N
PLANNED PEDIATRIC CLINICAL STUDIES			
Pediatric PK Studies+			
Age Group	Type of Study	Comments	Deferral Request Planned for the Study (Y/N)
1-<17 years	Phase 2 PK/PD study+	To determine appropriate dose based on an established PD endpoint	N
Clinical Effectiveness and Safety Studies			
Age Group	Type of Study	Comments	Deferral Request Planned for the Study (Y/N)
0-<1 year	Not applicable (plan to request waiver)	Studies are highly impracticable	
1-<6 years	Efficacy study (R, DB, PC)+	Endpoints to be determined	Y
6-<12 years	Efficacy study (R, DB, PC)	Endpoints to be determined	Y
12-<17 years	Efficacy study (R, DB, PC)	Study to be submitted with initial NDA	N

* May not be applicable for all drugs.

** See section 11 of the Initial Pediatric Study Plan Template.

+ PK = pharmacokinetic; PD = pharmacodynamic; R = randomized; DB = double-blind; PC = placebo-controlled

7. Age-Appropriate Formulation Development

This section should provide details of any pediatric-specific formulation development plans, if appropriate, including whether the formulation being developed can be used for all pediatric populations (1 to 3 pages). If the current formulation is not suitable for all pediatric age groups, sponsors should provide specific plans for the development of an age-appropriate formulation for all pediatric age groups that will be studied. Sponsors should include information regarding planned excipients, to the extent practicable, which will be contained in a pediatric formulation. Sponsors also should provide details of measures taken to ensure appropriate design of a drug, including to the extent practicable the design of delivery systems (i.e., capsules, tablets, infusions, devices) to be used in pediatric studies.[45]

8. Nonclinical Studies

This section should provide a brief summary (1 to 3 pages) of the data from relevant nonclinical studies that support the use of the drug in all pediatric age groups the sponsor will study in the proposed clinical trials. The sponsor should include information that supports the maximum dose and duration of treatment to be used in pediatric studies. If the sponsor has determined that the nonclinical data are sufficient to support the proposed clinical trials and additional nonclinical studies are **not** planned, this summary should so state and include justification for this conclusion.

If the existing nonclinical data are not sufficient to support the proposed clinical trials, sponsors should provide a brief description for each of the studies they will conduct, including, at a minimum:

- The species to be studied
- The age of animals at the start of dosing
- The duration of dosing
- The route of administration
- The target organ systems of concern with key developmental endpoints to be evaluated, as appropriate

[45] More detail on considerations for age-appropriate formulations can be found in the 2014 EMA Guideline on Pharmaceutical Development of Medicines for Pediatric Use (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000362.jsp&mid=WC0b01ac0580028eb2).

For further information see other guidances, as appropriate.[46]

These studies should be listed in the table in section 6 and the timeline for conduct of any studies should be noted as described in section 11.

9. Clinical Data to Support Design and/or Initiation of Studies in Pediatric Patients

This section should provide a brief summary (1 to 5 pages) of any clinical data that support the design and/or initiation of pediatric studies. This section also can include a summary of available data in adult or pediatric patients who have received treatment with the drug (or related drugs) for the proposed indication, for other conditions, or in earlier studies. This section is intended to provide an overview of information already available to support initiation of pediatric studies; therefore, a detailed review of available data is not needed in this section.

10. Planned Pediatric Clinical Studies

10.1 Pediatric Pharmacokinetic Studies

This section should provide an outline of each of the pediatric pharmacokinetic/pharmacodynamic (PK/PD) study (or studies) planned, if applicable (1 to 10 pages). The studies should be discussed in the order they are presented in the table in section 6. For each study, to the extent practicable, the sponsor should address the following:

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

[46] See the guidance for industry *Nonclinical Safety Evaluation of Pediatric Drug Products* and the ICH guidances for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* and *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals.*

A statement should be included indicating that a final protocol(s) will be agreed upon with the FDA before initiation of the studies.

10.2 Clinical Effectiveness and Safety Studies

This section should provide a brief outline of each pediatric study planned, discussed in the order they are presented in the table in section 6 (1 to 10 pages). For each study, to the extent practicable, the sponsor should address the following:

- The type of study/study design
- The objectives of the study
- The age group and population in which the study will be conducted
- The key inclusion and exclusion criteria for the study
- The endpoints (primary and key secondary) to be used
- The timing of endpoint assessments
- The safety assessments (including timing and length of follow-up)
- The statistical approach
- The modeling and simulation to be used to optimize the design of planned pediatric studies when applicable

This section should provide a brief outline of the planned pediatric studies. Therefore, a detailed study protocol and/or statistical analysis plan should not be included in the iPSP. Sponsors should be aware that agreement with the outline of planned clinical studies does not constitute agreement with the study protocol. Full study protocols and statistical analysis plans should be submitted separately for review and agreement with the FDA before initiation of pediatric studies outlined in this section.

11. Timeline of the Pediatric Development Plan

For each study listed in the table in section 6, a general timeline for completion should be included in this section (1 to 2 pages). A suggested template is provided below. The sponsor should estimate these dates based on current projections for the drug development program. As stated above, the intent of the iPSP is to identify needed pediatric studies early in drug development and begin planning for these studies. Therefore, the timeline of the pediatric development plan should be based on clinical and scientific considerations, and independent of an anticipated submission date of an application or approval date of a drug. For example, formulation development can begin well before the anticipated submission date of an application or approval date of a drug. If the dates provided in the iPSP change as drug development

proceeds, the sponsor should submit a request to amend the iPSP. Furthermore, the request should include justification for the change in the dates provided below for amendment of the iPSP.

1. Formulation development, if applicable

2. Nonclinical studies, if applicable
   - Estimated protocol submission date: No later than ___(month/year)
   - Estimated study initiation date: No later than ___(month/year)
   - Estimated study completion date: No later than ___(month/year)
   - Estimated final report submission date: No later than ___(month/year)

3. Clinical studies
   - PK studies, if applicable:
     - Estimated protocol submission date: No later than ___(month/year)
     - Estimated study initiation date: No later than ___(month/year)
     - Estimated study completion date: No later than ___(month/year)
     - Estimated final report submission date: No later than ___(month/year)

   - Efficacy/safety studies, if applicable
     - Estimated protocol submission date: No later than ___(month/year)
     - Estimated study initiation date: No later than ___(month/year)
     - Estimated study completion date: No later than ___(month/year)
     - Estimated final report submission date: No later than ___(month/year)

4. Target date of application submission

12. Agreements for Pediatric Studies With Other Regulatory Authorities

Sponsors should include, if available, a summary (1 to 3 pages) of the most recent agreed pediatric investigation plan with other regulatory authorities (e.g., European Medicines Agency (EMA)). If negotiations with a regulatory authority are in progress or previous plans are under modification, a summary of the most recent draft plan should be included. Sponsors should highlight and comment on any differences with what is submitted to the FDA. The purpose of including a summary of agreements with other regulatory authorities is to encourage global alignment in pediatric development plans across regulatory authorities when possible.

VI. RELATIONSHIP OF AGREED iPSP TO THE REQUIREMENT TO SUBMIT A PEDIATRIC PLAN WITH AN APPLICATION

For NDAs, BLAs, or supplemental applications that are subject to PREA, sponsors must include an iPSP in the application when a deferral of pediatric studies is requested.[47] In such cases, the agreed iPSP or amended agreed iPSP serves as that plan and must be included in the appropriate

[47] See section 505B(a)(3)(A)(ii)(II) of the FD&C Act.

section of the application.[48] Furthermore, any planned requests for waivers and/or deferrals included in the agreed iPSP or amended agreed iPSP will serve as the official request to either defer and/or waive studies if requested at the time of the application submission. The agreed iPSP (or amended agreed iPSP), including any requests for waivers or deferrals under PREA, will be reviewed by the Pediatric Review Committee (PeRC), and a decision about granting or denying any such requests will be made during the review of the marketing application.

VII. CONTENTS AND TIMING OF REQUESTED AMENDMENT TO AN INITIAL PSP

As stated above, sponsors can request to amend an agreed iPSP at any time. Requests can include, for example, changes to an original milestone submission date that would significantly delay the initiation and/or completion of pediatric studies (e.g., more than 12 months), changing planned requests for a deferral to planned requests for a waiver or partial waiver, or changing a planned request for a waiver or partial waiver to a planned request for a deferral. For example, emerging safety data from nonclinical juvenile animal studies and/or adult human clinical trials may support converting a planned request for a deferral to a planned request for a waiver for reasons of safety. Alternatively, the need for additional safety data from adult human clinical trials may support a delay in the initiation of pediatric clinical trials. Significant amendments to an agreed iPSP will be reviewed by the PeRC.

A request for an amendment to an agreed iPSP should include:

- Specifications of the requested change(s), along with a justification for the requested change(s)
- A copy of the agreed iPSP with the requested change(s) shown in red
- A clean copy of the amended iPSP

Amendments should not be considered agreed with the FDA until a letter stating that the amendments are acceptable has been received.

If an amendment to an agreed iPSP is submitted within 210 days of the planned submission of an NDA, BLA, or supplement, the amendment may not be considered agreed absent sufficient time for the FDA review. However, the NDA, BLA, or supplement can be submitted as long as the applicant includes the previously agreed iPSP as part of the application.[49] Any changes will be considered during the application review cycle (see section VIII., Non-Agreed Initial Pediatric Study Plans).

[48] See section 505B(a)(3)(A)(ii)(II) of the FD&C Act.

[49] See 21 CFR 314.101(d). Section 505B(a) of the FD&C Act requires that the necessary pediatric assessments must be submitted with the application; if the assessments will not be ready for submission with the NDA or BLA, the sponsor must include in its iPSP plans to request a deferral.

However, if, under certain situations, the agreed iPSP included nonclinical and/or pediatric clinical studies that were expected to have been completed before submission of the NDA, BLA, or supplement, failure of the sponsor to complete these agreed studies in a timely manner may result in a refusal to file. In this situation, a sponsor should submit a request for an amendment to the agreed iPSP that includes a justification for the delay in completing one or more of the agreed pediatric studies.

VIII. NON-AGREED INITIAL PEDIATRIC STUDY PLANS

If the FDA and the sponsor are unable to reach agreement on an iPSP at the end of the 210-day review period, the FDA will issue correspondence stating that the iPSP is considered a non-agreed iPSP. As discussed in section IX., Reaching Agreement on the Non-Agreed Initial Pediatric Study Plan, there is no established timeline for the review and agreement of a non-agreed iPSP. Therefore, every attempt should be made to reach agreement during the initial 210-day review period. Furthermore, as stated in section VII., Contents and Timing of Requested Amendment to an Initial PSP, an agreed iPSP or agreed amended iPSP must be submitted when a deferral of pediatric studies is requested.

Sponsors also can request amendments to an agreed iPSP (see section VI., Relationship of Agreed iPSP to the Requirement to Submit a Pediatric Plan With an Application). If the FDA and the sponsor are unable to reach agreement on the proposed amendments, the FDA will issue correspondence stating that the amended iPSP is considered a *non-agreed amended iPSP*. Under this circumstance, the agreed iPSP will be considered to be in force until such time that agreement on an amended iPSP is reached. If agreement is not reached before the submission of a marketing application when a deferral of pediatric studies is requested, then the agreed iPSP and all correspondence with the FDA regarding any non-agreed amendments must be included in the appropriate section of the application.[50]

IX. REACHING AGREEMENT ON THE NON-AGREED INITIAL PEDIATRIC STUDY PLAN

If a sponsor receives a letter of non-agreement, the FDA will make every effort to work with the sponsor and resolve the area(s) of disagreement as quickly as possible; however, there is no statutory timeline attached to this process. If the sponsor disagrees with the FDA's recommendations, it can request a meeting with the FDA to discuss any disagreement. After the sponsor and the FDA have resolved any disagreement, the sponsor should submit the proposed agreed iPSP or proposed agreed amended iPSP for FDA review.

[50] See 21 CFR 314.101(d). Section 505B(a) of the FD&C Act requires that the necessary pediatric assessments must be submitted with the application; if the assessments will not be ready for submission with the NDA or BLA, the sponsor must include in its iPSP plans to request a deferral.

APPENDIX 1: INITIAL PEDIATRIC STUDY PLAN TEMPLATE[51]

When submitting an iPSP, sponsors should mark the submission "**INITIAL PEDIATRIC STUDY PLAN**" in large font, bolded type at the beginning of the title page.

INITIAL PEDIATRIC STUDY PLAN TITLE PAGE

The proprietary name and the established name of the drug, if any, or, for biological products, the proper name including any appropriate descriptors

Dosage form:

NDA/BLA/IND #:

Drug class:

Approved indication (if applicable):

Proposed indication (if applicable):

Proposed General Plan: (i.e., full or partial waiver, deferral, and inclusion of a pediatric assessment in the future application)

Cross-reference to other INDs for which an iPSP is submitted for this drug development program

1. **OVERVIEW OF THE DISEASE IN THE PEDIATRIC POPULATION (1-3 pages)**

2. **OVERVIEW OF THE DRUG OR BIOLOGICAL PRODUCT (1-3 pages)**

3. **OVERVIEW OF PLANNED EXTRAPOLATION OF EFFECTIVENESS TO SPECIFIC PEDIATRIC POPULATIONS (1-3 pages)**

4. **PLANNED REQUEST FOR DRUG-SPECIFIC WAIVER(S) (1-3 pages)**

5. **PLAN TO REQUEST DEFERRAL OF PEDIATRIC STUDIES (1-3 pages)**

6. **TABULAR SUMMARY OF PLANNED NONCLINICAL AND CLINICAL STUDIES**

[51] This template is also available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM338453.pdf.

7. AGE-APPROPRIATE FORMULATION DEVELOPMENT (1-3 pages)

8. NONCLINICAL STUDIES (1-3 pages)

9. CLINICAL DATA TO SUPPORT DESIGN AND/OR INITIATION OF STUDIES IN PEDIATRIC PATIENTS (1-5 pages)

10. PLANNED PEDIATRIC CLINICAL STUDIES

10.1 Pediatric Pharmacokinetic Studies (1-10 pages)

10.2 Clinical Effectiveness and Safety Studies (1-10 pages)

11. TIMELINE OF THE PEDIATRIC DEVELOPMENT PLAN (1 page)

12. AGREEMENTS FOR PEDIATRIC STUDIES WITH OTHER REGULATORY AUTHORITIES (1-3 pages)

If there is a pending or agreed pediatric investigational plan with EMA, sponsors should provide the corresponding application number (e.g., EMEA-000206-PIP01-08).