Pediatric Study Plans for Oncology Drugs: Transitional Information Until Full Implementation of FDARA Section 504 Questions and Answers

Guidance for Industry

DRAFT GUIDANCE

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Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
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Pediatric Study Plans for Oncology Drugs: Transitional Information Until Full Implementation of FDARA Section 504 Questions and Answers 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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), as required by section 505B(e) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for oncology drugs[2] only. Specifically, this guidance provides FDA's current thinking regarding iPSPs for oncology drugs in light of the amendments to section 505B of the FD&C Act (also referred to as the Pediatric Research Equity Act, or PREA) made by section 504 of the FDA Reauthorization Act of 2017 (FDARA).[3] FDA has received a number of questions on this topic and, as a result, is providing guidance in a question and answer format, addressing the most frequently asked questions.

This guidance does not contain a complete discussion of general requirements for development of drugs for pediatric use under PREA or section 505A of the FD&C Act (also referred to as the Best Pharmaceuticals for Children Act or BPCA).[4]

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

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

[2] For purposes of this guidance, references to drugs 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).

[3] Public Law 115-52, 131 Stat. 1005 (August 18, 2017).

[4] For additional information on pediatric study plans, see the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (March 2016). When final, this guidance will represent FDA's current thinking on this topic. FDA updates guidances periodically. 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.

the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Section 504 of FDARA amended section 505B of the FD&C Act to require—for original applications submitted on or after August 18, 2020—pediatric investigations of certain targeted cancer drugs with new active ingredients, based on molecular mechanism of action rather than clinical indication. FDARA thus created a mechanism to require evaluation of certain novel medicines that may have the potential to address an unmet medical need in the pediatric population. Timely investigation in children of the antitumor activity of potentially effective targeted drugs under development in adults and of those drugs' toxicities relative to the unique growth and developmental considerations of pediatric patients, is intended to accelerate early pediatric evaluation of these products and ultimately facilitate development of appropriate new therapies for pediatric patients.

Section 505B of the FD&C Act, as amended by FDARA, requires that any **original** new drug application (NDA) or biologics license application (BLA) submitted on or after August 18, 2020, for a new active ingredient, must contain reports of molecularly targeted pediatric cancer investigations described in section 505B(a)(3) of the FD&C Act, unless a deferral or waiver of that requirement is granted, if the drug that is the subject of the application is:

(1) intended for the treatment of an adult cancer, and

(2) directed at a molecular target that the Secretary determines to be substantially relevant to the growth or progression of a pediatric cancer.[5]

This requirement for pediatric investigations applies even if the adult cancer indication does not occur in the pediatric population, and, per section 505B(k)(2) of the FD&C Act, even if the drug is for an adult indication for which orphan designation has been granted.

Therefore, an iPSP for such an NDA/BLA must include an outline of the molecularly targeted pediatric cancer investigation(s) that are planned (including, to the extent practicable, study objectives and design, age groups, relevant endpoints, and statistical approach) and any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting information.[6]

III. QUESTIONS AND ANSWERS

Q1: When is an iPSP required and does the iPSP have to address molecularly targeted pediatric cancer drug investigations?

[5] Section 505B(a)(1)(B) of the FD&C Act.

[6] See section 505B(e)(2)(B) of the FD&C Act.

A1:

The answers below pertain to drugs for the treatment of adult cancers with molecular targets determined to be substantially relevant to the growth or progression of a pediatric cancer (see sections 505B(a)(1)(B) and (a)(3) of the FD&C Act).[7]

- Prior to August 18, 2020
  - Original Application for a New Active Ingredient or Supplemental Application: A sponsor who is planning to submit a marketing application (or supplemental 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, unless the drug is for an indication for which orphan designation has been granted.[8] The iPSP is not required to contain an outline of planned molecularly targeted pediatric cancer investigation(s) because section 505B(a)(1)(B) of the FD&C Act does not apply to applications submitted prior to August 18, 2020; however, FDA encourages sponsors of **original** adult oncology drug applications submitted prior to August 18, 2020, to address molecularly targeted pediatric cancer investigations in their development plans.

- On or after August 18, 2020
  - Original Application for a New Active Ingredient: A sponsor who is planning to submit a marketing application for an adult cancer drug meeting the statutory criteria in section 505B(a)(1)(B) of the FD&C Act is required to submit an iPSP in accordance with section 505B(e), regardless of the drug's proposed adult cancer indication or of whether it is a drug for an indication for which orphan designation has been granted. The iPSP should address the drug's molecular target and its relevance to one or more cancers which occur in the pediatric population. Sponsors should consult the relevant Pediatric Molecular Target List.[9] In accordance with section 505B(e)(2)(B) of the FD&C Act, the iPSP must contain an outline of the planned molecularly targeted pediatric cancer investigation(s) and any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation.

  - Supplemental Application: A sponsor who is planning to submit a supplemental application for a new indication, new dosage form, new dosing regimen, or new route

[7] Note that, 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, see section 505B(l)(1) of the FD&C Act.

[8] See sections 505B(a)(1), 505B(e), and 505B(k) of the FD&C Act.

[9] For the latest version of the Pediatric Molecular Target List, please refer to https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology. We note that this is not an exhaustive list of all molecular targets the Secretary may ultimately determine are substantially relevant to the growth or progression of a pediatric cancer. This list includes 1) molecular targets considered to be substantially relevant to the growth and progression of a pediatric cancer and that therefore may trigger the pediatric study requirements under PREA and 2) molecular targets for which the pediatric cancer study requirements under PREA will be automatically waived.

of administration is required to submit an iPSP, unless the drug is for an indication for which orphan designation has been granted.[10]

Section 505B(a)(1)(B) of the FD&C Act applies only to original applications, not supplemental applications. Thus, an iPSP for a supplemental application will not be required to contain a description of molecularly targeted pediatric cancer investigations.

Q2: What is the content of an iPSP?

A2: The required content of an iPSP is set forth in section 505B(e)(2)(B) of the FD&C Act. Additionally, FDA has issued a draft guidance for industry, "Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans" (the Draft iPSP Guidance). Once finalized, the Draft iPSP guidance will describe, among other things, FDA's recommendations regarding iPSP content. An iPSP template is included in Appendix 1 of that draft guidance.

Q3: Can an iPSP be abbreviated for sponsors seeking a waiver?

A3:

- Prior to August 18, 2020
  - Original Application for a New Active Ingredient or Supplemental Application: As stated in the Draft iPSP Guidance, sponsors seeking a full waiver of pediatric studies, including because the new active ingredient is being developed for an indication included on the current "Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics" list,[11] should complete only certain sections of the iPSP template included in Appendix 1 of the Draft iPSP Guidance.[12] iPSPs should also be abbreviated as described in the Draft iPSP Guidance for certain supplemental applications if the sponsor is seeking a full waiver of pediatric studies. This may include, for example, supplemental applications for indications on the "Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics" list,[13] including applications for different treatment settings (stage, adjuvant, neo-adjuvant, etc.) for the same disease, if there is previous agreement for a planned waiver of pediatric studies with respect to an earlier application submitted by the applicant for the same product and disease.

[10] See sections 505B(a)(1)(A), 505B(e), and 505B(k) of the FD&C Act.
[11] For the list of "Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics" see https://www.fda.gov/media/101440/download.
[12] See the Draft iPSP Guidance for additional information related to content of iPSPs. When final, this guidance will represent the FDA's current thinking on this topic.
[13] See footnote 11.

- On or after August 18, 2020
  - Original Application for a New Active Ingredient or Supplemental Application: Sponsors seeking a full waiver of pediatric studies for oncology drugs containing a new active ingredient, including for products directed at a molecular target that is included on the list of Non-Relevant Molecular Targets which Warrant Waiver,[14] should submit an abbreviated iPSP as described in the Draft iPSP Guidance.

  - Supplemental Application: Sponsors seeking a full waiver of pediatric studies for certain supplemental applications should continue to submit abbreviated iPSPs as described in the Draft iPSP Guidance. This may include, for example, supplemental applications for indications on the "Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics " list,[15] including applications for different treatment settings (stage, adjuvant, neo-adjuvant, etc.) for the same disease, if there is previous agreement for a planned waiver of pediatric studies with respect to an earlier application submitted by the applicant for the same product and disease.

    Section 505B(a)(1)(B) of the FD&C Act applies only to original applications, not supplemental applications.

Q4: If a sponsor is planning to file an application for one of the drugs in a cross labeled oncology drug combination regimen, does the sponsor need to submit separate iPSPs and conduct a molecularly targeted pediatric investigation for each of the drugs in the combination?

A4:

- For original applications submitted prior to August 18, 2020: An iPSP is required under section 505B(e) of the FD&C Act for each application that is subject to PREA.

- For original applications submitted on or after August 18, 2020: Requirements for iPSPs are the same as above. A molecularly targeted pediatric investigation may be required if the drug that is the subject of the application is intended for the treatment of adult cancer and directed at a molecular target determined to be substantially relevant to the growth or progression of a pediatric cancer.[16]

Q5: If a product with a new active ingredient is granted orphan designation for the indication being sought but is directed at a molecular target that would be considered substantially relevant to pediatric cancers, is a sponsor exempt from PREA? What should sponsors do if they are unsure if the application will be submitted before or after August 18, 2020?

[14] See footnote 9.
[15] See footnote 11.
[16] See section 505B(a)(1)(B) of the FD&C Act.

A5: An original application for such a product, if intended for the treatment of an adult cancer and directed at a molecular target determined to be substantially relevant to the growth or progression of a pediatric cancer, is exempt from PREA on the basis of orphan designation under section 505B(k) of the FD&C Act **only** if submitted prior to August 18, 2020. However, FDA recommends all sponsors developing such drugs submit an iPSP anyway because development timelines can be unpredictable and pediatric investigations will be required, unless waived, if the original application is submitted on or after August 18, 2020. Early discussion with FDA prior to application submission may help in planning the timing of the submission and, if necessary, facilitate the development of studies to ensure PREA requirements are met.

Q6: What if a sponsor has a new active ingredient under development for a drug intended for the treatment of an adult cancer, with a proposed indication on the "Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics" list, but it is directed at a molecular target that would be considered substantially relevant to pediatric cancers, and the sponsor is unsure whether the application will be submitted on or after August 18, 2020?

A6: An original application for such a drug intended for the treatment of an adult cancer, with a new active ingredient and a molecular target that is determined to be substantially relevant to a pediatric cancer, and that has a proposed indication on the "Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics" list,[17] will qualify for a waiver on the basis of an indication that appears on that list **only** if the application is submitted prior to August 18, 2020. Beginning on that date, such an application would fall under section 505B(a)(1)(B) of the FD&C Act and would no longer be subject to section 505B(a)(1)(A). Accordingly, the required pediatric assessments would no longer be based on indication (see section 505B(a)(2)) and would instead be based on the molecular target (see section 505B(a)(3)), so an indication that rarely or never occurs in pediatrics would not necessarily mean that the application qualifies for a waiver on the basis that the necessary studies are impossible or highly impracticable.

Nevertheless, even for products whose marketing applications are likely to be submitted before August 18, 2020, FDA recommends submission of an iPSP because, depending on the ultimate submission date of the marketing application, molecularly targeted pediatric cancer investigations may be required, and early discussion with the Agency prior to application submission may facilitate the development of studies to ensure that all relevant PREA requirements are met.

Q7: What should a sponsor do if their planned application is for a new active ingredient, and the sponsor is unsure as to whether its molecular target is considered substantially relevant to a pediatric cancer?

[17] See footnote 11.

A7: Sponsors should consult the relevant Pediatric Molecular Target List,[18] evaluate current scientific literature, seek input from pediatric cancer experts, and consider pre-clinical evaluation of their product in pediatric tumor model systems in order to best inform their iPSP. Sponsors are also advised of the opportunity to seek early interaction with FDA to address their pediatric development. Questions can be addressed to the Pediatric Oncology Program in FDA's Oncology Center of Excellence at OCEPeRC@fda.hhs.gov.

Q8: The molecular target for the drug being studied is not addressed on the relevant Pediatric Molecular Target List. Does that mean a pediatric investigation is not required?

A8: No. The relevant Pediatric Molecular Target List[19] is not an all-inclusive list. It is intended as a starting point to provide information on the likelihood of molecularly targeted pediatric cancer investigations being required. The sponsor should seek input from pediatric cancer experts regarding product development and seek early interaction with the Agency (Pediatric Oncology Program in the Oncology Center of Excellence) to address the need for pediatric investigations and any possible subsequent development plans.

Q9: Will an investigation be required if the drug being studied is directed at a molecular target determined to be substantially relevant to pediatric cancers?

A9: If the marketing application for a drug that is intended to treat a cancer in adults is submitted on or after August 18, 2020, a pediatric investigation may be required under section 505B(a)(1)(B) of the FD&C Act unless the applicant provides sufficient justification that such clinical evaluation should be waived.

[18] See footnote 9.
[19] See footnote 9.