# FDA Briefing Document

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

## May 11, 2022

### 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 the development of a conceptual framework that will inform the decision-making of the FDA on sponsor plans and requests for waivers of early pediatric investigations of molecularly-targeted cancer drugs and biologics when multiple same-in-class products are approved and/or in development, recognizing that the rarity of pediatric cancers may preclude the feasibility of investigations of multiple products. Investigation of more than one product may be appropriate when specific product characteristics predict an improved benefit-risk assessment that warrants clinical investigation.

The 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.

# Memorandum

Date: April 22, 2022

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

From: Gregory Reaman, MD
Associate Director for Pediatric Oncology, Oncology Center of Excellence, Office of the Commissioner, FDA

Subject: FDA Background Package for May 11, 2022 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 the development of a conceptual framework that will inform the decision-making of the FDA on sponsor plans and requests for waivers of early pediatric investigations of molecularly-targeted cancer drugs and biologics when multiple same-in-class products are approved and/or in development, recognizing that the rarity of pediatric cancers may preclude the feasibility of investigations of multiple products. Investigation of more than one product may be appropriate when specific product characteristics predict an improved benefit-risk assessment that warrants clinical investigation.

The Pediatric Oncology Subcommitee of the ODAC will address the need and content for a consistent, transparent approach to the development of a conceptual framework to inform sponsors of the information required to support plans for waiver requests for pediatric investigation of same in class molecularly targeted agents. The framework is also intended to guide FDA in decision-making when considering such requests.

As always, we appreciate your time and commitment and look forward to an informative meeting on May 11, 2022.

## Development of a conceptual framework to inform decision-making by the FDA on sponsor plans for waivers of pediatric investigatons of multiple, same-in-class molecularly-targeted cancer drugs and biologics

The focus of the Pediatric Research Equity Act (PREA) to protect children through mandated clinical investigation to ensure access to safe and effective drugs has resulted in meaningful advances in the development of drugs for many diseases that occur in children, but it has had no impact on providing new treatment options for children with cancer for two reasons. Orphan designation rendered new drug applications exempt from PREA requirements and waivers from the requirement for pediatric assessments were permitted for drugs intended to treat an adult cancer (e.g., breast cancer and lung cancer) that either does not occur in children or occurs so rarely that the necessary pediatric studies would be impossible or highly impracticable to conduct.

To address this unintended exclusion, 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) to amend Sec 505B of the FD&C Act. It requires, for original applications submitted on or after August 18, 2020, pediatric investigations of certain targeted cancer drugs based on molecular mechanism of action rather than clinical indication. FDARA thereby created a mechanism to require evaluation of certain novel agents that may potentially address an unmet medical need in the pediatric population. Specifically, if an initial new drug application or biologics licensing application 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 Federal Food, Drug, and Cosmetic Act (FD&C) Act must be submitted with the marketing application, unless the required investigations are waived or deferred (US Food and Drug Administration 2021). A synopsis of the proposed clinical investigation, designed to yield meaningful data regarding dosing, safety, and preliminary efficacy to inform pediatric labeling, must be included in the initial Pediatric Study Plan (iPSP) or a plan to request a waiver or deferral with appropriate justification. The iPSP must be agreed upon by the FDA in advance of the application submission to assure its filing.

FDA, in consultation with the National Cancer Institute, and members of the committee established under section 505C of the FD&C Act, the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee, created and 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 requirement for pediatric investigations. Of note, a molecular target to which a specific drug is directed is not required to be on the "The Relevant Molecular Target List" to require early clinical evaluation of the drug in the pediatric population. There is also a separate list of molecular targets that are considered "not substantially relevant" to the growth or progression of pediatric cancers and that could warrant a waiver of pediatric study requirements.

The links to the Molecular Target lists can be found below:

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

An anticipated, albeit unintended consequence of this legislation relates to the fact that manufacturers of multiple targeted agents in the same class (i.e. against the same target) or against multiple targets relevant to the same tumor type, may be required to propose parallel development plans requiring the enrollment of patients with clinical indications where there may be small numbers of eligible patients annually. The FDARA Implementation Guidance does address the problem with multiple same in class agents and the patient population constraints associated with rare pediatric cancer diagnoses, now made more difficult by the sub-classification of already rare diseases based on tumor molecular profiling. Advice is provided to sponsors to plan requests for waiver for investigation of agents with the same mechanism of action directed at the same molecular target unless there is evidence of improved activity or effectiveness in a particular cancer, generally based on adult clinical data or limited pediatric clinical data, non-clinical data, improved toxicity profile, preferential PK parameters including central nervous system (CNS) penetration of an agent, preferred routes of administration, and more tolerable pediatric-appropriate formulations. Evidence of comparative effectiveness can be provided by non-clinical data as well, although there is currently no statutory requirement for non-clinical studies in pediatric specific tumor models.

To date, initial Pediatric Study Plans (iPSPs) incorporating planned waiver requests have been agreed to by the FDA for multiple same in class products, including PD-1/PD-L1 axis inhibitors, PI3K delta isoform inhibitors, BTK inhibitors, EGFR inhibitors, FGFR inhibitors, anti-CD20 antibody-directed agents, and others. The timelines associated with opening and attempting to enroll patients in multiple competing studies challenges study completion and almost ensures that any results may be irrelevant by the time duplicative studies are completed. This is a situation that does not suit the needs of patients or sponsors and may seriously jeopardize progress in pediatric cancer drug development opportunities afforded by legislative change. Although not always feasible, decisions regarding the waiver of early pediatric assessment of same in class drugs should consider the context of the specific disease indication in children and the extent of unmet clinical need.

The patient sample constraints are not limited to required investigations in the U.S. as a result of FDARA Sec. 504 but also extend to decisions related to the elimination of certain class waivers for new drug products that are the subject of Pediatric Investigation Plans (PIPs) for the European Medicines Agency (EMA). In fact, given the global nature of pediatric drug development, the challenge of unnecessarily duplicative studies of same in class drugs threatens ongoing as well as future international clinical research collaboration and ultimately patient access to novel drugs with proven efficacy and safety. Merely requiring studies of first in class products poses the problem of missed opportunity to require an assessment of what may be a preferred drug product for use in the pediatric population and also limits the opportunity to take advantage of "next generation" products with potential therapeutic or safety advantage. It is important to note the difference in timelines for decision-making with respect to the description

of the planned molecularly-targeted pediatric cancer investigation in an iPSP for which agreement with the FDA is required prior to the submission of a new drug application or biologics licensing application. The PIPs submitted to the EMA, on the other hand, are expected to consider more definitive pediatric development plans that may be disease-specific and, therefore, the timeline may allow for the opportunity to compare same in class products in a less time constrained manner to effectively prioritize one product over others for pediatric development. The principles to be used when making these decisions overlap. The FDA and EMA seek to collaboratively develop a consistent and transparent contextual framework with input from relevant stakeholders for decision-making surrounding the required pediatric assessment of new drugs when multiple same in class products are in development or when a new same in class product emerges during or following pediatric clinical investigation of another product. Discussion during this open public forum is expected to provide direction to regulatory agencies to advise and direct pharmaceutical sponsors as to the extent of the efforts and evidence required to comparatively evaluate therapeutic attributes (efficacy, safety, pharmacologic parameters) of a new product that may warrant plans for waiver requests and inform regulatory decisions surrounding such planned waivers.

**REFERENCES:**


HR 1231 RACE for Children Act 115th Congress 2017-2018

HR 2430 FDA Reauthorization Act 115th Congress 2017-2018

Federal Register v86, no99, Mar 25, 2021 FDA Reauthorization Act Implementation Guidance for Pediatric Studies of Molecularly-Targeted Oncology Drugs  Guidance for Industry

FDARA Implementation Guidance for Industry on Pediatric Studies of Molecularly Targeted Oncology Drugs

RACE Act poised to advance pediatric cancer research. Cancer Discov, 2020, 10, 1434 https://doi.org/101/1198/2159-820

## Discussion Topics Related to Considerations for Evaluating Planned Waivers of Pediatric Investigations of Same in Class Agents.

1. Consider the importance of unmet clinical need in a specific disease context that could or should influence decision-making with respect to early investigation of multiple same-in-class novel agents for pediatric cancer.

2. Consider the importance of any comparative efficacy results of same in class agents in one or more adult cancers (discuss specific cancers) as well as comparative adult toxicity data (type, magnitude, and frequency) that could contribute to a decision to evaluate multiple same in class products in children.

3. Consider differences in specific product quality indicators, pediatric-appropriate dosage forms, route of administration that might impact clinical benefit and influence a decision to investigate multiple same in class products in children.

4. Consider the importance of non-clinical data of activity to decisions related to investigation of same -in-class products in children and if/when pre-clinical studies in pediatric-specific models might be required.

5. Consider specific pharmacological parameters that should be considered and the importance of CNS penetration when primary CNS tumors may be a key target tumors of interest when evaluating the need for pediatric investigation of more than one in class agent. Discuss the requirement for sponsors to include sufficient data in iPSPs to inform assessment and decisions.