WHITE PAPER

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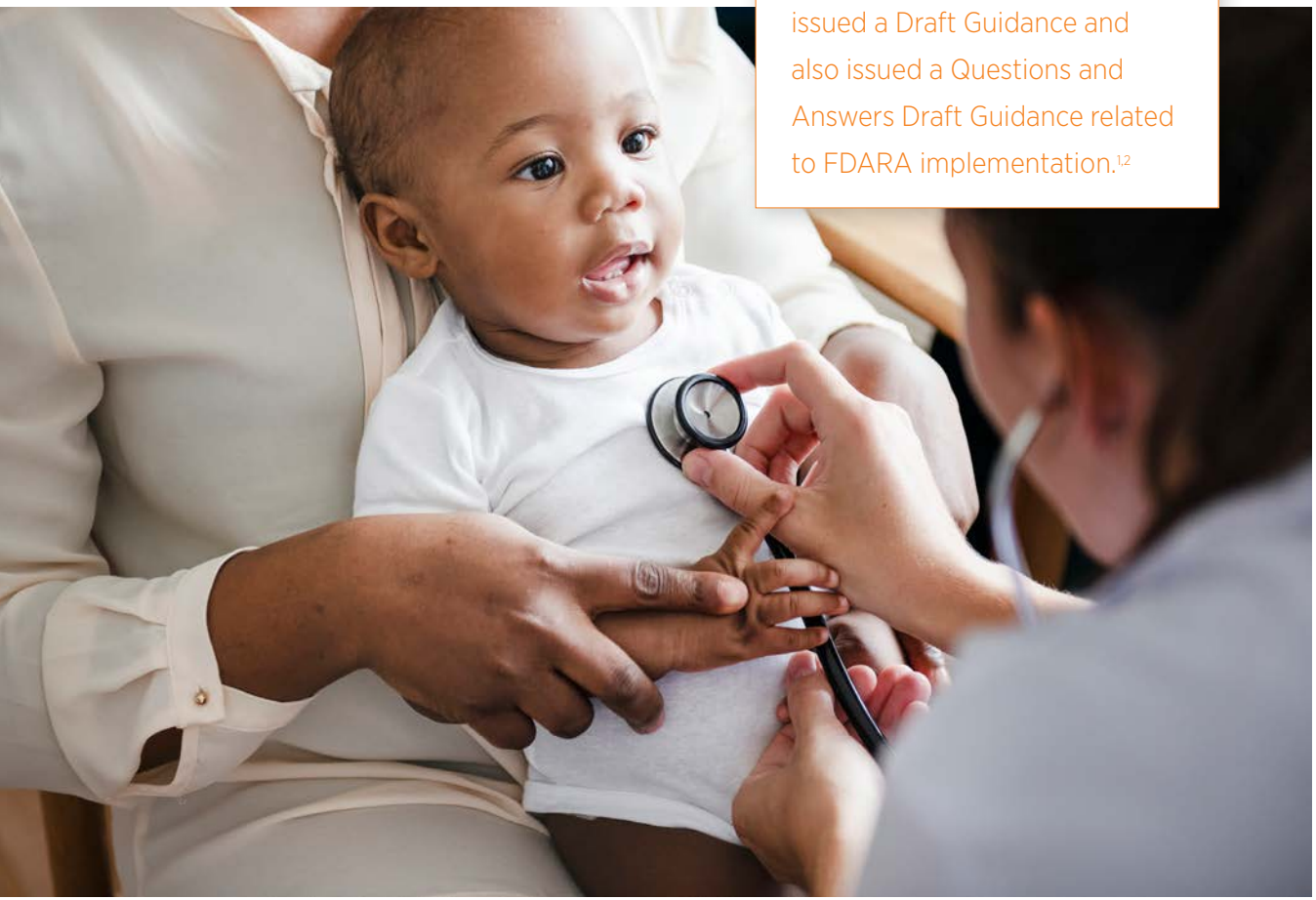
ONCOLOGY

Understanding New FDA Guidance For Pediatric Oncology Studies

OVERVIEW

A Sponsor's Guide to the FDA Research to Accelerate Cures and Equity for Children Act



In December 2019, the FDA issued a Draft Guidance and also issued a Questions and Answers Draft Guidance related to FDARA implementation.[1,2]

Introduction

The Research to Accelerate Cures and Equity (RACE) for Children Act aims to improve and expand treatment options for pediatric cancer patients by mandating that all new adult oncology drugs also be tested in children when the molecular targets are relevant to a particular childhood cancer. Enacted August 18, 2017, as part of the Food and Drug Administration (FDA) Reauthorization Act (FDARA), it amends the Federal Food, Drug, and Cosmetic Act (FFDCA) to revise and extend the user-fee programs for drugs, medical devices, generic drugs, and biosimilar biological products and for other purposes.

RACE requires that any original new drug application or biologics license application submitted on or after August 18, 2020, for a new active ingredient must contain reports of molecularly targeted pediatric cancer investigations – unless a deferral or waiver of that requirement is granted – if the drug is:

- Intended for the treatment of an adult cancer, and
- Directed at a molecular target that the FDA determines to be substantially relevant to the growth or progression of a pediatric cancer

This requirement for pediatric investigation applies even if the adult cancer indication does not occur in the pediatric population and the drug is for an adult indication for which orphan designation has been granted. In December 2019, the FDA issued a Draft Guidance that is the subject of this white paper.[1] In January 2020, the agency also issued a Questions and Answers Draft Guidance related to FDARA implementation.[2]

Legislative background

This is not the first time that Congress and the FDA have passed legislation and created policies to encourage pediatric drug development. The Best Pharmaceuticals for Children Act (BPCA) of 2002 provides an incentive of additional marketing exclusivity to sponsors who voluntarily complete pediatric clinical studies outlined in a written request issued by the FDA, and the Pediatric Research Equity Act (PREA) of 2003 authorizes the agency to require drug manufacturers to complete studies in children for the same adult indications when the drugs are expected to be used in a substantial number of children.

Specifically, PREA mandates submission of the initial pediatric study plan (iPSP) prior to commencement of Phase 3 studies – or new drug application (NDA)/biologics license application (BLA) submission in the absence of a Phase 3 study – for studies involving a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. The iPSP is expected to contain an assessment of safety and effectiveness of the investigational drug for the proposed indication in all relevant pediatric subpopulations. In certain situations, a deferral or waiver for conducting pediatric studies can be obtained.

Oncology drug development presents a particular challenge in children because young patients often have different cancers from those found in adults. Therefore, most adult oncology therapeutics receive waivers from studies in children based on the fact that cancer is typically a disease of old age, and thus it is highly impracticable to conduct studies in pediatric populations.

Furthermore, under the PREA orphan exemption, PREA does not apply to any drug application for an indication for which orphan drug designation has been granted when that application would otherwise trigger PREA.

RACE for Children Act

Scientific advances have transformed the paradigm of cancer drug development with molecularly targeted drugs, advancing the concept of precision medicine in oncology. The advances seen in the treatment of adult oncology indications have rarely been extended to development of pediatric cancer treatments. But extensive research has demonstrated that malignancies occurring in children and adolescents can harbor the same molecular abnormalities as those found in adult cancers, indicating that the new targeted oncology drugs may prove effective in treating pediatric patients with cancer, even if the adult cancer indication does not occur in the pediatric population.[3,4] This is further supported by the notion that up to 50 percent of pediatric cancers harbor a druggable molecular target that can potentially be addressed by a targeted drug already approved in adults.

Prior to the RACE for Children 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 did not occur, or occurred only rarely, in pediatric patients, making pediatric studies impossible or highly impracticable. The RACE for Children Act amended PREA to require pediatric investigation of certain targeted cancer drugs based on molecular mechanisms of action rather than the clinical indication for original BLAs/NDAs submitted on or after August 18, 2020, unless a deferral or waiver is granted. FDARA also eliminated the orphan exemption for pediatric studies for cancer drugs directed at relevant molecular targets.

Relevant and non-relevant molecular targets

In collaboration with the government, academic and industry experts, and advocates, the FDA established, published, and updates two lists:

- Relevant Molecular Targets: considered to be substantially relevant to the growth or progression of a pediatric cancer
- Non-Relevant Molecular Targets That Warrant Waiver From Required Evaluation: considered not substantially relevant

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. However, sponsors of molecularly targeted oncology drugs are encouraged to seek early advice from the FDA.

IPSP content[5]

An iPSP for a molecularly targeted oncology drug should address the drug's molecular target and its relevance to one or more cancers that occur in the pediatric population. An iPSP is expected to 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 or studies
- Timeline of the pediatric development plan
- Agreements for pediatric studies with other regulatory agencies

Description of recommended studies to be included

Studies to be described in the iPSP should evaluate dosing, whether based on pharmacokinetics (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 (ORR) and duration of response (DOR). Objectives of the studies described in the iPSP should include:

- Evaluating tolerability and determining dose-limiting toxicity (DLT) in pediatric patients
- Evaluating PK across age groups
- Determining the pediatric recommended Phase 2 dose (RP2D)
- Assessing activity (ORR) across the entire study population or in biomarker-enriched population

If warranted based on the initial pediatric evaluation described in iPSP, more definite evaluation of a product may be the subject of a Proposed Pediatric Study Request (PPSR). Following review of the PPSR and discussions with the sponsor, the FDA may issue a written request. Completion of the studies in the PPSR would qualify sponsors for an extra six months of product exclusivity.

If evaluation of the investigational drug is expected to be performed in a biomarker-enriched or -restricted population, early discussion with the Center for Devices and Radiological Health regarding investigational device exemption and the use of companion diagnostics is encouraged.

Considerations for rare cancers

The following options should be considered in situations where scarcity of affected pediatric patients may preclude conventionally designed studies:

- Include a pediatric cohort in an existing adult trial during the expansion phase or embed a pediatric trial within an existing trial in adults. In both situations, sponsors may be able to leverage already existing clinical sites and resources of the ongoing adult clinical trial.
- Include adolescent patients by lowering the age requirement for enrollment. Systemic exposure and clearance of drugs are generally similar in adolescent and adult patients when adjusted for the effect of body size. Furthermore, this may generate clinical data to be included in the label. For more information, consult the FDA guidance.[6]
- Consider tissue- and histology-agnostic development, which would facilitate development of targeted therapies in multiple pediatric cancers with shared genetic abnormalities.
- Use master protocols, such as umbrella or basket trial designs, that minimize the number of subjects exposed to ineffective therapies. Be aware, however, that master protocols typically require precompetitive discussions, negotiations, and planning by multiple sponsors. The FDA encourages consideration of this approach given the large number of similar- and same-in-class products to avoid unnecessary duplication.

Early advice on pediatric development meetings

Sponsors may seek early interaction with the FDA to address their pediatric development. Questions can be addressed to the Pediatric Oncology Program in the agency's Oncology Center of Excellence.

Sponsors may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program and members of the Oncology Subcommittee of the Pediatric Review Committee through the appropriate review division or office to assist with development of the iPSP. These meetings 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."

Planned deferrals and waivers

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
- When there is uncertainty regarding the single-agent activity of a drug until such time that one or more biologically rational combinations demonstrate a clinical effect
- Until an appropriate pediatric formulation for investigational purposes is available, provided there has been due diligence in formulation development

A full or partial waiver may be appropriate if known or strongly suspected serious toxicity of a drug precludes its use in all, or in one or more, pediatric age groups. Age-group-specific waivers may be appropriate if there are known or strongly suspected severe developmental toxicities that may present an unreasonable risk to pediatric patients of a particular maturational stage or 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.

Conclusion

The passage of FDARA is a significant milestone in promoting pediatric cancer drug development that is bound to have significant implications on how sponsors plan and prepare for NDA/BLA filing of molecularly targeted oncology drugs. The FDA is encouraging sponsors of original adult oncology drug applications submitted before August 18, 2020 to nevertheless address molecularly targeted pediatric cancer investigations in their development plans.

After August 18, 2020, sponsors of adult molecularly targeted cancer drugs will be required to submit an iPSP that includes an outline of the pediatric cancer investigation(s) that are planned – including, to the extent practicable, study objectives and design, age groups, relevant endpoints, and statistical approach – and any request for a deferral, partial waiver, or waiver along with any supporting information, regardless of the drug's proposed adult cancer indication or whether it is a drug for an indication for which orphan designation has been granted. For more details, contact Premier Consulting, a division of Premier Research, for a consultation.

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Our end-to-end solutions in strategy, regulatory, nonclinical, clinical, CMC, quality, and commercial help sponsors build and execute development plans that meet regulatory requirements and deliver results for sponsors and the patients they serve.

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