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

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DRAFT GUIDANCE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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December 2019
Procedural

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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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 the pharmaceutical industry, clinical investigators, and institutional review boards (IRBs) with information to facilitate pediatric studies of molecularly targeted (also referred to as "targeted" in this guidance) oncology drugs.[2] This guidance addresses early planning for pediatric evaluation of certain molecularly targeted oncology drugs for which original New Drug Applications (NDAs) and Biologics License Applications (BLAs) are expected to be submitted to the FDA on or after August 18, 2020 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).[3]

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 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).

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

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

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 the required investigations are waived or deferred.[4] 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 (i.e., children ages 0-2 years, 2-11 years and adolescents ages 12-<17 years).[5] 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). Often, the types of cancers in pediatric patients and adults differ in etiology, biology, organ of origin, and natural history, which could result in pediatric trials not being required under the pre-FDARA iteration of PREA (e.g., if 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).

However, malignancies occurring in children and adolescents can harbor the same molecular abnormalities as those found in adult cancers, 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

[4] Sections 505B(a)(1)(B) and 505B(a)(3)(C) of the FD&C Act.

[5] 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.

to Generate Effect Treatments (TARGET) program[6], the Pediatric Cancer Genome Project[7], and the International Cancer Genome Consortium's PedBrain Tumor[8] and ICGC-MMML-seq[9] 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.[10,11] 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.[12]

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 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.[13]

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.

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 Oncology Subcommittee of the Oncologic Drugs Advisory Committee, 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 the requirements for pediatric investigations under PREA (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 pediatric study 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

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[6] For additional information, see https://ocg.cancer.gov/programs/target (accessed October 8, 2019).

[7] For additional information, see https://www.stjude.org/research/pediatric-cancer-genome-project.html (accessed October 8, 2019).

[8] For additional information, see http://www.pedbraintumor.org/icgc/index.php/ct-menu-item-7 (accessed October 8, 2019).

[9] For additional information, see https://icgc.org/icgc/cgp/64/345/53049 (accessed October 8, 2019).

[10] Gröbner SN, Worst BC, Weischenfeldt J, et.al., 2018, The Landscape of Genomic Alterations Across Childhood Cancers, Nature, 555:321-327.

[11] 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.

[12] See footnotes 10 and 11.

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

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. The statute neither stipulates that a molecular target to which a specific drug is directed must appear on The Relevant Molecular Target List to require a clinical evaluation of the drug in the pediatric population nor specifies that the presence of a target on the relevant target list in itself constitutes a requirement for a clinical study. 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[14]

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 the molecule with a drug produces a predictable therapeutic effect resulting in alteration of the disease process.

B. Factors Considered in the Determination of Relevance

FDA intends to consider the totality of 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 available evidence base among targets, and continued 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 to reflect additional determinations regarding the relevance of molecular targets.

One or more of the following may, as appropriate, inform FDA's determination that a molecular target is substantially relevant for purposes of section 505B:

- The target has been identified in a cancer which occurs in pediatric patients. For targets within a cancer cell lineage, the target is intrinsically or differentially expressed in the cancer of interest compared to normal site-specific tissues.
- The biological function of the target is relevant to the etiology, growth, and survival of a cancer that occurs in pediatric patients. For a gene abnormality, modulation of

[14] While this guidance focuses on requirements 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.

the affected gene product or a critical downstream pathway or correction/deletion of the affected gene defect adversely affects cancer cells.

- Non-clinical in vitro or in vivo evidence supports relevance of the target in one or more cancers 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 tumor stabilization 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 evidence for additive or synergistic activity when an agent which effects target modulation is used as part of a biologically rational combination in appropriate model systems.
- Clinical activity in adults with specific cancers, for which direct evidence demonstrates that target modulation by investigational drugs is known to affect tumor growth
- Biomarkers expressed by tumor cells of cancers that occur in pediatric patients and that may predict response to target modulation may contribute to the concept of substantial relevance and also be useful in selection of the appropriate pediatric study population.

Data from a non-clinical evaluation of a drug that interferes with a known molecular target in a pediatric-specific model system can contribute evidence for determining the target's relevance to a cancer which occurs in pediatric patients. Therefore, every effort should be made to initiate pediatric non-clinical investigations early in the development timeline.

FDA may determine 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.

The lists may be updated based on information from, for example, semi-annual public workshops or meetings, including meetings of the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee. 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 existing lists.

C. Target Lists

1. The Relevant Molecular Target List

The list includes molecular targets for which adequate data exist to determine their substantial relevance to the growth or progression of one or more pediatric cancers. Categories 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. This includes targets for which there is 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 iPSPs) to request full waivers for pediatric evaluation of oncology drugs with a molecular target that is on the Non-Relevant Molecular Target Leading to Waiver List.

These lists are available at the following link: **Molecular Target Lists**.

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

Section 505B(e) of the FD&C Act requires applicants subject to PREA to submit an initial pediatric study plan prior to the submission of an NDA or BLA.[15] Prior to the enactment of FDARA, which added section 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 assessments 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 impossible or highly impracticable.[16] 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 because they rarely or never occur in pediatrics.[17] 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 not on clinical indication, but rather on the molecular mechanism of action of the investigational drug. Therefore, original applications for a new active ingredient that are 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

[15] See sections 505B(a)(1)(A), 505B(a)(1)(B), and 505B(e)(1) of the FD&C Act.
[16] See section 505B(a)(5) of the FD&C Act.
[17] 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.

pediatric cancer must include reports of molecularly targeted pediatric cancer investigations (which were described in an iPSP under section 505B(e) of the FD&C Act), unless a deferral or waiver is granted.[18] 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.

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 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 for a molecularly targeted oncology drug should include the following elements:

- Description of the cancer(s) in the pediatric population for which the drug warrants early evaluation
- Overview of the drug product
- Overview of planned extrapolation of effectiveness 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 proof-of-concept studies; planned and completed
- Data to support clinical studies in pediatric patients
- Planned pediatric clinical study(ies)
- Timeline of pediatric development plan
- Agreements for pediatric studies with other regulatory agencies

2. Description of recommended studies to be included

Studies to be described in the iPSP under section 505B(e) of the FD&C Act should evaluate dosing whether based on PK or PK-based modeling, safety, and preliminary efficacy. Trials should typically be non-hypothesis testing, single-arm studies using standard response assessments such as overall response rate and duration of response at a minimum.

Objectives of the 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).

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

- Assessment of activity (defined as overall response rate (ORR)) across the entire study population, in biomarker enriched population(s), in pre-specified disease cohorts, or in adaptive design settings, 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.

More definite evaluation of a product, if warranted based upon the initial pediatric evaluation described in the iPSP, may be the subject of a Proposed Pediatric Study request (PPSR). Following review of the PPSR and discussions with the sponsor, FDA may issue a Written Request, if appropriate.[19]

Early in the development of the iPSP, sponsors are encouraged to collaborate and seek advice from recognized subject matter experts, including those involved in clinical trial networks and academic investigators, to develop an appropriate non-clinical rationale for the iPSP and to facilitate scientifically rigorous study designs 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. If evaluation of the investigational drug is expected to be performed in a biomarker-enriched or restricted population, 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.

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 on or after August 18, 2020, or sponsors who are uncertain of their submission date, may request a meeting[20] with the Oncology Center of Excellence Pediatric Oncology Program and members of the Oncology Subcommittee of the Pediatric Review Committee (PeRC) through the appropriate review division or office, to assist with development of the iPSP. 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." Please contact the review division or office for any questions regarding these meetings.[21]

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[19] For additional information regarding Written Requests, see section 505A of the FD&C Act; 21 U.S.C. 355a.
[20] See section 505B(e)(2)(C)(i)(I) of the FD&C Act, added by section 503 of FDARA, which describes early meetings on pediatric study plans for drugs intended to treat a serious or life-threatening disease or condition.
[21] Sponsors should consult FDA's guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*, when finalized, to help ensure open lines of dialogue before and during their drug development process. When final, this guidance will represent the FDA's current thinking on this topic.

E. 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 and encourages sponsors to request feedback from FDA about any planned clinical trials for such investigational drugs. In situations where a conventionally designed pediatric trial may be inefficient and extremely difficult to conduct given the scarcity of affected pediatric patients, the following scenarios may provide options to maintain the objective of early pediatric assessment of drugs directed at substantially relevant targets and satisfy requirements of section 505B of the FD&C Act:

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 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.[22, 23]

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 would allow those patients access to investigational drugs with

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[22] 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.

[23] See draft guidance for industry *Cancer Clinical Trial Eligibility Criteria: Minimum Age for Pediatric Patients* (March 2019). When final, this guidance will represent the FDA's current thinking on this topic.

potential for benefit and generate clinical trial data in this population that could be included in prescribing information for safe and effective use at the time of approval.[24]

In some instances, efficacy in adolescent patients may be extrapolated from adult data; however, adequate approaches to evaluate safety in this population are required.[25]

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 require pre-competitive discussions, negotiations, and planning by multiple sponsors.[26] 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.

F. Considerations for Planned Waivers and Deferrals

There may be circumstances, including those listed below, when a waiver or deferral of pediatric studies may be appropriate for a molecularly targeted pediatric cancer investigation.[27]

1. Deferrals

- Deferral of a pediatric study may be appropriate until sufficient evidence of clinical activity is observed in response to the known inhibition of a defined molecular target(s) or pathway.
- Deferral of a pediatric study may be appropriate when there is uncertainty regarding the single agent activity of a drug until such time that one or more biologically rational combinations demonstrates a clinical effect.
- Deferral of a pediatric study may be appropriate until such time that an appropriate pediatric formulation for investigational purposes is available, provided there has been due diligence in formulation development.

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[24] See the guidance for industry *Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials* (March 2019).

[25] See sections 505B(a)(2)(B) and 505B(a)(3)(B) of the FD&C Act.

[26] See draft guidance for industry *Master Protocols: Efficient Clinical Trial Design Strategies to Expedited Development of Oncology Drugs and Biologics* (September 2018). When final, this guidance will represent the FDA's current thinking on this topic.

[27] See sections 505B(a)(3)(C), 505B(a)(4) and 505B(a)(5) of the FD&C Act.

2. Waivers

- A full or partial waiver (as appropriate) may be appropriate 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.
- Age group-specific waivers may be appropriate 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.
- Age group-specific waivers may be appropriate when a sponsor is not able to develop an appropriate pediatric formulation for an age group.
- A waiver may be appropriate for the third or later generation/same in class product (with identical mechanism of action) when ongoing competing studies in the pediatric population are being conducted and when there is no convincing evidence that the new drug provides a superior pharmacologic, toxicity, or activity profile to the same in class product(s) already studied or under investigation, potentially resulting in a very small number of patients available to participate in a new investigation.

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 will aid in preventing duplication of studies and competition for scarce patients and limit 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 or EMA that their drug product 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.
- Applies to drug products for which a pediatric development plan has been submitted to both FDA and the EMA and is under review, preferably early in the regulatory process.
- 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.

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.
- Information regarding the PSA procedure, including how to apply, is available.[28]

Additionally, FDA encourages participation in international multi-stakeholder meetings including the Pediatric Strategy Forums organized by the ACCELERATE Platform[29] which bring sponsors, investigators, patient advocates, and 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

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

[29] For additional information, see https://www.accelerate-platform.eu/paediatric-strategy-forum/ (accessed October 8, 2019).

476 investigational drugs to both avoid unnecessary duplication and provide a framework for a
477 longer-term development strategy of promising new drugs.