FDA Briefing Document

Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (ODAC)

May 22, 2024

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office.

We have brought the following issues to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package will not include issues relevant to any final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee.

The subcommittee will discuss considerations related to amendments made by Section 504 of the 2017 FDA Reauthorization Act (FDARA) to Section 505B of the Food, Drug, and Cosmetic Act, which required, for original applications submitted on or after August 18, 2020, pediatric investigations of certain targeted cancer drugs[1] with new active ingredients, based on molecular target rather than clinical indication. Specifically, the Committee will discuss perspectives relating to implementation of this legislation and its impact on pediatric cancer drug development to date. Representatives from the European Medicines Agency (EMA), the pediatric oncology investigator community, and the pharmaceutical industry have also been invited to present their perspectives.

FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

[1] For purposes of this document, references to drugs and drug products include drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (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).

Memorandum

Date: April 25, 2024

To: Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (ODAC) Members, Consultants, and Guests

From: Martha Donoghue, MD
Associate Director for Pediatric Oncology and Rare Cancers,
Oncology Center of Excellence, Office of the Commissioner, FDA

Subject: FDA Background Package for the May 22, 2024, Meeting

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Thank you for agreeing to participate in the upcoming Pediatric Oncology Subcommittee of the ODAC meeting. The Subcommittee will discuss considerations related to amendments made by Section 504 of the 2017 FDA Reauthorization Act (FDARA) to Section 505B of the Food, Drug, and Cosmetic Act, which required, for original applications submitted on or after August 18, 2020, pediatric investigations of certain targeted cancer drugs with new active ingredients, based on molecular target rather than clinical indication.

In this meeting, the Subcommittee will discuss perspectives on the impact of FDARA on the field of pediatric oncology, considerations related to implementation of FDARA for new molecularly targeted drugs and biological products, and the role of proof-of-concept studies using relevant pediatric preclinical models. The Subcommittee will also discuss the role of international collaboration and how coordinated approaches to the design and conduct of molecularly targeted pediatric cancer investigations can be best achieved.

As always, we appreciate your time and commitment and look forward to an informative meeting on May 22, 2024.

Relevant Molecular Targets in Pediatric Cancers: Applicability to Pediatric Therapeutic Investigations Required Under FDARA 2017 and the Impact on Pediatric Oncology to Date

Legislative and Regulatory Landscape Affecting Pediatric Cancer Drug Development in the United States

Pediatric cancer drug development typically leverages adult cancer drug discovery but has lagged far behind development of cancer drugs for adults. Historically, manufacturers have been reluctant to study drugs[2] and biological products in children due to economic, ethical, and perceived legal concerns, amongst other obstacles. This is particularly true for children with cancer, a vulnerable population with rare and ultra-rare diseases for whom there is less financial incentive for industry sponsor to develop innovative therapies. Accordingly, approval of a new cancer drug for a pediatric cancer indication rarely occurs without prior approval for an adult cancer indication, and there is an urgent unmet need for new and less toxic treatments for pediatric malignancies.

On December 3, 2003, the Pediatric Research Equity Act (PREA) was signed into law, giving FDA the authority to require pediatric assessments of new drugs and biological products under certain circumstances. This legislation required applications (or supplements to an application) submitted under section 505 of the Act (21 U.S.C. 355) or section 351 of the Public Health Service Act (PHSA) (42 U.S.C. 262) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a pediatric assessment unless the applicant has obtained a waiver or deferral (section 505B(a) of the Act). It also authorized FDA to require holders of approved new drug applications (NDAs) and biologics license applications (BLAs) for marketed drugs and biological products to conduct pediatric studies under certain circumstances (section 505B(b) of the Act); however, this authority generally applied only to those drugs and biological products developed for diseases or conditions that occur in both the adult and pediatric populations. Additionally, it exempted products for orphan-designated indications from the requirement for pediatric studies and did not require submission of a proposed timeline and

[2] For purposes of this document, references to drugs and drug products include drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (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).

plan for the submission of pediatric studies during the investigational new drug application (IND) phase of drug development.

In 2012, PREA was amended under the FDA Safety and Innovation Act (FDASIA) to require pharmaceutical sponsors to submit an initial Pediatric Study Plan (iPSP) early in development (no later than 60 days after an end-of-Phase 2 meeting or such other time as agreed upon between FDA and the applicant) and reach agreement with the FDA on the iPSP prior to the submission of an NDA or a BLA. This was done in order to require consideration of pediatric development earlier in a product's development timeline, thereby facilitating responsible and timely access of safe and effective drugs to children. PREA had a sunset provision requiring reauthorization; it was reauthorized under the Food and Drug Administration Amendments Act (FDAAA) in 2007 and permanently reauthorized under FDASIA in 2012.[3]

Until recently, PREA was not an effective mechanism to support the development of drugs for pediatric cancers because the requirement for conduct of pediatric studies was linked to the indication sought in adults and most adult cancers occur rarely, if ever, in children (e.g., cancers of the lung, prostate and breast). Therefore, sponsors typically obtained waivers for conducting assessments of oncology products in pediatric patients because such studies would be impossible or highly impracticable. Additionally, in the infrequent circumstances in which oncology products were under development for a type of cancer that occurs both in adult and pediatric patients, orphan designation often exempted the development program from PREA requirements.

The Research to Accelerate Cures and Equity (RACE) for Children Act was signed into law on August 18, 2017, as Title V of the 2017 FDA Reauthorization Act (FDARA). This law amended PREA, Sec. 505B of the FD&C Act, to require pediatric investigations of certain targeted cancer drugs with new active ingredients, based on molecular mechanism of action rather than clinical indication, for original applications submitted on or after August 18, 2020. These pediatric investigations are referred to as molecularly targeted pediatric cancer investigations, and may include clinical studies designed to yield clinically meaningful pediatric study data, gathered using

[3] FDA Draft Guidance for Industry: Pediatric Drug Development Under the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act: Scientific Considerations. May 2023. https://www.fda.gov/media/168202/download

appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling [FDARA Title V Sec 504 (a)(3)(A), FD&C Act Sec. 505B (a)(3)(A), 21 USC 355c(a)(3)(A)].

FDARA thereby created a mechanism to require evaluation of certain novel targeted therapies that may potentially address an unmet medical need in pediatric patients with cancer. Specifically, if an initial NDA or BLA (excluding supplemental applications) is for a new active ingredient, and the product that is the subject of the application is intended for treatment of an adult cancer and directed at a molecular target FDA determines to be substantially relevant to the growth or progression of a pediatric cancer, reports on the molecularly targeted pediatric cancer investigation required under section 505B(a)(3) of the FD&C Act must be submitted with the marketing application, unless the required investigations are waived or deferred. Importantly, Title V of FDARA also specifies that the requirement for early pediatric investigations of drugs directed at molecular targets considered substantially relevant to the growth or progression of a pediatric cancer be applied even when the adult indication has received an orphan designation or when the adult cancer indication does not occur or is biologically different in the pediatric population.

Implementation of the FDARA Provisions of PREA

In 2019 and 2021, respectively, FDA issued a draft and final guidance on implementation of the FDARA provisions of PREA[4] (referred to as the "FDA Guidance on FDARA Implementation" elsewhere in this document; see Appendix A). This guidance describes the regulatory considerations relating to the FDA interpretation of the term "molecular target", considerations used to determine target relevance, the process utilized for construction and maintenance of molecular target lists, and recommendations regarding the content of initial pediatric study plans (iPSPs) submitted to address the FDARA requirements. The guidance also provides information reflecting FDA's thinking with respect to the need for consideration of innovative study designs and international collaboration in implementation of FDARA given the rarity of pediatric cancers and the high unmet medical need for more effective and safer treatments.

[4]FDA Guidance for Industry: FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act. May 2021. https://www.fda.gov/media/133440/download

Considerations Regarding Molecular Targets and Target Relevance

For purposes of section 505B of the FD&C Act, the FDA generally interprets a "molecular target" in cancer drug development as a molecule in human cells (either normal or cancer cells) that is intrinsically associated with a particular malignant disease process such as etiology, progression, and/or drug resistance. For a molecule to be considered a molecular target for purposes of section 505B, there should be evidence that addressing (i.e., binding to, interacting with) the molecule with a drug produces a measurable effect on a cancer in vivo or in vitro which may translate clinically to a favorable objective change in the disease process. An example of what FDA currently considers to be a molecular target for purposes of section 505B is the CD19 antigen on B cell precursor malignancies, wherein exposure of antigen-positive tumor cells to anti-CD19 antibodies, bi-specific antibodies, antibody-drug conjugates, or specifically engineered cell products, results in tumor cell killing.

FDA, in consultation with the National Cancer Institute and members of the internal committee established under section 505C of the FD&C Act, the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee, maintains a publicly accessible list of molecular targets that are considered to be substantially relevant to the growth or progression of a pediatric cancer and that may trigger the requirements for pediatric investigations.[5] Of note, a molecular target to which a specific drug is directed is not required to be on "The Relevant Molecular Target List" in order for FDA to require a clinical evaluation of the drug in the pediatric population.

There is also a separate list of molecular targets that are considered "non-relevant" to the growth or progression of pediatric cancers and that could warrant a waiver of pediatric study requirements.[6] As part of the requirements of FDARA, FDA periodically updates the lists of relevant and non-relevant molecular targets and encourages public comments on the published lists.[7]

[5] The Relevant Molecular Target List. https://www.fda.gov/media/161463/download?attachment
[6] The Non-Relevant Molecular Target List. https://www.fda.gov/media/161462/download?attachment
[7] Docket for public comments: https://www.regulations.gov/document/FDA-2018-N-3633-0001

Initial Pediatric Study Plans for Oncology Products

iPSP Preparation and Content

The intent of the pediatric study plan (PSP), as required under PREA, is to identify necessary pediatric studies early in drug development and to begin planning for these studies. As recommended in the FDA Guidance on FDARA Implementation, sponsors should make efforts to initiate pediatric nonclinical investigations early in the development timeline of a new molecularly targeted drug. An appropriate pediatric pre-clinical model should be used whenever such a relevant pediatric model is available to evaluate proof-of-concept for the proposed molecularly targeted pediatric cancer investigation. These may include, but are not limited to, the following models derived from a tumor or tumors that occur in children: cell lines; xenografts, including patient-derived xenografts and orthotopic xenografts; and organoids. Sponsors are also encouraged to collaborate with academic and other investigators in pediatric pre-clinical testing consortia, such as the NCI-supported Pediatric Preclinical In Vivo Testing (PIVOT) program and related activities and groups.

FDA also recommends collaboration with recognized subject matter experts, including those involved in clinical trial networks, academic investigators, and patient advocates early in the development of the iPSP to develop an appropriate clinical rationale and scientifically rigorous study design. FDA anticipates that this will facilitate assessment of the level of stakeholder interest in conducting pediatric trials of specific molecularly targeted drugs and promote feasibility and efficiency of molecularly targeted investigations required under FDARA in the pediatric patient population proposed for enrollment.

An iPSP for a molecularly targeted oncology drug must include an outline of the planned pediatric study or studies, and additional elements, as outlined in the FDA Guidance on FDARA Implementation (Appendix A). FDA grants waivers or deferrals for a molecularly targeted pediatric cancer investigation, when appropriate, when the criteria set forth in section 505B(a)(5) of the FD&C act are met. Although decisions about each application are made based on the information supporting a given pediatric study plan, a full or partial waiver of the requirement to conduct a molecularly targeted pediatric cancer investigation may be appropriate in the following

circumstances (note this is not a comprehensive list of circumstances that may provide grounds for a full or partial waiver):

- If known or strongly suspected serious toxicity of a drug precludes its use in all or one or more pediatric age groups
- If there are known or strongly suspected severe developmental toxicities which may present an unreasonable risk to pediatric patients of a particular maturational stage
- When a sponsor is not able to develop an appropriate pediatric formulation for an age group
- For studies of subsequently developed (i.e., later-generation) products with the identical mechanism of action when ongoing, competing studies in the pediatric population are being or have been conducted and when there is no convincing evidence that the new active ingredient would provide a superior pharmacologic, toxicity, or activity profile when compared to products with the same molecular mechanism of action already studied or under investigation, potentially resulting in a very small number of patients available to participate in a new investigation
- When a drug or drugs with the same mechanism of action directed at the same molecular target expressed in the same cancer(s) in children has/have failed to demonstrate evidence of activity.

The FDA Guidance on FDARA implementation also describes circumstances that may support a request for deferral of submission of reports on the molecularly targeted pediatric cancer investigation.[8] For example, FDA may consider granting a deferral appropriate if one of the following circumstances apply:

- If the pediatric study(ies) should be delayed until additional safety or effectiveness data have been collected (including data from planned or ongoing proof of concept studies in relevant pediatric nonclinical models)
- Until an appropriate pediatric formulation is available (provided due diligence in formulation development is undertaken)

[8] FDA Guidance for Industry: FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act. May 2021. https://www.fda.gov/media/133440/download

- If the drug is ready for approval for use in adults before the pediatric study(ies) is completed.

Considerations For Pediatric Oncology Drug Development

Timely enrollment and conduct of clinical trials in pediatric oncology have been long-standing challenges due to limited patient populations, and the FDA has taken steps intended to help address these challenges. For example, FDA has issued guidances that include recommendations to broaden eligibility criteria to permit enrollment of adolescent patients in adult oncology trials when scientifically appropriate,[9] use of innovative study designs and statistical approaches,[10,11,12] use of pharmacokinetic/pharmacodynamic modeling and simulation,[13] and international collaboration[14].

Drug developers may consider a variety of ways to pursue early pediatric assessment of drugs directed at a relevant molecular target, including but not limited to those described below.

- Adolescent patients should be considered for inclusion in adult oncology trials at all relevant stages of development when the histology and biologic behavior of the cancer(s) being studied is the same as, or the molecular target of the drug is relevant to, the cancer(s) in both adult and adolescent patients (provided that there are not specific scientific, safety or developmental considerations that would preclude enrolling adolescents). As systemic exposure and clearance of a product is generally similar in adults and adolescents after accounting for the effect of body size on pharmacokinetics, it is often feasible to lower the age requirement of an adult trial to 12 years.

[9] FDA Guidance for Industry: Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials. March 2019. https://www.fda.gov/media/113499/download
[10] FDA Guidance for Industry: Rare Diseases: Considerations for the Development of Drugs and Biological Products. December 2023. https://www.fda.gov/media/119757/download
[11] FDA Guidance for Industry: Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products. August 2023. https://www.fda.gov/media/171667/download
[12] FDA Guidance for Industry: Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products. February 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-design-and-conduct-externally-controlled-trials-drug-and-biological-products
[13] FDA Guidance for Industry: E11A Pediatric Extrapolation. August 2022. https://www.fda.gov/media/161190/download
[14] FDA Guidance for Industry: FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act. May 2021. https://www.fda.gov/media/133440/download

- A pediatric cohort can be included in the expansion phase of an adult clinical trial investigating a target that also occurs in a specific pediatric tumor(s), thereby enabling earlier development in children without having to initiate a dedicated pediatric trial and leveraging resources of existing global studies at multiple clinical sites, enhancing enrollment and utilizing infrastructure that is already in place.
- Tissue agnostic drug development[15] has the potential to provide pediatric patients more timely access to safe and effective targeted therapies that are effective against an oncogenic driver that is essential to the growth of multiple cancers of varying histologies. Investigation of targeted agents in diverse cancers that share a genetic aberration (e.g., neurotrophic receptor tyrosine kinase (NTRK)-fusion positive tumors) or inclusion of pediatric cohorts in adult trials that share a molecular target with pediatric cancers allows for simultaneous study and potential approval of an agent across multiple tumor histologies, resulting in a more widespread impact on patients, particularly those with rare tumor types.
- Master protocols, in the form of basket, umbrella and platform trials, are being utilized more often in pediatric cancer drug development. Such pediatric precision oncology trials are generally designed to permit streamlined and potentially adaptive biomarker-driven clinical trials while saving time, cost and other resources.
- Model informed drug development (MIDD) can be useful to predict clinical outcomes, inform clinical trial designs, support evidence of effectiveness, optimize dosing, predict product safety, and evaluate potential adverse events. MIDD approaches may also provide a starting point for pediatric drug development and, in some disease areas, inform dosing in pediatrics[16].

European Regulations and International Multistakeholder Collaboration

Because of the limited number of patients diagnosed with pediatric malignancies who may be eligible to enroll in clinical trials, particularly with the subdivision of pediatric cancers into smaller

[15]FDA Draft Guidance for Industry: Tissue Agnostic Drug Development in Oncology. October 2022. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/tissue-agnostic-drug-development-oncology

[16] FDA Draft Guidance for Industry: General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products September 2022 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-clinical-pharmacology-considerations-pediatric-studies-drugs-including-biological-products

subsets based on tumor molecular characteristics, international multistakeholder collaboration to facilitate the conduct of global pediatric clinical trials has become increasingly important. Prioritization of drugs of interest in general and for specific pediatric cancers, especially for drugs of the same class, requires global collaboration to prevent duplication of studies and competition for scarce patients.

According to current European Union regulation, the obligation to conduct a paediatric investigation plan (PIP) for studies in children is waived in certain situations, such as when an adult product is intended for a disease that does not occur in children. However, a proposal for a revision of this regulation was published in 2023[17] and describes potential changes to PIPs for drug products for children, based on the product's mechanism of action. Under this proposal, the product will be required to be studied in children in cases where a particular molecule may be efficacious against a disease in children that is different from the one for which it was initially designed for use in adults due to its mechanism of action.

In order to avoid to exposing children to unnecessary clinical trials, the proposal states that the obligation to agree and conduct pediatric studies in children should be waived when the drug product is likely to be ineffective or unsafe in part or all of the pediatric population, the specific product does not represent a significant therapeutic benefit over existing treatments for children, or the disease for which the product is intended occurs only in adult populations. However, if the product is expected to be effective against a different disease in children than in adults due to its molecular mechanism of action, the obligation will be maintained. In addition to increasing the number of drug products adequately studied for use in children, this proposal is also expected to promote innovation and research in pediatric oncology. Although the European Medicines Agency (EMA) is not involved in the legislative process for negotiating the current proposal, the Agency will be tasked with implementing its requirements once agreed upon.

[17] Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/20. https://eur-lex.europa.eu/resource.html?uri=cellar:e3f40e76-e437-11ed-a05c-01aa75ed71a1.0001.02/DOC_1&format=PDF

These proposed changes to European Union regulation largely align with the current requirements under FDARA and will likely create the potential for increased collaboration between the agencies. There are several existing channels through which coordinated global approaches are facilitated, described below, with additional details in Appendix A of this document.

- Pediatric Cluster Teleconferences: Informal teleconferences held between the FDA and the EMA, Health Canada, the Japanese Pharmaceutical and Medical Devices Agency, and the Australian Therapeutic Goods Administration occur at least monthly. These teleconferences, coordinated by FDA's Office of Pediatric Therapeutics, provide opportunities for high-level scientific discussion of issues relating to development of specific drug products. Relevant documents and information are shared between participating regulatory agencies under the terms of existing confidentiality agreements. Sponsors are informed of specific comments resulting from the discussions and may receive details of the discussions after the teleconference.
- Common Commentary Process: This process was established by FDA and the EMA to inform sponsors of the outcome of scientific exchanges related to select drug products or topics discussed at Pediatric Cluster teleconferences. The Common Commentary is a non-binding document that summarizes the discussion and generally includes recommendations discussed during the Pediatric Cluster teleconference. After review and clearance by both agencies, the Common Commentary document is shared with the sponsor. FDA considers this a useful mechanism to facilitate provision of timely, high-level advice regarding design concepts for iPSPs and Pediatric Investigation Plans (PIPs) and to enable alignment of this advice, when possible. The FDA and EMA have issued a document summarizing key issues commonly requested by the respective regulatory agency on pediatric oncology development plans.[18]
- Formal Parallel Scientific Advice (PSA): Provides a formal mechanism for provision of concurrent exchange of advice from EMA assessors and FDA reviewers with sponsors on scientific issues to optimize drug development. This interaction can be initiated by the

[18] Common Commentary – EMA/FDA. Common issues requested for discussion by the respective agency (EMA/PDCO and FDA) concerning paediatric oncology development plans (Paediatric Investigation Plans [PIPs] and initial Pediatric Study Plans [iPSPs]). March 2021. https://www.fda.gov/media/147197/download?attachment

commercial sponsor to present their overall product development with both Agencies concurrently and is not limited to the pediatric program for that drug.

Additionally, FDA encourages participation in international multi-stakeholder meetings such as the Pediatric Strategy Forums organized by the ACCELERATE Platform and other international meetings or conferences which bring sponsors, investigators, patient advocates, and regulators together to discuss drug development strategies for pediatric patients with cancer. The FDA also hosts minisymposia with external constituents, often including international regulators to discuss disease-specific research strategies, without discussing individual drug development programs.

Early Results of the RACE for Children Act

FDARA 2017 included a provision for the GAO to review the effectiveness of the pediatric study requirements enacted by the RACE for Children Act.[19] To this end, the GAO conducted a review of data provided by FDA, analyzing 85 iPSPs for new molecularly targeted adult cancer drugs that FDA received, reviewed, and agreed to during the period from August 18, 2020 (the date amended PREA requirements under FDARA came into effect) through August 18, 2022. These data were largely used to determine the number of pediatric cancer studies sponsors planned to conduct and the number expected to receive waivers and how these would have compared with the number of pediatric studies required pre-RACE Act. A summary of the data is provided in Table 1. A total of 32 iPSPs (5 for approved drugs and 27 for drugs under development) were submitted to the FDA with a plan to conduct a pediatric study during the evaluated timeframe. Under the original provisions of PREA (e.g., before the implementation of the RACE Act), FDA would have agreed to a plan to request a full waiver of the requirement to conduct a pediatric study under PREA or the application would have been exempt from PREA requirements for 25 (78%) of the 32 products.

[19] Pediatric Cancer Studies: Early Results of the Research to Accelerate Cures and Equity for Children Act. GAO-23-105947 Published Jan 31, 2023. https://www.gao.gov/products/gao-23-105947

Table 1: Planned Pediatric Studies from August 18, 2020, through August 18, 2022

Planned pediatric studies	Approved drugs	Drugs under development
Under RACE Act (n)	5	27
Total	32	
Would have received waiver or exemption pre-RACE Act (n)	5	20
Total	25	
Reason would have received waiver/exemption pre-RACE Act (n)		
Orphan status	4	17
Condition rarely/never occurs in pediatric patients	1	3

During this same timeframe, 53 iPSPs were submitted in which FDA agreed with the sponsor's plan to request a full waiver of pediatric study requirements. For 29 (55%), necessary studies were considered impossible or highly impracticable to conduct given the small number of patients, for 23 (43%), the drug was not considered to represent a meaningful therapeutic benefit over existing therapies for pediatric patients, and for 1 (2%), the evidence strongly suggested that the drug would be unsafe or ineffective in all pediatric age groups.

As part of their assessment, GAO also conducted interviews with FDA officials and a sample of 14 nonfederal stakeholders selected to include a broad range of perspectives, including those of pediatric cancer advocacy groups, researchers, industry groups, and drug sponsors.

The GAO concluded that early results indicate that the RACE act has contributed to an increase in the number of planned studies to test certain molecularly targeted drugs in pediatric patients, but that it was too soon to determine whether the RACE act will increase the number of drugs approved to treat pediatric cancers.

In an updated analysis, the FDA Office of Oncologic Diseases issued a total of 131 agreed iPSPs for investigational new molecularly targeted drugs from August 18, 2020, through April 18, 2024. Of the 131 agreed iPSPs, 76 (58%) included plans for a full waiver, 37 (28%) included plans for a

partial waiver and deferral, 11 (8%) included plans for a deferral, and 7 (5%) included plans for a partial waiver of submission of a molecularly targeted pediatric cancer investigation(s). There was a total of 97 agreed iPSPs for a new molecularly targeted drug directed at a target considered substantially relevant to one or more pediatric cancers; of these, FDA agreed to a planned request for a full waiver in 42 (43%), and 55 (57%) contained a plan for a molecularly targeted pediatric cancer investigation. Among the 55 agreed iPSPs that included a plan for a molecularly targeted pediatric cancer investigation, 47 (85%) included a plan to request a deferral.

Over the same time period, the Office of Oncologic Diseases issued 22 postmarketing requirements (PMR) for pediatric studies under PREA as part of the approval for 17 unique drug applications (5 approvals contained 2 PREA PMRs). Fourteen of the 17 approved applications were original applications for new targeted therapies subject to the FDARA provisions of PREA. Molecularly targeted pediatric cancer investigations are deferred pending availability of additional clinical data or data from proof-of-concept studies in relevant pediatric models for 3 targeted drugs.

Based upon the updated FDA analysis of iPSPs for molecularly targeted drugs and the results of the GAO audit, it appears that the RACE act has contributed to an increase in the number of planned studies to test certain molecularly targeted drugs in pediatric patients with cancer. However, given the amount of time needed to design and conduct clinical trials evaluating new drugs for the treatment of pediatric cancers, it is too early to determine the extent to which implementation of the FDARA provisions of PREA will advance the development of new treatments for pediatric cancers. Continued focus on multistakeholder engagement and international collaboration is necessary to thoughtfully and fully leverage the potential of this legislation and facilitate timely investigation of the molecularly targeted drugs that hold the most potential to result in a meaningful improvement over current standard of care for pediatric patients with cancer.

Draft Points of Consideration Related to Implementation of PREA Requirements for Molecularly Targeted Pediatric Cancer Investigations under FDARA

1. Please discuss your perspectives on how FDARA is impacting pediatric oncology and development of new molecularly targeted therapies for pediatric patients with cancer. Describe positive effects or challenges associated with the legislation, and thoughts regarding how to improve its implementation.

2. Please discuss factors that should be considered when determining whether nonclinical proof-of-concept studies should be conducted prior to initiating a molecularly targeted pediatric cancer investigation in pediatric patients with cancer. Also discuss the degree of preclinical antitumor activity that would be considered sufficient to warrant clinical development.

3. Please discuss the role of pediatric clinical trial networks and international collaboration in efficient development of new medical products for pediatric patients with cancer including identification of relevant molecular targets, specific efforts that have been most valuable, and ideas for improved collaboration. Additionally, please discuss barriers to the conduct of international trials in pediatric oncology and potential ways to address these barriers.

APPENDIX A

2021 FDA Guidance for Industry: *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act*

FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2021
Procedural

FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act

Guidance for Industry

Additional copies are available from:
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Contains Nonbinding Recommendations

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Contains Nonbinding Recommendations

FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act Guidance for Industry[1]

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 staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance addresses early planning for pediatric evaluation of certain molecularly targeted oncology drugs[2] for which original New Drug Applications (NDAs) and Biologics License Applications (BLAs)[3] are expected to be submitted to the FDA, in accordance with section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (also referred to as the Pediatric Research Equity Act, or PREA) as amended by the FDA Reauthorization Act of 2017 (FDARA).[4] Early pediatric evaluation of certain molecularly targeted oncology drugs as required by section 505B(a)(1)(B) of the FD&C Act is expected to accelerate the creation of a pediatric development plan and ultimately the development of promising drugs for pediatric patients.

This guidance addresses the implementation of amendments made by FDARA section 504 to section 505B of the FD&C Act regarding molecularly targeted oncology drugs. This guidance does not address in detail the 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).

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations,

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[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 and drug products include drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (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).

[3] For additional information about PREA requirements and proposed biosimilar products, see Q.I.16. in the draft guidance for industry *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act* (Revision 2) (December 2018) (when final, this guidance will represent FDA's current thinking on this topic).

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

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

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. Specifically, if an original NDA or BLA is for a new active ingredient, and the drug that is the subject of the application is intended for treatment of an adult cancer and directed at a molecular target FDA determines to be substantially relevant to the growth or progression of a pediatric cancer, reports on the molecularly targeted pediatric cancer investigation required under section 505B(a)(3) of the FD&C Act must be submitted with the marketing application, unless FDA waives or defers the requirement.[5] FDARA thus created a mechanism to require evaluation of certain novel drugs that may have the potential to address an unmet medical need in the pediatric population (specifically, pediatric cancer patients <17 years of age).[6] Timely investigation in pediatric patients 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.

Advances in the understanding of the molecular etiology and genetic epidemiology of human cancer have transformed the paradigm of cancer drug development; molecularly targeted drugs have advanced the concept of precision medicine in oncology. However, the extension of this scientific development to pediatric cancers has been both delayed and limited due in part to the fact that the requirements for pediatric assessments of new cancer drugs have historically been based on indication (i.e., requirements for assessment of the safety and effectiveness of a drug for intended or approved indications in relevant pediatric subpopulations). Generally, the types of cancers in pediatric patients and adults differ in etiology, biology, organ of origin, and natural history, which has sometimes resulted in pediatric trials not being required under the pre-FDARA iteration of PREA (e.g., the requirements were waived because the drug in question was being developed for a cancer that rarely or never occurs in children, thereby making the necessary studies impossible or highly impracticable). In addition, new drugs developed for rare cancers which do occur in both adults and pediatric patients are generally exempt from PREA assessment requirements under section 505B(a)(1)(A) because they are for indications for which orphan designation has been granted (see section 505B(k)(1) of the FD&C Act).

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[5] Sections 505B(a)(1)(B) and 505B(a)(3)(C) of the FD&C Act. FDA anticipates that there may be additional considerations for proposed biosimilar product applicants. For additional information about PREA requirements and proposed biosimilar products, see Q.I.16. in the draft guidance for industry *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act* (Revision 2) (when final, this guidance will represent FDA's current thinking on this topic).

[6] The amendments to 505B of the FD&C Act made by FDARA section 504 are sometimes referred to as The Research Acceleration for Cure and Equity (RACE) for Children Act.

However, malignancies occurring in children and adolescents can harbor the same molecular abnormalities as those found in adult cancers despite differences in site of origin or histology, and therefore, many new targeted oncology drugs may prove effective in the treatment of pediatric patients with cancer, even if the adult cancer indication does not occur in the pediatric population. Large scale pediatric cancer genome sequencing efforts, such as the National Cancer Institute's Therapeutically Applicable Research to Generate Effective Treatments (TARGET) program[7], the Pediatric Cancer Genome Project[8], and the International Cancer Genome Consortium's PedBrain Tumor[9] and ICGC-MMML-seq[10] projects provide evidence that the genetic and epigenetic repertoires of driver gene aberrations may differ between adult and pediatric cancers. A growing body of evidence suggests that genetic and other molecular biological vulnerabilities of certain adult cancers also exist in pediatric cancers.[11, 12] Up to 50% of pediatric cancers have been reported to harbor a potentially druggable event, i.e., a molecular abnormality which can be potentially addressed by a targeted drug already approved for use in adults.[13]

Section 505B of the FD&C Act, as amended by FDARA, requires that any **original** NDA or BLA submitted on or after August 18, 2020, for a new active ingredient, must contain reports on the molecularly targeted pediatric cancer investigation described in section 505B(a)(3) of the FD&C Act, unless the requirement is waived or deferred, 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.[14]

This requirement 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.

A supplemental application will not trigger the requirement to submit reports on the molecularly targeted pediatric cancer investigation described in section 505B(a)(3) of the FD&C Act (see section 505B(a)(1)(B) of the FD&C Act).

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[7] For additional information, see https://ocg.cancer.gov/programs/target (accessed May 18, 2021).
[8] For additional information, see https://www.stjude.org/research/pediatric-cancer-genome-project.html and https://pecan.stjude.cloud/ (accessed May 18, 2021).
[9] For additional information, see http://www.pedbraintumor.org/ (accessed May 18, 2021).
[10] For additional information, see the ICGC data portal at https://dcc.icgc.org (accessed May 18, 2021).
[11] Gröbner SN, Worst BC, Weischenfeldt J, et.al., 2018, The Landscape of Genomic Alterations Across Childhood Cancers, Nature, 555:321-327.
[12] Ma X, Liu Y, Liu Y, et. al., 2018, Pan-Cancer Genome and Transcriptome Analyses of 1,699 Paediatric Leukaemias and Solid Tumours, Nature, 555:371-376.
[13] See footnotes 11 and 12.
[14] Section 505B(a)(1)(B) of the FD&C Act. FDA anticipates that there may be additional considerations for proposed biosimilar product applicants. For additional information about PREA requirements and proposed biosimilar products, see Q.I.16. in the draft guidance for industry *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act* (Revision 2) (when final, this guidance will represent FDA's current thinking on this topic).

The statute directs FDA, in consultation with the National Cancer Institute (NCI), members of the internal committee established under section 505C of the FD&C Act, and the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (ODAC), to establish, publish, and regularly update a list of molecular targets considered, on the basis of data the Agency determines to be adequate, to be substantially relevant to the growth or progression of a pediatric cancer, and that may trigger PREA requirements (see sections 505B(m)(1)(A) and 505B(m)(2) of the FD&C Act).

Molecular targets that are considered "not substantially relevant" to the growth or progression of pediatric cancers, and that would warrant a waiver of molecularly targeted pediatric cancer investigation requirements under PREA constitute a second list (see section 505B(m)(1)(B) of the FD&C Act) (see section III.C for more information regarding the lists). FDA sometimes refers to these as "The Relevant Molecular Target List" and "The Non-Relevant Molecular Target Leading to Waiver List," respectively. It is important to note, however, that the fact that a drug is directed at a molecular target on the "relevant" list does not necessarily mean that submission of reports on the molecularly targeted pediatric cancer investigation described in section 505B(a)(3) of the FD&C Act is required. In some cases, for example, a waiver may be warranted (see section 505B(a)(5) of the FD&C Act). Nor does the absence of the molecular target on the Relevant Molecular Target List necessarily mean that submission of such reports is not required under section 505B(a)(1)(B) of the FD&C Act; the requirement depends, in part, on whether FDA has determined the molecular target to be substantially relevant to the growth or progression of a pediatric cancer but does not depend on the presence of absence of the molecular target on any list. Nevertheless, the lists are a guide to sponsors as they consider development plans for new targeted drugs and early pediatric assessments in light of the amended PREA provisions.

III. REGULATORY CONSIDERATIONS[15]

A. Molecular Target

For purposes of section 505B of the FD&C Act, the Agency interprets a "molecular target" in cancer drug development as a molecule in human cells (normal or cancer cells) that is intrinsically associated with a particular malignant disease process such as etiology, progression, and/or drug resistance. For a molecule to be considered a *molecular target* for purposes of section 505B, there should be evidence that addressing (i.e., binding to, interacting with) the molecule with a drug produces a measurable effect on a cancer in vivo or in vitro which may translate clinically to a favorable objective change in the disease process. An example of what FDA currently considers to be a molecular target for purposes of section 505B is the CD19 antigen on B cell precursor malignancies wherein exposure of antigen positive tumor cells to

[15] While this guidance focuses on requirements related to molecular targets under PREA, FDA also intends to take into account certain of the considerations described in this section of the guidance (e.g., considerations relating to whether a molecular target is substantially relevant to the growth or progression of a pediatric cancer and those relating to innovative study designs for rare cancers), as appropriate, to streamline and improve the Written Request process under section 505A of the FD&C Act, including amendments to Written Requests.

anti-CD19 antibodies, bi-specific antibodies, antibody-drug conjugates, or specifically engineered cell products, results in tumor cell killing.

B. Considerations in the Determination of Relevance

FDA intends to consider all available evidence when determining whether a molecular target is substantially relevant to the growth or progression of pediatric cancer. A specific or minimum evidence standard for determining target relevance is not feasible because of the different classes and characteristics of molecular targets, variability in the existing scientific evidence base among targets, and continuously emerging science. FDA is responsible for determining whether a molecular target is *substantially relevant* for purposes of section 505B of the FD&C Act. Molecular targets that lack sufficient evidence for FDA to determine whether they are "substantially relevant" or "not substantially relevant" will not be included in a target list; however, the lists will be updated regularly[16] to reflect new information regarding the relevance of molecular targets.

Although this list is not exhaustive, one or more of the following considerations may, as appropriate, inform FDA's determination that a molecular target is substantially relevant for purposes of section 505B:

- Acceptable levels of evidence that the target has been shown to be associated with one or more types of cancer which occur in pediatric patients. For targets within a cancer cell lineage, the target is intrinsically or may be differentially expressed in the cancer cells of interest compared to normal site-specific tissues.
- The biological function of the target may be functionally related to the etiology, growth, and therapy resistance of a cancer that occurs in pediatric patients. For a gene abnormality, modulation of the affected gene product or a critical downstream pathway or correction/deletion of the affected gene defect may adversely affect cancer cells.
- Non-clinical in vitro or in vivo evidence of the target in one or more human cancers, especially those occurring in pediatric patients.
    - In vitro activity: Target modulation shows in vitro selectivity for cancer cell lines containing/expressing the molecular target compared to the sensitivity of cell lines not containing/expressing the target
    - In vivo activity: Target modulation shows in vivo activity manifested as stabilization of tumor growth or regression in models of pediatric cancers with the molecular target of interest or relevant adult cancer models
    - In vitro or in vivo activity of drugs in combination: When single agents do not result in target modulation, support for substantial relevance may be found in acceptable levels of evidence for additive or synergistic activity when an agent which effects target modulation is used as part of a biologically rational combination in appropriate in vitro and/or in vivo model systems.
- Clinical activity in adults with specific cancers (including, where available, objective responses and improvement in outcomes), for which direct evidence demonstrates that target modulation by investigational drugs is known to affect tumor growth.

[16] See section 505B(m)(1) of the FD&C Act.

- Predictive biomarkers associated with responsive tumor types which occur in adults and also expressed by cancers that occur in pediatric patients and predict response to target modulation. These may also aid in selection of the appropriate pediatric study population for assessment of a novel, targeted drug.

Data from non-clinical evaluations of a drug's activity in adult tumors can contribute some evidence for the substantial relevance of a target to the growth or progression of a pediatric cancer. Additional evidence, when necessary, can be obtained from non-clinical studies using a pediatric-specific model system. Therefore, efforts should be made to initiate pediatric non-clinical investigations early in the development timeline of a new molecularly targeted drug. An appropriate pediatric pre-clinical model should be used whenever such a relevant pediatric model is available. These may include, but are not limited to, the following models derived from a tumor or tumors that occur in children: cell lines; xenografts, including patient-derived xenografts and orthotopic xenografts; and organoids. Sponsors are encouraged to collaborate with academic and other investigators in pediatric pre-clinical testing consortia, such as the NCI-supported pediatric pre-clinical testing program and related activities and groups.

FDA, with input from NCI, may determine that available evidence demonstrates that a molecular target is not substantially relevant to the growth or progression of pediatric cancer based on, for example, the absence of a biologic rationale for a specific target's function as an oncogenic driver, or a lineage associated target that is not a component of a pediatric cancer cell, or pre-clinical data that demonstrates no tumor cell growth effect by inhibition of the target.

C. Target Lists

A variety of information sources have been examined by FDA and NCI in the development of the Relevant Molecular Target List and the Non-Relevant Molecular Target Leading to Waiver List. These information sources, which include those listed below, have been supplemented by input from international subject matter experts, reviewed by members of the Pediatric Subcommittee of the ODAC, and vetted during public meetings:

- TARGET database (https://ocg.cancer.gov/programs/target)
- St. Jude's Pediatric Cancer Genome Project (https://www.stjude.org/research/pediatric-cancer-genome-project.html)
- St. Jude's PeCan data portal (https://pecan.stjude.cloud/)
- NCI MATCH Trial (https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match)
- INdividualized Therapy FOr Relapsed Malignancies in Childhood-INFORM (https://www.dkfz.de/en/inform/)
- The International Cancer Genome Consortium's (ICGC) PedBrain Tumor (http://www.pedbraintumor.org/
- ClinicalTrials.gov (https://clinicaltrials.gov/)
- Literature search (e.g., PubMed, Embase, and Google scholar). Published data supporting target relevance were considered most informative when independently validated reports of associations between a target and tumor type(s) were found in subsequent peer-reviewed publications. Single case reports of an association between a target and a pediatric cancer without evidence of effect on tumor growth by

interference with the target were considered less informative. Efforts to expand the evidence base of currently published targets and identify additional targets using text-mining algorithms to assess publications for evidence are ongoing in the Office of Clinical Pharmacology Division of Applied Regulatory Science and the Oncology Center of Excellence.

1. The Relevant Molecular Target List

The list includes molecular targets considered, on the basis of data the Agency determines to be adequate, to be substantially relevant to the growth or progression of one or more pediatric cancers (see section 505B(m)(1)(A) of the FD&C Act). Categories may include, for example:

- Targets Related to Specific Gene Abnormalities
- Targets Associated with Cell Lineage Determinants
- Targets on Normal Immune Cells and Cellular Components of the Tumor Microenvironment
- Other Targets Associated with Specific Pathways or Functional Mechanisms of Normal and/or Malignant Cells.

2. The Non-Relevant Molecular Target Leading to Waiver List

The list includes molecular targets of new cancer drugs in development for which pediatric cancer study requirements under PREA will be automatically waived (see section 505B(m)(1)(B) of the FD&C Act). This includes targets for which there are adequate data to determine that the targets are not substantially relevant to the growth or progression of one or more pediatric cancers. FDA anticipates that it will agree with sponsors' plans (as outlined in their initial pediatric study plans (iPSPs)) to request full waivers for pediatric evaluation under section 505B(a)(1)(B) of the FD&C Act of oncology drugs with a molecular target that is on the Non-Relevant Molecular Target Leading to Waiver List.

FDA plans to regularly update the lists based on information from, for example, public workshops or meetings, including meetings of the Pediatric Subcommittee of the ODAC. In addition, the Federal Register Notice [Docket No. FDA-2018-N-3633] published on October 17, 2018, announced the opening of a docket to allow public comment with respect to possible additions to or deletions from the published lists. The Pediatric Subcommittee of the ODAC reviews all such comments.

These lists are available at the following link: **Molecular Target Lists** (https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology).

D. Content of the Initial Pediatric Study Plan and Description of Recommended Study(ies)

Section 505B(e) of the FD&C Act requires applicants subject to PREA to submit an iPSP prior to the submission of an NDA or BLA.[17] Prior to the enactment of FDARA, which added sections 505B(a)(1)(B) and 505B(a)(3) to the FD&C Act, the pediatric study plans for oncology drugs were generally proposals to request waivers for pediatric studies because the adult cancer indications for which a drug was developed often did not occur or occurred only rarely in pediatric patients, making pediatric studies in those indications impossible or highly impracticable.[18] An extensive list of cancer diagnoses occurring almost exclusively in adults thus is included in a list of adult-related conditions that qualify for a waiver of assessments required under section 505B(a)(1)(A) of the FD&C Act because they rarely or never occur in pediatrics.[19] The provisions for PREA mandated studies for oncology drugs under section 505B(a)(1)(B), however, require that certain oncology drugs for adult cancer indications be studied based on the molecular mechanism of action of the investigational drug rather than clinical indication. Therefore, an original application for a new active ingredient that is submitted on or after August 18, 2020, and for which 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 determined to be substantially relevant to the growth or progression of a pediatric cancer, must include reports on the molecularly targeted pediatric cancer investigation described in section 505B(a)(3) of the FD&C Act, unless the requirement is waived or deferred.[20] Applicants subject to this requirement will be required to submit iPSPs outlining the planned pediatric study or studies, in accordance with section 505B(e) of the FD&C Act. Sponsors are 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 the FDA's Oncology Center of Excellence and sponsors may submit a request for an early advice meeting through the appropriate review division or office (see section III.D.3).

1. iPSP content

Details of the required iPSP contents and format can be found in section 505B(e)(2)(B) of the FD&C Act. Additionally, FDA has issued a guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (the iPSP Guidance) (July 2020). The iPSP Guidance describes, among other things, FDA's recommendations regarding iPSP content. A suggested iPSP template is included in an appendix of the iPSP Guidance. An iPSP for a molecularly targeted oncology

[17] See sections 505B(a)(1)(A), 505B(a)(1)(B), and 505B(e)(1) of the FD&C Act.
[18] See section 505B(a)(5) of the FD&C Act.
[19] See the list of "Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics" at https://www.fda.gov/media/101440/download.
[20] See section 505B(a)(1)(B) of the FD&C Act. FDA anticipates that there may be additional considerations for proposed biosimilar product applicants. For additional information about PREA requirements and proposed biosimilar products, see Q.I.16. in the draft guidance for industry *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act* (Revision 2) (when final, this guidance will represent FDA's current thinking on this topic).

drug must include an outline of the planned pediatric study or studies[21] and should include the following elements, where applicable:

- Description of the cancer(s) in the pediatric population for which the drug may or may not warrant early evaluation based on the molecular mechanism of action of the drug
- Overview of the drug product including mechanism of action and the molecular target to which the drug is directed
- Overview of planned extrapolation, where appropriate, of effectiveness in adults to the pediatric population
- Planned request for drug-specific waivers and partial waivers with justification
- Planned request for deferrals of pediatric studies
- Tabular summary of proposed non-clinical and clinical studies
- Age-appropriate formulation including details of existing/planned excipients
- Non-clinical studies, including, for example:
  - Data from proof-of-concept studies (planned and completed) for the adult development program, if relevant
  - Data from proof-of-concept studies in pediatric tumor models to support clinical studies in pediatric patients
- Adult clinical data and any pediatric clinical data, if available, to support the pediatric study or studies
- Planned pediatric safety, dosing, and preliminary efficacy study(ies) and other studies that the sponsor may plan to include as part of a broad or focused pediatric development program
- Timeline of pediatric development plan
- Agreements for pediatric studies with other regulatory agencies

2. Description of recommended study or studies to be included

A study(ies) to be described in the iPSP under section 505B(e) of the FD&C Act should evaluate dosing based on PK, allometric scaling of adult PK, or physiologically-based PK-modeling; safety; and preliminary efficacy. The study(ies) should typically be a non-hypothesis-testing, single-arm study(ies) using standard response assessments such as overall response rate and duration of response at a minimum.

Objectives of the study or studies described in the iPSP under section 505B(e) of the FD&C Act should include the following:

- Evaluating tolerability and identifying dose limiting toxicities in pediatric patients
- Evaluation of PK across various age groups as appropriate
- Definition of the pediatric Recommended Phase 2 Dose(s) (RP2D) and schedule
- Preliminary assessment of activity (defined as overall response rate (ORR) or other agreed relevant endpoint) across the entire study population, in biomarker enriched

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

population(s), in pre-specified disease cohorts, or in adaptive design settings, in successively opened disease cohorts as evidence of activity warrants

Sample size may vary but should support the study objectives. Factors to consider should include the frequency of the molecular target expected across pediatric cancers in general and/or within a specified histology or sub-type, the number of dose levels to be evaluated to identify a recommended pediatric dose, and statistical considerations including estimated response rate that would support further development, recognizing that in some circumstances, the numbers of patients included in studies may be too small to provide statistically significant differences.

More definitive evaluation of a product, if warranted based upon the initial pediatric evaluation(s) described in the iPSP, may be the subject of a proposed pediatric study request (PPSR). Following review of the PPSR, which may include the study(ies) described in the agreed iPSP, and discussions with the sponsor, FDA may issue a Written Request, if appropriate.[22] Although not a requirement, planning for and including in the iPSP an additional study(ies), contingent upon the results of the required molecularly targeted pediatric cancer investigation described in section 505B(a)(3) of the FD&C Act, may facilitate early discussions between the sponsor and FDA regarding a comprehensive pediatric development plan, despite the fact that the timelines for submission and review for iPSPs and PPSRs differ.

Requirements relating to the protection of human subjects in FDA-regulated clinical investigations are set forth in 21 CFR parts 50 and 56; additional safeguards for children are included in 21 CFR part 50, subpart D (*Additional Safeguards for Children in Clinical Investigations)*. Institutional review boards (IRBs) are required to review clinical investigations involving children as subjects covered by 21 CFR part 50, subpart D and approve only those clinical investigations that satisfy the criteria and other conditions set forth in subpart D (see 21 CFR 50.50). Unless the risks of a molecularly targeted drug in a clinical investigation are no more than a minor increase over minimal risk (see 21 CFR 50.53), the administration of a molecularly targeted drug in children must offer the prospect of direct benefit to individual subjects, the risk must be justified by the anticipated benefit to the subjects, and the anticipated risk-benefit profile must be at least as favorable as that presented by available alternative approaches (see 21 CFR 50.52). Additionally, adequate provisions must be made to obtain the permission of the parents or guardians and, if appropriate, the assent of the children (see 21 CFR 50.52(c) and 50.55).

FDA recommends collaboration with recognized subject matter experts, including those involved in clinical trial networks, academic investigators, and patient advocates early in the development of the iPSP to develop an appropriate clinical rationale and scientifically rigorous study design in clinically relevant diagnoses or subgroups of patients with the same diagnosis, or groups defined by biomarker detection of the target of interest irrespective of specific diagnosis. FDA anticipates that this will facilitate assessment of the feasibility of clinical evaluations in the targeted patient population. If a diagnostic test (e.g., for a biomarker) is utilized as part of a study, early discussion with FDA's Center for Devices and Radiological Health (CDRH) is encouraged regarding Investigational Device Exemptions and the use of companion or complementary diagnostics.

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

3. Early advice on pediatric development meetings for oncology projects subject to the amended provisions of section 505B of the FD&C Act

Sponsors planning to submit applications may request a meeting[23] with the Oncology Center of Excellence Pediatric Oncology Program, including, for example, pediatric oncologists from review divisions in the Office of Oncologic Diseases in CDER or the Office of Tissue and Advanced Therapies in CBER, and other disciplines (e.g., clinical pharmacology; statistics; pharm tox; and chemistry, manufacturing, and controls (CMC), as appropriate). These meetings are intended to provide an opportunity to discuss the Agency's current thinking about the relevance of a specific target and the expectations for early assessment in the pediatric population unless justification for a waiver or deferral can be provided. The cover letter for these meeting requests should clearly state "REQUEST FOR FDARA iPSP MEETING." In addition, sponsors should include a briefing document with the meeting request that includes all relevant information, including the investigational drug's mechanism of action and the molecular target to which it is directed, the prevalence of the molecular target in one or more cancers that predominate in the pediatric age group or the incidence in children of the rare cancer for which the drug is being developed, known potential developmental toxicities from non-clinical studies, extant adult efficacy and safety data, detailed chemical composition of the product's active and inactive ingredients, current formulation and plans for a pediatric appropriate formulation if available, any anticipated unique toxicities for children, and the status of any regulatory filings with other health authorities. Please contact the review division or office to schedule these meetings and for any questions regarding these meetings.[24]

E. Oncology Drug Combination Regimens

As discussed above, section 505B(a)(1)(B) of the FD&C Act applies to an original application for a new active ingredient, if the drug that is the subject of the application is intended for the treatment of an adult cancer and directed at a target that FDA determines to be substantially relevant to the growth or progression of a pediatric cancer. Importantly, this requirement applies to an original NDA or BLA for a new active ingredient for use in an oncology drug combination regimen with a previously approved product, provided that the other criteria in section 505B(a)(1)(B) of the FD&C Act are satisfied. Thus, for such applications, an iPSP must be submitted to the Agency containing an outline of the pediatric study or studies (of the new active ingredient or the combination regimen, as appropriate) that the applicant plans to conduct and any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting information (section 505B(e) of the FD&C Act).

[23] See section 505B(e)(2)(C)(i)(I) of the FD&C Act, which describes early meetings on pediatric study plans for drugs intended to treat a serious or life-threatening disease or condition.

[24] Sponsors should consult the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (December 2017) or the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products* (June 2018), when finalized, to help ensure open lines of dialogue before and during their drug development process. When final, these guidances will represent the FDA's current thinking on the topics therein.

F. Additional Consideration for Rare Cancers

Given the challenges of stand-alone trials of investigational drugs in pediatric patients with a rare cancer associated with a specific molecular target, FDA encourages innovation in study design, which may, as appropriate, include Bayesian adaptive designs, the use of external controls derived from patient-level data, the use of real world evidence, and the use of alternative outcome measures such as patient reported outcomes (PROs) and pediatric PRO Common Terminology Criteria for Adverse Events (CTCAE). FDA also encourages sponsors to request feedback from FDA regarding plans for trial design and endpoints. Although not an exhaustive list, the following scenarios may provide some options for maintaining the objective of early pediatric assessment of drugs directed at substantially relevant targets and satisfy requirements of section 505B of the FD&C Act in situations where a conventionally designed pediatric trial may be inefficient or extremely difficult to conduct given the scarcity of affected pediatric patients.

1. Pediatric cohorts in existing adult trials

When a target being investigated in an adult clinical trial also occurs in a specific pediatric tumor(s), sponsors may consider including a pediatric cohort during the initial or expansion phase of a clinical trial. Including a pediatric cohort in an existing adult trial allows for the inclusion of a specific pediatric population earlier in development of a targeted drug without having to open an entirely new pediatric trial. This allows sponsors to use already existing clinical sites and resources of the ongoing clinical trial, thus minimizing the resources and infrastructure required to study the targeted drug in the pediatric population.[25, 26]

2. Embedded pediatric trials

Embedding pediatric trials within an existing trial in adults may be particularly useful for the evaluation of drugs with a molecular target that is rare in the pediatric population. Embedding a pediatric trial within an adult trial could leverage resources of pre-existing global studies at multiple sites, improving enrollment. The embedded study could also take advantage of existing infrastructure arrangements (e.g., adding a sub-investigator rather than initiating a new study, having consistent personnel) within study sites for adult patients.

3. Adolescent patients

When the molecular target of the drug is relevant to cancers in both adult and adolescent patients, sponsors may consider including adolescent patients by lowering the age requirement for enrollment. Systemic exposure and clearance of drugs are generally similar in adolescent and adult patients after taking into account the effect of body size on pharmacokinetics. Inclusion of adolescents in adult trials, when appropriate, would allow adolescent patients access to investigational drugs with potential for benefit, and generate clinical trial data in this population

[25] See draft guidance for industry *Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics* (August 2018). When final, this guidance will represent the FDA's current thinking on this topic.

[26] See guidance for industry and IRBs *Cancer Clinical Trial Eligibility Criteria: Minimum Age Considerations for Inclusion of Pediatric Patients* (July 2020).

that could be included in prescribing information for safe and effective use at the time of approval.[27]

In some instances, efficacy in adolescent patients may be extrapolated from adult data; however, adequate approaches to evaluate safety in this population are required, regardless of whether adolescents are included in adult studies or whether they are studied separately as part of the broader pediatric population.[28]

4. Tissue/histology agnostic development

Tissue agnostic studies may facilitate the development of targeted therapies in multiple pediatric cancers with shared genetic aberrations (e.g., MSI-H/dMMR tumors, NTRK-fusion positive tumors) or may incorporate pediatric cohorts in adult studies which share genetic aberrations with pediatric cancers.

5. Master protocols

Master protocols, including basket and umbrella trials, may be appropriate mechanisms to assure efficiency in light of the limited number of available patients for study and to minimize the number of pediatric patients who may be exposed to ineffective therapies. Such master protocols may involve pre-competitive discussions, negotiations, and planning by multiple sponsors.[29] FDA encourages sponsors and investigators to consider this approach given the large number of similar- and same-in-class products to avoid unnecessary competition and duplication.

6. Model informed drug development (MIDD)

FDA encourages integration of MIDD approaches into pediatric cancer drug development as appropriate. MIDD has been applied to predict clinical outcomes, inform clincial trial designs, support evidence of effectiveness, optimize dosing, predict product safety, and evaluate potential adverse events. MIDD approaches may provide a starting point for pediatric drug development and, in some disease areas, inform dosing in pediatrics.

G. Basis for Planned Waivers and Deferrals

There may be circumstances, including those listed below, when a waiver or deferral may be appropriate for a molecularly targeted pediatric cancer investigation.[30]

[27] See the guidance for industry *Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials* (March 2019).
[28] See sections 505B(a)(2)(B) and 505B(a)(3)(B) of the FD&C Act.
[29] See draft guidance for industry *Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics* (September 2018). When final, this guidance will represent the FDA's current thinking on this topic.
[30] See sections 505B(a)(3)(C), 505B(a)(4) and 505B(a)(5) of the FD&C Act.

1. Waivers

FDA will grant a full or partial waiver, as appropriate, of the requirement to submit reports on the investigation when the criteria set forth in section 505B(a)(5) of the FD&C Act are met. Although decisions about each application will be made based on the facts of that application, FDA anticipates that a full or partial waiver of such requirement may be appropriate in the following circumstances (note that this is not an exhaustive list):

- If known (e.g., from studies conducted in adult humans or animals) or strongly suspected (e.g., based on target biology) serious toxicity of a drug precludes its use in all or one or more pediatric age groups.
- If there are known (e.g., from studies conducted in adult humans or animals) or strongly suspected (e.g., based on target biology) severe developmental toxicities which may present an unreasonable risk to pediatric patients of a particular maturational stage.
- When a sponsor is not able to develop an appropriate pediatric formulation for an age group.
- For studies of subsequently developed (i.e., later-generation) products with the identical mechanism of action when ongoing, competing studies in the pediatric population are being or have been conducted and when there is no convincing evidence that the new active ingredient would provide a superior pharmacologic, toxicity, or activity profile when compared to products with the same molecular mechanism of action already studied or under investigation, potentially resulting in a very small number of patients available to participate in a new investigation.
- When a drug or drugs with the same mechanism of action directed at the same molecular target expressed in the same cancer(s) in children has/have failed to demonstrate evidence of activity.

2. Deferrals

FDA may defer submission of reports on the investigation when the criteria set forth in section 505B(a)(4) of the FD&C Act are met. Although decisions about each application will be made based on the facts of that application, a deferral of submission may be appropriate in the following circumstances (note that this is not an exhaustive list):[31]

- If the pediatric study(ies) should be delayed until additional safety or effectiveness data have been collected; for example:
  - until sufficient non-clinical evidence demonstrates tumor response to the known inhibition of a defined molecular target(s) or pathway.
  - when there is uncertainty regarding whether the activity of a drug occurs only in combination with another agent, until such time that one or more biologically rational combinations demonstrate an effect.

[31] To qualify for a deferral, the applicant must submit (i) certification of the grounds for deferring the assessments or reports on the investigation; (ii) a pediatric study plan as described in section 505B(e) of the FD&C Act; (iii) evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time; and (iv) a timeline for the completion of such studies. Section 505B(a)(4)(A)(ii) of the FD&C Act.

  - until additional clinical evidence of safety or effectiveness of the drug has been collected.
- Until such time that an appropriate pediatric formulation for investigational purposes is available, provided there has been due diligence in formulation development.
- If the drug is ready for approval for use in adults before the pediatric study(ies) is completed.

IV. GLOBAL IMPLICATIONS AND INTERNATIONAL COLLABORATION

FDA recognizes the global scope of drug development and strongly encourages all stakeholders to support internationally coordinated and collaborative approaches to development of drugs to treat cancers in pediatric patients. Due to the rarity of pediatric cancers, which are frequently being subdivided into even rarer subpopulations based on underlying molecular features, international collaboration is increasingly important for facilitating the development of new treatments. Furthermore, the number of investigational drugs of potential interest far exceeds the number of pediatric patients available to enroll in clinical trials. Therefore, global coordination is increasingly important for prioritizing drugs of interest in general and for specific cancers in pediatric patients, especially for drugs of the same class, for early pediatric evaluation. This aids in preventing duplication of studies and competition for scarce patients and limiting unnecessary exposure of pediatric patients to investigational drugs.

The following opportunities exist to facilitate coordinated, global approaches to pediatric development:

A. Pediatric Cluster Teleconferences

- Informal at least monthly teleconferences between the FDA and the European Medicines Agency (EMA), together with representatives from Health Canada, the Japanese Pharmaceutical and Medical Devices Agency, and the Australian Therapeutic Goods Administration coordinated by FDA's Office of Pediatric Therapeutics.
- Provide opportunities for high-level scientific discussion of issues relating to development of specific drug products. Relevant documents and information are shared between participating regulatory agencies under the terms of existing confidentiality agreements.
- Regulatory agencies may request that a particular topic be placed on the agenda for discussion. Sponsors are informed of specific comments resulting from the discussions and may receive details of the discussions after the teleconference.
- Sponsors also can submit a request to either the FDA (to either the appropriate review division or office or the Oncology Center of Excellence Pediatric Oncology Program) or EMA that their drug product – or more generally, the appropriateness of potential indications by drug class – be considered for discussion.

B. Common Commentary Process

- Established by FDA and the EMA to inform sponsors of the outcome of scientific exchanges related to select drug products or topics discussed at Pediatric Cluster teleconferences.
- Is intended to facilitate early sponsor interactions with the relevant agencies and neither alter nor replace routine review procedures.
- FDA recommends this mechanism for high level scientific review of early pediatric development plans and reaching consensus, when possible, to facilitate alignment of advice to sponsors seeking uniformity of design concepts for iPSPs and Pediatric Investigation Plans (PIPs).
- Applies to drug products for which a pediatric development plan is contemplated or has been submitted to both FDA and the EMA and is under review, preferably early in the regulatory process.
- FDA or EMA can nominate a product or topic for discussion.
- FDA has assumed primary responsibility for drafting a document that summarizes the discussion and generally includes recommendations. After review and clearance by both agencies, the Common Commentary document is shared with the sponsor. This document is nonbinding, and it does not provide final regulatory decisions.
- Sponsors may advise the appropriate review division or office or the OCE Pediatric Oncology Program that they wish to have their product's iPSP (and PIP, if already submitted to EMA) and their proposed global pediatric development be the subject of a Common Commentary. Sponsors may seek FDA clarification following receipt of the Common Commentary by requesting a Type C meeting with the review division or office.

C. Formal Parallel Scientific Advice (PSA)

- Provides formal mechanism for provision of concurrent exchange of advice from EMA assessors and FDA reviewers with sponsors on scientific issues to optimize drug development.
- Consideration of PSA and a request for this process should be made to the appropriate review division or office early and well in advance of the submission of the iPSP in order to help avoid any possible delay in submission of the NDA/BLA due to the failure to reach agreement on the iPSP.
- Information regarding the PSA procedure, including how to apply, is available.[32]

Additionally, FDA encourages participation in international multi-stakeholder meetings such as the Pediatric Strategy Forums organized by the ACCELERATE Platform[33] and other international meetings or conferences which bring sponsors, investigators, patient advocates, and

[32] GENERAL PRINCIPLES EMA-FDA PARALLEL SCIENTIFIC ADVICE (HUMAN MEDICINAL PRODUCTS) https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/OfficeofInternationalPrograms/UCM557100.pdf.

[33] For additional information, see https://www.accelerate-platform.eu/paediatric-strategy-forum/ (accessed May 18, 2021).

regulators together to discuss development strategies for specific pediatric cancers in the context of the number of investigational drugs available for assessment and the highly variable unmet medical needs of distinct pediatric populations with specific childhood cancers. We recommend stakeholders, including sponsors, investigators, and patient advocates consider coordinating early multi-stakeholder input to inform decision-making related to the initial pediatric clinical evaluation of appropriate investigational drugs to both avoid unnecessary duplication and provide an efficient framework for a longer-term development strategy of promising new drugs. An international perspective on clinical trial feasibility and the extent of unmet clinical need, as well as the scientific rationale for early evaluation and continued development of a class of molecularly targeted products or individual investigational drugs may help inform appropriate development plans of promising drugs for children with cancer globally.