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Dockets Management Staff
U.S. Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2021-N-1302

Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee: Points for Consideration Regarding Sponsor Plans and Waiver Requests for Early Pediatric Investigations of Same-in-Class Molecularly Targeted Cancer Drugs/Biologics

Dear Members of the Pediatric Oncology Subcommittee:

The Biotechnology Innovation Organization (BIO) thanks the U.S. Food and Drug Administration (FDA) for the opportunity to submit comments regarding FDA's planned development of a conceptual framework that will inform decision making 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.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

We agree with your assertion in the background materials for the May 11, 2022, Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (ODAC) meeting that the rarity of pediatric cancers may render investigations of multiple same-in-class products infeasible. In general, BIO believes the construction of a conceptual framework to assist FDA's regulatory decision making should avoid unduly burdening one sponsor more than its competitors, utilize scientific data (e.g., mechanistic, nonclinical, clinical, etc.), and have a patient-centric approach.

We greatly appreciate the Subcommittee's consideration of stakeholder feedback on and public discussion of these important matters, and we would welcome opportunities for continued dialogue and collaboration with the Agency following the conclusion of this meeting.

Background

Conducting regulatory-quality oncology clinical trials is widely acknowledged to be challenging. In fact, the overall likelihood for a therapy to advance from Phase I clinical testing to approval (LOA) for all indications outside oncology is 11.9%, whereas the LOA for oncology indications, both general and specific to pediatrics, is only approximately 5%.[1,2] Challenges faced when developing oncology therapies for adults are further complicated when developing oncology therapies for pediatric indications due to limited patient populations. The American Cancer Society estimates that over 1.9 million new cancer cases will be diagnosed in the United States in 2022 compared to about 16,000 diagnoses for children and adolescents specifically, indicating a significantly smaller population of potential pediatric cancer trial participants.[3] Conduct of these trials can become further complicated when multiple sponsors are under regulatory obligation to conduct pediatric oncology studies of the same molecular target and/or in the same cancer. Additionally, recent trends suggested the oncology therapy pipeline included approximately 2700 clinical programs (Phase I-III).[4]

The absence of an effective mechanism for making decisions about the feasibility of preliminary efficacy studies may increase the likelihood that studies cannot be fully enrolled, an outcome undesirable to all stakeholders. Situations where the available patients for a given clinical trial are limited may include, but are not limited to, circumstances when there are multiple ongoing studies aimed at a single molecular

[1] Thomas, D.W., Burns J., Audette, J., Carroll, A., Dow-Hygelund, C., Hay, M. Clinical Development Success rates 2006-2015.

[2]Wasylewski, M. T., Strzebonska, K., Koperny, M., Polak, M., Kimmelman, J., & Waligora, M. (2020). Clinical development success rates and social value of pediatric Phase 1 trials in oncology. *PloS one*, *15*(6), e0234911. https://doi.org/10.1371/journal.pone.0234911

[3] *Cancer facts & figures 2022*. American Cancer Society. Retrieved April 25, 2022, from https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2022.html

[4] Thomas, D.W., Wessel, C., Emerging Therapeutic Companies Investment and Deal Trends 2008-2017.

target or multiple studies aimed at different molecular targets within the same pediatric sub-population; circumstances when other therapies exist for a particular pediatric population and thus the available population for study only consists of pediatric patients with refractory or resistant cancers, or; circumstances when the size of a particular pediatric patient sub-population is extremely limited.

Not only is initiation of infeasible clinical trials unsatisfactory to either industry sponsors or FDA when a clinical trial cannot evaluate its primary objectives, these trials represent unnecessary expenditure of precious patient resources given the overall rarity of pediatric cancer. To ensure that studies of preliminary efficacy outlined in FDARA Section 504 can be fully enrolled and yield data that can actually inform pediatric labeling of oncology products, there must be a process for sponsors, whether individually or collectively, to discuss the feasibility of preliminary efficacy studies with the FDA.

In addition to case-by-case impracticability concerns, determination about the feasibility of a preliminary efficacy study must consider global harmonization and international activities as they relate to pediatric oncology drug development. BIO welcomes future opportunities for dialogue with the Pediatric Subcommittee of the ODAC on this matter and intends to elaborate on how such harmonization efforts serve to enhance the feasibility and likely completion of pediatric studies following this meeting.

Process for Determination of Feasibility of Preliminary Efficacy Studies:
Determination of the feasibility of a preliminary efficacy study in the context of FDARA Section 504 should occur after determination has been made that a particular drug or biologic is active against a molecular target that the FDA has deemed substantially relevant to the growth or progression of a pediatric cancer, using considerations including but not limited to pediatric and adult clinical evidence, biological function of the target, non-clinical in vitro/in vivo evidence, and expression of predictive biomarkers.[5] Making the determination that a particular drug or biologic is or is not active against a molecular target that the FDA has deemed substantially relevant to the growth or progression of a pediatric cancer prior to making determinations regarding feasibility of

[5] US Food and Drug Administration. *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act*. Retrieved April 25, 2022, from https://www.fda.gov/media/133440/download

a study of preliminary efficacy will reduce the numbers of drugs or biologics that require discussions around feasibility. The FDA's final decision to grant waivers or deferrals should occur at the time of NDA/BLA approval, as is current practice.

Opportunities for Sponsors to Engage with the FDA

FDA has indicated in its 2021 procedural guidance, *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act*, that drugs or biologics that are first in class will likely be required to conduct a study that includes an evaluation of preliminary efficacy. The guidance also notes that drugs or biologics that are second, third, or more in class will likely receive waivers of the requirement to conduct an investigation of preliminary efficacy.

- Given the well-established challenges associated with pediatric oncology clinical research noted above, there may be feasibility challenges that warrant a PREA waiver even for oncology drugs or biologics that are first (or only) in class. Notably, out of the 12 applications for new molecular entities (NMEs) directed at relevant molecular targets between August 2020 and January 2022 with pediatric study requirements under Title V Section 504 of FDARA, FDA granted 6 full waivers for same-in-class products, i.e., in half of such applications, due to impracticability.[6]

- Additionally, in many cases, an iPSP must be submitted no later than 60 days after an EOP2 meeting and may be submitted earlier for oncology products. As such, there may not necessarily be a first in class therapy (i.e., no therapies have yet been approved) at this point in development. Further, the leading drug/biologic candidate to reach first human dose may not be the leading candidate at the end of Phase II. For these reasons there will need to be a process for sponsors, whether individually or collectively, to discuss the feasibility of preliminary efficacy studies with the FDA and potentially reevaluate the feasibility of such studies as development of a drug or biologic advances, as noted above.

[6] Reaman, G. ACCELERATE Paediatric Oncology Conference 2022. In *The RACE for Children Act: Early Implementation Experience*.

Companies may use meetings outlined in FDARA Section 503 and other meeting types to discuss with the FDA the feasibility of preliminary efficacy studies.

- If a sponsor is required to complete an assessment of preliminary efficacy but later learns that completing the study is not feasible due to enrollment or other factors, it will be important for the sponsor to have the opportunities both to discuss the issue with the FDA and request a waiver for the study via submission of an amended PSP. The FDA should also make clear in guidance what evidence will need to be provided by sponsors to demonstrate that a preliminary efficacy study is not feasible.

- In addition to multiple sponsors developing therapies aimed at a single molecular target relevant to the growth and progression of a pediatric cancer, a single sponsor may also be developing multiple therapies aimed at a single molecular target or multiple molecules aimed at a single disease or cancer type. In such cases, a determination of the feasibility for which of these molecules within a sponsor's portfolio should be evaluated in a pediatric patient population might be appropriate. To help resolve these situations, BIO requests that FDA continues to allow sponsors to discuss the prioritization of their own pipelines with FDA through pipeline meetings.

BIO appreciates this opportunity to submit comments regarding FDA's planned development of a conceptual framework that will inform decision making 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 for the Pediatric Subcommittee of the ODAC's consideration. We would be pleased to provide further input or clarification of our comments, as needed, and look forward to sharing additional feedback on this critically important topic to FDA.

Sincerely,

Alex May, M.S.
Director, Science & Regulatory Affairs
Biotechnology Innovation Organization