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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**

**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)**

**July 2020  
Procedural**

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*Contains Nonbinding Recommendations*

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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<sup>1</sup>**

This guidance represents 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 office responsible for this guidance as listed on the title page.

**I. INTRODUCTION**

The purpose of this guidance is to provide recommendations to sponsors regarding the submission of an initial pediatric study plan (iPSP) and any amendments to the iPSP. Specifically, this guidance provides the current thinking of the Food and Drug Administration (FDA) regarding implementation of the requirement for sponsors to submit an iPSP, described in section 505B(e) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

This guidance addresses the following:

- Applications for which an iPSP is required
- Timing of an iPSP submission
- Content of an iPSP
- Content and timing of a requested amendment to an agreed iPSP
- A template that is recommend to be used for an iPSP submission<sup>2</sup>

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<sup>1</sup> 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.

<sup>2</sup> In addition to consulting guidance, a sponsor is encouraged to contact the specific CDER/CBER review division to discuss specific issues that arise during preparation of the iPSP.

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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).<sup>3</sup>

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 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.<sup>4</sup> 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 regarding use in the pediatric subpopulation, and product labeling frequently failed to provide directions for safe and effective use in pediatric patients.

To address this continuing problem, the Food and Drug Administration Modernization Act of 1997<sup>5</sup> 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.<sup>6</sup> This rule partially addressed the lack of pediatric use information by requiring manufacturers of certain new and marketed drugs to conduct studies to provide sufficient data and information to support directions for pediatric use for the claimed indications. This pediatric rule also stated that the FDA would provide sponsors with its best judgment on whether pediatric studies would be required and whether their submission would be deferred until after approval. This input was

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<sup>3</sup> For purposes of this guidance, references to *drugs* and *drug products* include drugs approved under section 505 of the FD&C Act (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262).

<sup>4</sup> 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).

<sup>5</sup> Public Law 105-115, 111 Stat. 2296 (Nov. 21, 1997).

<sup>6</sup> 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).

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given by the FDA at the end-of-phase 1 meeting, for drugs for life-threatening diseases,<sup>7</sup> and at the end-of-phase 2 meeting, for other drugs.<sup>8</sup>

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 enjoined the rule's enforcement.<sup>9</sup>

Congress subsequently passed PREA, which was signed into law on December 3, 2003.<sup>10</sup> 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,<sup>11</sup> a sponsor was not required to submit a proposed timeline and plan for the submission of pediatric studies during the investigational new drug application (IND) phase of drug development. Under the Food and Drug Administration Safety and Innovation Act (FDASIA), signed into law on July 9, 2012, for the first time PREA<sup>12</sup> includes a provision that requires a sponsor planning to submit an application for a drug subject to PREA to submit an iPSP early in the development process.<sup>13</sup> The intent of the iPSP is for a sponsor to identify needed pediatric studies early in development and begin planning for these studies. Early dialogue with the FDA 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. The timing and content of the submission of an iPSP are described below. The FD&C Act, as amended by FDASIA, requires the FDA to issue regulations and guidance to implement these and other provisions.<sup>14</sup>

The FDA Reauthorization Act of 2017 (FDARA), further updated PREA with respect to certain drugs intended for the treatment of an adult cancer and directed at a molecular target determined

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<sup>7</sup> See 21 CFR 312.81(a).

<sup>8</sup> For additional information on end-of-phase 1 meetings and end-of-phase 2 meetings, see 21 CFR 312.47(b) and 312.82(b).

<sup>9</sup> *Association of Am. Physicians & Surgeons, Inc. v. FDA*, 226 F. Supp. 2d 204, 222 (D.D.C. 2002).

<sup>10</sup> Public Law 108-155, 117 Stat. 1936 (Dec. 3, 2003).

<sup>11</sup> Public Law 110-85, 121 Stat. 823 (Sept. 27, 2007).

<sup>12</sup> By convention, section 505B is often referred to as *PREA*, after the act that added that section to the FD&C Act. We follow that naming convention in this guidance.

<sup>13</sup> Public Law 112-144, 126 Stat. 993 (July 9, 2012).

<sup>14</sup> See section 505B(e)(7) of the FD&C Act; 21 U.S.C. 355c(e)(7).

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to be substantially relevant to the growth or progression of a pediatric cancer, and for which an original marketing application is submitted on or after August 18, 2020.<sup>15</sup>

### **III. APPLICATIONS THAT REQUIRE SUBMISSION OF AN INITIAL PSP**

A sponsor who is planning to submit a marketing application (or supplement to an application) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration is required to submit an iPSP<sup>16</sup> unless the drug is for an indication for which orphan designation has been granted.<sup>17</sup> In addition, a sponsor who is planning to submit, on or after August 18, 2020, an original application for a new active ingredient that is subject to the molecularly targeted cancer drug provision of PREA (i.e., the drug that is the subject of the application is intended for the treatment of an adult cancer and is directed at a molecular target that the FDA determines to be substantially relevant to the growth or progression of a pediatric cancer) is also required to submit an iPSP,<sup>18</sup> regardless of whether the drug is for an indication for which orphan designation has been granted.<sup>19</sup> 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.<sup>20</sup>

The sponsor must submit an iPSP for any new application or supplement that is subject to PREA, regardless of whether the FDA has previously granted waivers or deferrals under PREA for the same drug.<sup>21</sup> Additionally, for drugs that are being developed specifically for use in pediatric populations, the sponsor should submit an iPSP.

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<sup>15</sup> Public Law 115-52, 131 Stat. 1005 (Aug. 18, 2017). For additional information on FDA's implementation of these amendments to PREA and on the submission of iPSPs for oncology drugs in light of the amendments, see the draft guidances for industry *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act* (December 2019) and *Pediatric Study Plans for Oncology Drugs: Transitional Information Until Full Implementation of FDARA Section 504: Questions and Answers* (January 2020). When finalized, these guidances will represent FDA's current thinking on these topics. 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>.

<sup>16</sup> See section 505B(e)(1) of the FD&C Act; 21 U.S.C. 355c(e)(1); and section 505B(a)(1)(A) of the FD&C Act; 21 U.S.C. 355c(a)(1)(A).

<sup>17</sup> See section 505B(k)(1) of the FD&C Act; 21 U.S.C. 355c(k)(1).

<sup>18</sup> See section 505B(e)(1) of the FD&C Act; 21 U.S.C. 355c(e)(1); and section 505B(a)(1)(B) of the FD&C Act; 21 U.S.C. 355c(a)(1)(B).

<sup>19</sup> See section 505B(k)(2) of the FD&C Act; 21 U.S.C. 355c(k)(2).

<sup>20</sup> See section 505B(l) of the FD&C Act; 21 U.S.C. 355c(l).

<sup>21</sup> See section 505B(e)(1) of the FD&C Act; 21 U.S.C. 355c(e)(1).

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### **IV. TIMELINES FOR AN INITIAL PSP SUBMISSION**

A sponsor must submit an iPSP, if required under PREA, before the date on which the sponsor submits 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 sponsor.<sup>22</sup> The FDA expects to agree to time frames other than those described in this guidance only if there are exceptional circumstances. In the absence of an end-of-phase 2 meeting, the sponsor should submit the iPSP as early as 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 or will be conducted but not under IND, the sponsor should submit the iPSP no later than 210 calendar days before it submits a marketing application or supplement. Sponsors should contact the appropriate component of the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research if they believe exceptional circumstances exist.

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. In cases where the sponsor has no active IND for the drug but the sponsor expects to open the IND with an initial phase 3 study, the sponsor should submit the iPSP as a pre-IND submission. In this situation, the FDA encourages the sponsor to schedule a pre-IND meeting before submission of the iPSP, and such submission should precede initiation of any phase 3 studies or combined phase 2 and phase 3 studies. In cases where the drug development program includes the possibility of using expedited programs,<sup>23</sup> the FDA encourages the sponsor to have discussions about the pediatric development plans with the review division as early as possible.

After the sponsor submits an iPSP, the FDA has 90 days to review the iPSP and provide a written response to the iPSP, or meet with the sponsor to discuss the iPSP, as appropriate.<sup>24</sup> This review process includes consultation with FDA's internal Pediatric Review Committee (PeRC).<sup>25</sup> The sponsor then has a second 90-day period during which it may review FDA comments and initiate any needed negotiations to discuss the iPSP. By the end of this second 90-day review period, the sponsor must submit an agreed iPSP.<sup>26</sup> The FDA then has 30 days after receipt of the agreed iPSP to review and issue correspondence confirming agreement or issue correspondence stating disagreement.<sup>27</sup> If the FDA does not agree, the iPSP is considered a *non-agreed iPSP* (see section VIII., Non-Agreed Initial PSPs). The total length of time for

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<sup>22</sup> See section 505B(e)(2)(A) of the FD&C Act; 21 U.S.C. 355c(e)(2)(A).

<sup>23</sup> For further information on expedited programs, see the guidance for industry *Expedited Programs for Serious Conditions—Drugs and Biologics* (May 2014).

<sup>24</sup> See section 505B(e)(2)(C)(i)(II) and (e)(2)(C)(ii) of the FD&C Act; 21 U.S.C. 355c(e)(2)(C)(i)(II) and (e)(2)(C)(ii).

<sup>25</sup> See section 505B(e)(6) of the FD&C Act; 21 U.S.C. 355c(e)(6).

<sup>26</sup> See section 505B(e)(3) of the FD&C Act; 21 U.S.C. 355c(e)(3).

<sup>27</sup> See section 505B(e)(3) of the FD&C Act; 21 U.S.C. 355c(e)(3).

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review of an iPSP should not exceed 210 days. A sponsor should not submit a marketing application or supplement until the FDA confirms agreement on the iPSP.

### **V. CONTENT 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” issued by the FDA.<sup>28</sup> This section of the guidance describes information that is required or recommended to be included in the iPSP submission. 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 the lack of more detailed information. The sponsor receives feedback at the time of the review of the iPSP on the planned request for waivers and/or deferrals. For example, the FDA feedback may indicate concurrence with the planned deferral and/or waiver or, if FDA does not concur, include recommendations for the sponsor on the timing of pediatric drug development and on whether to include pediatric data in the initial marketing application instead of obtaining a deferral. However, FDA does not make a formal decision about granting a waiver and/or deferral of required pediatric assessments, or reports on the molecularly targeted pediatric cancer investigation, until the time of the approval of the marketing application.

Appendix: Initial Pediatric Study Plan Template provides a template that we recommend sponsors complete for the iPSP submission.<sup>29</sup> The FDA acknowledges that the development program for a drug, including the design of the pediatric studies, may change as the sponsor collects new data from nonclinical studies, clinical trials, and/or other clinical development programs (e.g., data from drugs in the same or similar class). The iPSP should include a well-constructed pediatric plan based upon current knowledge of the drug and disease epidemiology; sponsors can submit amendments to an agreed iPSP at any time,<sup>30</sup> including changes to the pediatric plan that need to be considered based on additional data described above (see also section VII., Content and Timing of Requested Amendment to an Initial PSP).

In addition, sponsors can include information in the iPSP (see section 2 in section V.B., Recommendations for the Content of Each Section of the iPSP) about plans for submission of a concurrent or future proposed pediatric study request (PPSR), as appropriate. However, the sponsor should submit the iPSP and PPSR as separate documents to facilitate the FDA’s appropriate review and comment.

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<sup>28</sup> See section 505B(e)(2)(B) of the FD&C Act; 21 U.S.C. 355c(e)(2)(B).

<sup>29</sup> The template also is available at <https://www.fda.gov/media/84944/download>.

<sup>30</sup> See section 505B(e)(5) of the FD&C Act; 21 U.S.C. 355c(e)(5).

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Although, as stated above, the FDA does not make a formal decision about granting a waiver and/or deferral of required pediatric assessments or reports on the molecularly targeted pediatric cancer investigation until approval of the marketing application, the FDA considers the information contained in an agreed iPSP when considering any requests for waiver and/or deferral at the time of the marketing application review.

### **A. Materially Incomplete iPSPs**

Failure to include required information may result in an iPSP that the FDA considers *materially incomplete*. For example, if a sponsor fails to address all pediatric age groups and all indications for which the drug is being developed that are subject to PREA, the FDA generally considers the iPSP to be materially incomplete.<sup>31</sup> Additionally, if a sponsor fails to provide justification for any planned waivers or deferrals, the FDA may consider the iPSP to be materially incomplete. If the iPSP is considered materially incomplete, the FDA intends to contact the sponsor, and the sponsor should submit a complete iPSP within 30 days to address the identified deficiencies. A new 210-day review period will start when the sponsor submits a complete iPSP.<sup>32</sup>

However, if the sponsor includes sufficient information for the FDA to evaluate the plan, even if the FDA disagrees with the proposed plan, the FDA in general considers the iPSP to be sufficient for initial review. For example, if a sponsor includes a plan to request a full waiver with a justification and the FDA disagrees with this plan, the FDA does not intend to consider such disagreement as grounds for a determination that the iPSP is materially incomplete.

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

This section provides specific recommendations for the content 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 or indications that apply) (see Appendix: Initial Pediatric Study Plan Template).

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<sup>31</sup> The FDA anticipates that there will be additional considerations for applications described in section 505B(a)(1)(B) of the FD&C Act that require submission of reports on the molecularly targeted pediatric cancer investigation described in section 505B(a)(3) of the FD&C Act. For additional information, see the draft guidances for industry *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act and Pediatric Study Plans for Oncology Drugs: Transitional Information Until Full Implementation of FDARA Section 504: Questions and Answers*. When finalized, these guidances will represent FDA's current thinking on these topics.

<sup>32</sup> See sections 505B(e)(2)(C) and 505B(e)(3) of the FD&C Act; 21 U.S.C. 355c(e)(2)(C) and 355c(e)(3).

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### **1. Overview of the Disease/Condition in the Pediatric Population**

This section should briefly summarize (1 to 3 pages)<sup>33</sup> 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 both the overall population and the pediatric population, including in specific age subgroups when appropriate. Additionally, the sponsor should discuss current understanding of and available evidence supporting any similarities and 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, the intended pediatric population that will be studied, and the indications that the sponsor is seeking. In considering the indications to include in an iPSP, the sponsor should consider any possible therapeutic uses of the drug in children beyond the disease or indication being sought in adults that 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 any 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 the sponsor may propose 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, the sponsor should include that information in this section of the iPSP as appropriate.<sup>34</sup> Sponsors should submit a separate PPSR when 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.

### **3. Overview of Planned Extrapolation to Specific Pediatric Populations**

The iPSP should address whether extrapolation of effectiveness to pediatric populations is planned for the proposed product (1 to 3 pages). 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.<sup>35</sup> 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

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<sup>33</sup> The recommended page count 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.

<sup>34</sup> For additional information regarding Written Requests, see section 505A of the FD&C Act; 21 U.S.C. 355a.

<sup>35</sup> See section 505B(a)(2)(B)(i) of the FD&C Act; 21 U.S.C. 355c(a)(2)(B)(i) and section 505B(a)(3)(B) of the FD&C Act; 21 U.S.C. 355c(a)(3)(B).

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pharmacodynamic or clinical endpoint to achieve the targeted effect.<sup>36</sup> Extrapolation of effectiveness from one pediatric age group to another pediatric age group also may be appropriate.<sup>37</sup> The sponsor should consider all age ranges of pediatric patients, including neonates, when applicable. 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, workshops). Extrapolation of effectiveness for other drugs in the same class, if previously accepted by the FDA, also may be considered supportive information.

In some cases, sponsors may include in the iPSP plans for studies to assess pediatric effectiveness because the ability to extrapolate effectiveness from adults to children is not known at the time of the iPSP submission. Subsequently, if information becomes available to support extrapolation to a pediatric population, the sponsor can then submit a proposed amendment to the agreed iPSP to address plans for extrapolation in the marketing application or supplement.

When determining whether the data are sufficient 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 to another, often from older to younger patients, and from one formulation to another should be discussed when applicable. The sponsor also should discuss use of modeling and simulation to optimize studies to support extrapolation, when applicable.

In certain circumstances, one may be able to leverage existing safety and dosing 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 (e.g., if the different disease populations likely have similar susceptibility to any potential adverse effects of the drug). For 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 sufficient to support safety in the pediatric population.

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<sup>36</sup> For further discussion, see the draft guidance for industry *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products* (December 2014) and the Pediatric Study Planning & Extrapolation Algorithm in its Appendix. When final, this guidance will represent the FDA's current thinking on this topic.

<sup>37</sup> See section 505B(a)(2)(B)(ii) of the FD&C Act; 21 U.S.C. 355c(a)(2)(B)(ii) and section 505B(a)(3)(B) of the FD&C Act; 21 U.S.C. 355c(a)(3)(B).

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### **4. Planned Request for Drug-Specific Waiver(s)**

Under PREA, sponsors may request a waiver of pediatric assessments, or reports on the molecularly targeted pediatric cancer investigation, at the time of the submission of the new drug application (NDA), biologics license application (BLA), or supplement.<sup>38</sup> FDA does not formally grant or deny a request for a waiver in response to the iPSP. The FDA formally grants a waiver(s) when it issues an approval letter for an NDA, BLA, or supplement. PREA authorizes the FDA to grant a full waiver of required pediatric assessments or reports on the molecularly targeted pediatric cancer investigation 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 would be ineffective or unsafe in all pediatric age groups; or (3) the drug 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.<sup>39</sup>

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 or reports on the molecularly targeted pediatric cancer investigation 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 patients in that age group are geographically dispersed); (2) there is evidence strongly suggesting that the drug would be ineffective or unsafe in that age group; (3) the drug does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group and is not likely to be used by a substantial number of pediatric patients in that age group; or (4) the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.<sup>40</sup>

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 the information in this section will be relevant to formal requests for a full or partial waiver when the sponsor submits the NDA/BLA, the information in this section should be as complete as possible and updated as needed. The sponsor should provide justification with a summary of supporting data, for all age groups for which the waiver will be sought. This justification should include supportive data from all available sources (e.g., sponsor data, published literature, expert panels, workshops).

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<sup>38</sup> 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.” Section 505B(a)(2)(A) of the FD&C Act; 21 U.S.C. 355c(a)(2)(A). 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.” Section 505B(a)(3)(A) of the FD&C Act; 21 U.S.C. 355c(a)(3)(A). For waiver requirements, see section 505B(a)(5) of the FD&C Act; 21 U.S.C. 355c(a)(5).

<sup>39</sup> See section 505B(a)(5)(A) of the FD&C Act; 21 U.S.C. 355c(a)(5)(A).

<sup>40</sup> See section 505B(a)(5)(B) of the FD&C Act; 21 U.S.C. 355c(a)(5)(B); see also section 505B(a)(5)(C) of the FD&C Act; 21 U.S.C. 355c(a)(5)(C).

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Full or partial waivers previously granted for other drugs in the same class can be considered supportive information.

For indications that have extremely limited applicability to the pediatric population because the pathophysiology of the relevant disease occurs for the most part only in adults, the FDA generally does not intend to require sponsors to provide additional evidence that studies are impossible or highly impracticable.<sup>41</sup> The FDA anticipates that the partial waiver provision based on failure to produce a pediatric formulation may, for example, apply to situations where the sponsor can demonstrate that unusually difficult technological problems prevented the development of a pediatric formulation for a particular pediatric age group.

If, early in the preapproval development period (e.g., end-of-phase 1 or end-of-phase 2 meeting), the FDA agrees that a plan for a waiver is reasonable, such agreement would reflect the FDA's best judgment at that time. However, the FDA does not formally grant a waiver until it issues an approval letter for an NDA, BLA, or supplement. If, before approval of an application, the sponsor becomes aware of new or additional information that affects the plan for a waiver of pediatric assessments or reports on the molecularly targeted pediatric cancer investigation, the sponsor should submit at the earliest possible time an amended iPSP with an updated plan. If the FDA becomes aware of new information, it intends to 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 Initial PSP to the Requirement to Submit a Pediatric Study Plan with an Application). Such a requested amendment could include a plan for deferral of pediatric studies if appropriate.

Sponsors submitting a plan for a full waiver of pediatric studies should complete only sections 1, 2, 4, and 12 of the iPSP template (see Appendix: Initial Pediatric Study Plan Template). For sponsors submitting a plan for a full waiver of pediatric studies, based on an indication that appears on the list of adult-related conditions that rarely or never occur in children,<sup>42</sup> the iPSP should be limited to a one-page plan that specifies that the drug product is intended for the treatment of such an adult-related condition. This one-page plan should also include a sentence that the sponsor plans to request a full waiver of pediatric studies.

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<sup>41</sup> The FDA anticipates that there will be additional considerations for applications described in section 505B(a)(1)(B) of the FD&C Act that require submission of reports on the molecularly targeted pediatric cancer investigation described in section 505B(a)(3) of the FD&C Act. For additional information, see the draft guidances for industry *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act* and *Pediatric Study Plans for Oncology Drugs: Transitional Information Until Full Implementation of FDARA Section 504: Questions and Answers*. When finalized, these guidances will represent FDA's current thinking on these topics.

<sup>42</sup> See *Adult-Related Conditions That Qualify for a Waiver Because They Rarely or Never Occur in Pediatrics*, available at <https://www.fda.gov/media/101440/download>. The FDA anticipates that there will be additional considerations for applications described in section 505B(a)(1)(B) of the FD&C Act that require submission of reports on the molecularly targeted pediatric cancer investigation described in section 505B(a)(3) of the FD&C Act. For additional information, see the draft guidances for industry *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act* and *Pediatric Study Plans for Oncology Drugs: Transitional Information Until Full Implementation of FDARA Section 504: Questions and Answers*. When finalized, these guidances will represent FDA's current thinking on these topics.

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If pediatric studies will be waived because evidence exists that the drug would be ineffective or unsafe in any pediatric age group, this information must be included in the product labeling.<sup>43</sup> Generally, this information would be included in the *Pediatric Use* subsection of labeling and also may 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.

### **5. Planned Request for Deferral(s) of Pediatric Studies**

Under PREA, sponsors may request deferral of pediatric assessments or reports on the molecularly targeted pediatric cancer investigation at the time of the submission of the NDA, BLA, or supplement.<sup>44</sup> The FDA does not formally grant or deny a request for a deferral at the time of iPSP review. Rather, the FDA formally grants a deferral when it issues an approval letter for an NDA, BLA, or supplement. It is important to include in the iPSP any plan to submit a request for a deferral for any study required under PREA that will not be submitted as part of a planned application (i.e., NDA, BLA, efficacy supplement). Because the sponsor must submit with the NDA/BLA an agreed iPSP when there are plans for requests for deferral of pediatric assessments or reports on the molecularly targeted pediatric cancer investigation,<sup>45</sup> the information in this section should be as complete as possible and updated as needed.

If new information, such as data from ongoing or planned studies, indicates that a criterion for a waiver (or partial waiver) is met, the sponsor can change planned requests for deferral of pediatric assessments or reports on the molecularly targeted pediatric cancer investigation in the iPSP to planned requests for waiver (or partial waiver). The sponsor should submit these changes as an amendment to an agreed or amended iPSP.

At the time of approval of an application, the FDA may grant a deferral of required pediatric assessments or reports on the molecularly targeted pediatric cancer investigation if it finds that: (1) the drug 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

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<sup>43</sup> See section 505B(a)(5)(D) of the FD&C Act; 21 U.S.C. 355c(a)(5)(D).

<sup>44</sup> See section 505B(a)(4) of the FD&C Act; 21 U.S.C. 355c(a)(4). Under PREA, a pediatric assessment required under section 505B(a)(1)(A) of the FD&C Act “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.” Section 505B(a)(2)(A) of the FD&C Act; 21 U.S.C. 355c(a)(2)(A). A molecularly targeted pediatric cancer investigation required under section 505B(a)(1)(B) of the FD&C Act “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.” Section 505B(a)(3)(A) of the FD&C Act; 21 U.S.C. 355c(a)(3)(A).

<sup>45</sup> See sections 505B(a)(1), 505B(a)(4)(A)(ii)(II), and 505B(e) of the FD&C Act; 21 U.S.C. 355c(a)(1), 355c(a)(4)(A)(ii)(II), and 355c(e).

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collected; or (3) there is another appropriate reason for deferral.<sup>46</sup> The planned request for a deferral should list the proposed deferred studies in the same order as they are presented in the table in section 6 of the iPSP.

The planned request for a deferral should include adequate justification and any currently available evidence supporting the justification 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 meeting), such agreement would reflect the FDA's best judgment at that time.

If the sponsor becomes aware of new or additional information that affects the decision to plan for any deferral of pediatric assessments or reports on the molecularly targeted pediatric cancer investigation, the sponsor should reconsider the agreed iPSP and should submit an amended iPSP at the earliest possible time. The FDA may also request that the sponsor amend the iPSP to reflect any new information (see section VI., Relationship of Agreed Initial PSP to the Requirement to Submit a Pediatric Study Plan with an Application).

### **6. Tabular Summary of Planned Nonclinical and Clinical Development**

This section should include a summary in tabular form of all planned: (1) nonclinical development to be conducted in support of the proposed pediatric clinical trials (see also section 8); and (2) clinical pediatric development (categorized by age). The table should include a column to identify whether the sponsor plans to request a deferral of the study (i.e., the sponsor does not plan to submit the data until after FDA approves the application). The table should also include any age groups for which the sponsor plans to request waivers. An example table is included below. The table is provided as an example only. The specific studies planned for a specific drug (e.g., the type of studies, the age groups studied) may differ from those studies listed in the example table.

Case example: Drug X is a new drug under development in adults for disease Y. The sponsor is seeking a partial waiver of pediatric studies required under PREA for patients less than 2 years of age because necessary studies are impossible or highly impracticable. The rarity of the diagnosis in children less than 2 years of age is supported by literature data. The course of disease Y and the effects of drugs in this class are expected to be sufficiently similar in adults and pediatric patients. However, the similarity of the exposure-response relationship between the two populations is not known. Therefore, the sponsor is proposing to include adolescents 12 to less than 17 years of age in the adult trial and is not seeking a deferral request. In patients 2 to less than 12 years of age, the sponsor plans to conduct a pharmacokinetic/pharmacodynamic (PK/PD) study followed by an efficacy/safety study. The sponsor is proposing stratification by body size in the phase 2 PK/PD study as age is not expected to be a significant covariate for PK or PD for

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<sup>46</sup> See section 505B(a)(4)(A)(i) of the FD&C Act; 21 U.S.C. 355c(a)(4)(A)(i). In addition, the sponsor must submit: (1) a certification of the grounds for deferring the assessments or reports on the molecularly targeted pediatric cancer investigation; (2) an 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)(4)(A)(ii) of the FD&C Act; 21 U.S.C. 355c(a)(4)(A)(ii).

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the drug. The sponsor did not propose further stratification by age for the efficacy/safety study in patients 2 to less than 12 years of age. The following is an example table based on this case:

**EXAMPLE TABLE: Table of Nonclinical and Clinical Development for Drug X**

<b>PLANNED NONCLINICAL DEVELOPMENT*</b>			
<b>Species</b>	<b>Type of Study (If known, include duration)</b>	<b>Comments</b>	<b>Deferral Request Planned for the Study (Y/N)**</b>
Rat (or appropriate animal species)	Toxicology study in juvenile animals ages x to xx	To support initiation of clinical studies in children ages x to xx	N
<b>PLANNED PEDIATRIC CLINICAL DEVELOPMENT</b>			
<b>Pediatric PK or PK/PD Studies<sup>+</sup></b>			
<b>Age Group</b>	<b>Type of Study (If known, include duration)</b>	<b>Comments</b>	<b>Deferral Request Planned for the Study (Y/N)</b>
2 to <12 years	Phase 2 PK/PD study <sup>+</sup>	To determine appropriate dose based on an established PD endpoint	N
<b>Clinical Effectiveness and Safety Evaluation</b>			
<b>Age Group</b>	<b>Type of Study (If known, include duration)</b>	<b>Comments</b>	<b>Deferral Request Planned for the Study (Y/N)</b>
0 to <1 month	Not applicable (plan to request waiver)	Studies are highly impracticable	
1 month to <2 years	Not applicable (plan to request waiver)	Studies are highly impracticable	
2 to <12 years	Efficacy/safety study (R, DB, PC) <sup>+</sup>	Endpoints to be determined	Y
12 to <17 years	Efficacy/safety 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.

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

Note: A table generated for a specific drug may not be the same as the sample case above and should be based on the planned studies needed for the drug.

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### **7. Age-Appropriate Formulation Development**

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. In this section (1 to 3 pages), sponsors should include information regarding planned excipients, to the extent practicable, which will be contained in any pediatric formulation being developed. Sponsors also should provide details of measures taken to ensure appropriate design of a drug formulation, including, to the extent practicable, the design of delivery systems (e.g., capsules, tablets, infusions, devices) to be used in pediatric studies.<sup>47</sup>

### **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 include such a statement and justification for this conclusion. If a sponsor plans to conduct a juvenile animal study, we recommend sponsors contact the review division for feedback before initiating this study.

If the existing nonclinical data are not sufficient to support the proposed clinical trials,<sup>48</sup> sponsors should provide a brief description for each of the nonclinical studies they will conduct, including, at a minimum the following:

- 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

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<sup>47</sup> For more on considerations for age-appropriate formulations, see the 2014 European Medicines Agency Guideline on Pharmaceutical Development of Medicines for Pediatric Use, available at <https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/paediatric-investigation-plans/paediatric-formulations>.

<sup>48</sup> 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.

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For further information see other guidances, as appropriate.<sup>49</sup>

Sponsors should also list the planned nonclinical studies in the table in section 6 and note (as described in section 11) the timeline for conduct of any such studies.

### **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 or initiation of pediatric studies. This section also should 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 design or 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 or Pharmacokinetic/Pharmacodynamic Studies**

This section (1 to 10 pages) should provide an outline of each of the pediatric PK/PD studies planned, if applicable.<sup>50</sup> Sponsors should discuss the studies 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

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<sup>49</sup> See the guidance for industry *Nonclinical Safety Evaluation of Pediatric Drug Products* (February 2006) and the ICH guidances for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010) and *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals* (March 2010).

<sup>50</sup> For further discussion, see the draft guidance for industry *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products*. When final, this guidance will represent the FDA's current thinking on this topic.

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- Any planned pharmacogenomic analyses
- Sample size justification

A sponsor must submit full protocols separately to the IND for FDA review and should obtain FDA agreement regarding all full protocols before initiation of pediatric studies outlined in this section.<sup>51</sup>

A dedicated 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. It may be appropriate for a sponsor to use confirmatory population PK studies to supplement such a program in which a dedicated PK study is not considered essential.<sup>52</sup>

### **10.2 Clinical Effectiveness and Safety Studies**

This section should provide a brief outline of each pediatric study planned, discussed in the order each is 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, sponsors should not include a detailed protocol and/or statistical analysis plan in the iPSP. Sponsors

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<sup>51</sup> See 21 CFR 312.23(a)(6) and 312.30.

<sup>52</sup> For additional information, see the draft guidance for industry, *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products*. When final, this guidance will represent the FDA's current thinking on this topic.

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should be aware that agreement with the outline of planned clinical studies does not constitute agreement with the protocol. Sponsors must submit full protocols separately to their INDs for FDA review and should obtain FDA agreement regarding all full protocols before initiation of pediatric studies outlined in this section.<sup>53</sup> Sponsors should also submit statistical analysis plans separately to their INDs for FDA review and agreement.

### **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 page). 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 to begin planning for these studies. Therefore, the timeline of the pediatric development plan should be based on clinical, scientific, and operational considerations and should be made independent of an anticipated submission date of an application or approval date of a drug. For example, pediatric formulation development can begin 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 and include justification for the change.

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 or PK/PD 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 and/or dedicated 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)

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<sup>53</sup> See 21 CFR 312.23(a)(6) and 312.30.

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4. Target date of application submission

### **12. Agreements for Pediatric Studies With Other Regulatory Authorities**

It is recommended that sponsors 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). If negotiations with a regulatory authority are in progress or previous plans are under modification, a sponsor should include a summary of the most recent draft plan. A sponsor should highlight and comment on any differences between the most recent plan with other regulatory authorities and the plan 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 INITIAL PSP TO THE REQUIREMENT TO SUBMIT A PEDIATRIC STUDY PLAN WITH AN APPLICATION**

For NDAs, BLAs, or supplemental applications subject to PREA, sponsors must include an agreed iPSP in the application when a deferral of pediatric studies is requested.<sup>54</sup> In such cases, submission of the iPSP (specifically, the agreed iPSP) fulfills the requirement of the sponsor to submit a pediatric study plan, which must be included in the appropriate section of the application.<sup>55</sup> Failure to fulfill the requirement to submit a pediatric study plan with the application may be grounds for refusal to file an application.<sup>56</sup> Any planned requests for waivers and/or deferrals included in the iPSP serve as the official request with the application submission.<sup>57</sup> The PeRC will review any requests for waivers and/or deferrals and make recommendations as needed to the review division.<sup>58</sup> A final decision about granting or denying such requests is made by the review division at the time of approval of the marketing application.

## **VII. CONTENT AND TIMING OF REQUESTED AMENDMENT TO AN INITIAL PSP**

Sponsors can request an amendment to an agreed iPSP at any time. Requests can include, for example, changing a date listed in section 11 of the iPSP that would significantly delay the initiation and/or completion of pediatric studies (e.g., by more than 12 months), changing planned requests for a deferral to planned requests for a waiver or partial waiver, or changing a

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<sup>54</sup> See sections 505B(a)(4)(A)(ii)(II), 505B(a)(1) and 505B(e) of the FD&C Act; 21 U.S.C. 355c(a)(4)(A)(ii)(II), 355c(a)(1), and 355c(e).

<sup>55</sup> See sections 505B(a)(4)(A)(ii)(II) and 505B(e)(3) of the FD&C Act; 21 U.S.C. 355c(a)(4)(A)(ii)(II) and 355c(e)(3).

<sup>56</sup> See 21 CFR 314.101(d).

<sup>57</sup> See section 505B(e)(2)(B)(ii) of the FD&C Act; 21 U.S.C. 355c(e)(2)(B)(ii).

<sup>58</sup> See section 505B(f)(4) of the FD&C Act; 21 U.S.C. 355c(f)(4).

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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. In addition, formulation data could necessitate a change in a development program. The PeRC will be consulted on the review of significant amendments to an agreed iPSP.<sup>59</sup>

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

- The requested change(s) supported with a justification
- A copy of the agreed iPSP with the requested change(s) tracked and clearly identified
- A clean copy of the proposed amended iPSP

Amendments should not be considered agreed upon until the FDA issues a letter stating that the amendments are acceptable.

Once the FDA accepts for filing an application or supplemental application, it is not necessary to submit amendments to the iPSP because changes to the plan for pediatric development can be negotiated during the review cycle as appropriate. For example, a sponsor submits a marketing application with an agreed iPSP, and the review division files the application. The sponsor proposes to modify the timeline for studies after filing the application; in this case, it is not necessary to submit an amended iPSP, but instead the newly proposed timeline can be negotiated with the review division during the review cycle of the application.

The timeline for submission, review, and agreement on an amended iPSP is the same as on an iPSP.<sup>60</sup> (See Section IV., Timing of an Initial PSP Submission). If the FDA does not agree to the amended iPSP, the original agreed iPSP remains in force. If the sponsor submits an amendment to an agreed iPSP 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 sponsor may submit the NDA, BLA, or supplement with the previously agreed iPSP. FDA intends to, as appropriate, consider changes to the plan for pediatric development during the application review cycle (see section VIII., Non-Agreed Initial PSPs).

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

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<sup>59</sup> See section 505B(e)(6) of the FD&C Act; 21 U.S.C. 355c(e)(6).

<sup>60</sup> See section 505B(e)(5) of the FD&C Act; 21 U.S.C. 355c(e)(5).

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result in a refusal to file.<sup>61</sup> In this situation, a sponsor should submit a request for an amendment to the agreed iPSP that includes an updated timeline for the studies and justification for the delay in completing one or more of the agreed pediatric studies. If the FDA considers the justification for the delay to be inadequate and does not agree with the proposed iPSP amendment, the agreed iPSP would remain in force until the FDA and sponsor agree on an amended iPSP (See Section VIII., Non-Agreed Initial PSPs), and the failure of the sponsor to complete the agreed nonclinical and/or pediatric clinical studies in a timely manner still may result in a refusal to file.

### **VIII. NON-AGREED INITIAL PSPs**

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 intends to issue a letter stating that the iPSP is considered a non-agreed iPSP. As discussed in section IX., Reaching Agreement on the Non-Agreed Initial PSP, there is no established timeline for the review and agreement of a non-agreed iPSP. Therefore, sponsors are encouraged to work with FDA to reach agreement during the initial 210-day review period.

If the FDA and the sponsor are unable to reach agreement on the proposed amendments to an agreed iPSP, the FDA intends to issue a letter stating that the amended iPSP is considered a *non-agreed amended iPSP*. Under this circumstance, the agreed iPSP would be considered to be in force until the FDA and sponsor agree on an amended iPSP.

As stated above, for NDAs, BLAs, or supplemental applications subject to PREA, sponsors must include an agreed iPSP in the application when a deferral of pediatric studies is requested, and the failure to submit an agreed iPSP when a deferral is requested may be grounds for refusal to file the application.<sup>62</sup> All correspondence with the FDA regarding any non-agreed amendments should be included in the appropriate section of the application.

### **IX. REACHING AGREEMENT ON THE NON-AGREED INITIAL PSP**

When a sponsor receives a letter of nonagreement, the FDA makes every effort to work with the sponsor and resolve the area(s) of disagreement as quickly as possible; however, no statutory timeline is attached to this process. If the sponsor disagrees with the FDA's recommendations, the sponsor can request a meeting with the FDA. After the sponsor and the FDA have resolved any disagreements, the sponsor should submit the proposed agreed iPSP for FDA review.

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<sup>61</sup> See section 505B(a)(1) of the FD&C Act (21 U.S.C. 355c(a)(1)), which requires that the assessments or reports on the molecularly targeted pediatric cancer investigation be submitted with the application or supplement to which PREA applies. See also 21 CFR 314.101(d).

<sup>62</sup> See sections 505B(a)(4)(A)(ii)(II), 505B(a)(1), and 505B(e) of the FD&C Act; 21 U.S.C. 355c(a)(4)(A)(ii)(II), 355c(a)(1), and 355c(e). See also 21 CFR 314.101(d).

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**APPENDIX: INITIAL PEDIATRIC STUDY PLAN TEMPLATE<sup>1</sup>**

When submitting an initial pediatric study plan (iPSP), sponsors should mark the submission “**INITIAL PEDIATRIC STUDY PLAN**” in large, bolded type at the beginning of the title page. For an agreed iPSP or amended iPSP, sponsors should mark the submission “**PROPOSED AGREED PEDIATRIC STUDY PLAN**” or “**AMENDED PEDIATRIC STUDY PLAN**,” respectively, in large, 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 or molecularly targeted pediatric cancer investigation in the future application)

Cross-reference to other investigational new drug applications for which an iPSP is submitted for this drug development program

- 1. OVERVIEW OF THE DISEASE/CONDITION IN THE PEDIATRIC POPULATION (1–3 pages)**
- 2. OVERVIEW OF THE DRUG OR BIOLOGICAL PRODUCT (1–3 pages)**
- 3. OVERVIEW OF PLANNED EXTRAPOLATION TO SPECIFIC PEDIATRIC POPULATIONS (1–3 pages)**
- 4. PLANNED REQUEST FOR DRUG-SPECIFIC WAIVER(S) (1–3 pages)**
- 5. PLANNED REQUEST FOR DEFERRAL(S) OF PEDIATRIC STUDIES (1–2 pages)**

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<sup>1</sup> This template is also available at <https://www.fda.gov/media/84944/download>.

*Contains Nonbinding Recommendations*

- 6. TABULAR SUMMARY OF PLANNED NONCLINICAL AND CLINICAL DEVELOPMENT**
- 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 or Pharmacokinetic/Pharmacodynamic 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 (European Medicines Agency), sponsors should provide the corresponding application number (e.g., EMEA-000206-PIP01-08).