September 30, 2019

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA–2014-D-1461: FDA Draft Guidance, Rare Pediatric Priority Review Vouchers.

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments in response to the FDA's Draft Guidance on Rare Pediatric Disease Priority Review Vouchers.

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 people afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

BIO commends the Agency's efforts to provide guidance on the implementation of Section 908 of the Food and Drug Administration Safety and Innovation Act (FDASIA), the Rare Pediatric Disease Priority Review Voucher (RPD PRV) Program. The Rare Pediatric Disease Priority Review Voucher Program, along with other incentives, is essential for encouraging investment and research into development for therapies to treat pediatric patients with rare diseases.

As FDA works to improve and streamline the implementation of the RPD PRV process, we recommend that the Agency consider a common application for Orphan Designation and the Rare Pediatric Diseases Designation and streamlining the process for transfer and use of the PRV. We believe that our recommendations not only provide clarity regarding some of the elements in the Draft Guidance but also serve to continue to incentivize the development of therapies for rare pediatric diseases, as intended by Congress.

PRVs are earned or purchased by a sponsor to be redeemed, along with a PRV fee, for Priority Review of an application. As such, we recommend that a voucher and fee would only be needed in a circumstance where the application would not receive a Priority Review based on its own merit. To this end, we request that FDA conduct a routine assessment to determine the review category (e.g., Priority or Standard review) for all applications and supplements.

BIO encourages the Agency to consider a common application pathway for its rare pediatric disease and orphan designations. Although there are instances where a product might be eligible for orphan designation but not rare pediatric disease designation (or eligible for rare pediatric disease designation but not orphan designation), there is significant overlap in the two product categories and information require to be submitted to the FDA. Creating a common application

1201 Maryland Avenue SW
Suite 900
Washington DC 20024
202.962.9200 P
202.488.6306 F
bio.org

path would serve to reduce administrative review burden by creating greater efficiency for FDA while eliminating duplicative applications for industry.

BIO also requests that the FDA provide additional clarity in the Draft Guidance regarding the transfer procedures for the RPD PRV. The Draft Guidance indicates that FDA must be notified within 30 days of a PRV transfer, and that the notification must be submitted with the NDA/BLA using the PRV. However, the guidance should clarify which FDA division/office should be notified within 30 days of the transfer in situations where the transferee has not decided at that time to which NDA/BLA it will be applying the PRV.

The guidance would also be strengthened if the Agency provided examples of diseases, briefly discussing the Agency's considerations and rationale when deciding on a product's eligibility (or ineligibility) for the RPD PRV Program. Examples along with an explanation as to why the particular diseases is or is not eligible for the PRV program can help Sponsors determine if their products are adequate for the RPD PRV, and also avoiding an undue burden on the Agency from the review of non-eligible applications.

BIO appreciates this opportunity to submit comments regarding FDA's Draft Guidance, Rare Pediatric Priority Disease Review Vouchers. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/
Danielle Friend, Ph.D.
Director, Science and Regulatory Affairs
Biotechnology Innovation Organization

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
II. BACKGROUND AND OVERVIEW		
III. DEFINITIONS, POLICIES, AND PROCEDURES-QUESTIONS AND ANSWERS		
A. Rare Pediatric Disease Product Applications		
Lines 108-117	In this section the FDA notes that "… if treatment for the disease or condition begins in childhood, but under current standard of care the manifestations of the disease or condition are not serious or life-threatening in children, the disease or condition is not a rare pediatric disease." BIO believes that associating the assessment of whether a condition is a rare pediatric disease to the current standard of care exceeds the FDA's statutory authority, is inconsistent with the intent of the rare pediatric disease priority review voucher program and is unnecessary as a policy matter. In particular, the Advancing Hope Act of 2016 and associated requirements stated therein indicate that a rare pediatric disease "is a serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years" (21 U.S.C. § 360ff(a)(3)(A)), does not contain any limitation regarding current treatments. Had Congress intended to limit qualifying treatments to diseases where there is an unmet need, they could have done so expressly, as they did in the case of the fast track program (*see* 21 U.S.C. § 356(b)(1)). Moreover, it is clear that	To ensure that the Guidance is consistent with statute and the intention of Congress, BIO recommends that the FDA eliminate the following text. ~~**Similarly, if treatment for the disease or condition begins in childhood, but under current standard of care the manifestations of the disease or condition are not serious or life-threatening in children, the disease or condition is not a rare pediatric disease.**~~ ~~**FDA will consider the manifestations of the disease or condition in the context of standard of care for the disease or condition. Specifically, FDA will consider what manifestations of the disease or condition are serious or life-threatening in children under standard treatment for the disease or condition. Therefore, FDA will not consider the serious or life-threatening manifestations of the disease or condition that only occur when the disease is left untreated if that is not the standard of care.**~~

SECTION	ISSUE	PROPOSED CHANGE
	Congress did not intend to limit the rare pediatric disease PRV program to diseases for which there is an unmet need, because the statute provides for the Comptroller General to conduct a study assessing (among other things) "[w]hether, and to what extent, an unmet need related to the treatment or prevention of a rare pediatric disease was met through the approval of such a rare disease product" (21 U.S.C. § 360ff(i)(1)(B)(ii)). If Congress intended the program to require an unmet need– i.e., that the manifestations of the disease continue to be serious and life threatening under existing standard of care – then there would be no need for the Comptroller General to study this. In addition, we note as a policy matter that one of the statutory criteria for qualifying for a rare pediatric disease PRV is that the application receives priority review (21 U.S.C. § 360ff(a)(4)(C)). To qualify for priority review, the product must provide a significant improvement in safety or effectiveness over available treatments. The requirement that the application receive priority review addresses the potential concern from a policy perspective that products that do not make a significant impact on treating a rare pediatric disease would be eligible to receive a PRV. It is therefore unnecessary for FDA to impose an additional statutory requirement to consider whether a condition is a rare pediatric disease in the context of current standard of care treatments.	
Lines 118-125	In this section, the FDA indicates that they "will assess the serious or life-threatening manifestations	To avoid confusion and to mitigate differing interpretations regarding the FDA's reference to the proportion of children

SECTION	ISSUE	PROPOSED CHANGE
	of the disease or condition and determine which manifestations primarily affect children and which primarily affect adults. Factors in determining if a manifestation primarily affects children include: timing and rate of disease progression (e.g., end-stage organ disease occurs in childhood), manifestations of abnormal growth or development, and **whether the proportion of children is greater than the proportion of adults with the given manifestation.** If the disease or condition has a manifestation that primarily affects children, FDA will consider the disease or condition to be a rare pediatric disease."	needing to be greater than the proportion of adults with the given manifestation, BIO requests the following edit: FDA will assess the serious or life-threatening manifestations of the disease or condition and determine which manifestations primarily affect children and which primarily affect adults. Factors in determining if a manifestation primarily affects children include: timing and rate of disease progression (e.g., end-stage organ disease occurs in childhood), manifestations of abnormal growth or development, and whether the **absolute number or** proportion of children is greater than the **absolute number or** proportion of adults with the given manifestation.
Lines 214-216	The FDA states that the "priority review voucher request should include scientific justification of how the approved indication will be clinically meaningful to pediatric patients with the disease or condition."	Greater detail on the approach to inclusion of this request in the application would be helpful. For example, for the tropical disease voucher, a specific location (Module 1) is specified. In the final guidance, BIO requests that the FDA include further details on expectations around submission of the justification and request, such as location in the submission.
Lines 235-241	FDA's expectation that applicants submit data adequate for labeling in the "full range of affected pediatric populations" is inconsistent with the statutory text. The statute requires examination of "a" pediatric population. It does not call for an examination of "the" pediatric population or all pediatric patients affected by the disease. We acknowledge that, in finalizing the guidance, FDA introduced some additional flexibility to allow limitation to pediatric age ranges that are	BIO requests the following edit: It is important that applicants seeking a voucher submit data adequate for labeling the drug for use **in the studied pediatric population.** ~~**by the full range of affected pediatric patients, within reasonable limits (i.e., all pediatric patient age ranges affected by the disease that are reasonable to include in the studies without undue delays in completing the studies and submitting the application). The studied pediatric population should be clinically meaningful and represent more**~~

SECTION	ISSUE	PROPOSED CHANGE
	"reasonable to include . . . without undue delays," so long as the population included is "clinically meaningful" and "represent[s] more than a token pediatric population." However, these limitations are inconsistent with the statute, which does not contemplate any limitation other than inclusion of "a" pediatric population. In addition, these concepts are undefined in the guidance and provide no basis on which sponsors can reasonably determine whether their study design would satisfy this requirement. For instance, the phrase "more than a token," and expectations for meeting that quantification with respect to applying this phrase, is unclear.	~~**than a token pediatric population. Such labeling aligns with the intent of section 529, which is to help address the unmet medical needs of pediatric patients with rare pediatric diseases.**~~
Lines 253-254	Regarding Q5: "What does 'Does not seek approval for an adult indication in the original rare pediatric disease product application?". In the answer, FDA notes that they interpret this criterion to mean that applicants cannot seek approval for a *different* adult indication (i.e., for a different disease/condition) in the original rare pediatric disease application.	BIO requests that the FDA provide clarity for the industry on products which are seeking a tissue agnostic approval for the original NDA or BLA where one of the listed tissue-agnostic indications is a pediatric rare disease (which otherwise meets all of the criterion to be eligible to be granted a pediatric disease designation), and the other tissue-agnostic indications are for adult-only rare diseases.
B. Requesting Rare Pediatric Disease Designation		
Lines 369-384	In this section the FDA indicates that "FDA recognizes that some sponsors may wish to submit a rare pediatric disease designation request at a different time – for example, if they had already submitted requests for orphan-drug and/or fast track designation before the enactment of FDASIA, or if for whatever reason they have no interest in submitting	To be inclusive of all expedited approval pathways, BIO requests that the FDA make the following edits: "FDA recognizes that some sponsors may wish to submit a rare pediatric disease designation request at a different time – for example, if they had already submitted requests for orphan-drug and/or ~~**fast track**~~ **an expedited approval**

SECTION	ISSUE	PROPOSED CHANGE
	either such request but do want to submit a rare pediatric disease designation request. FDA is willing to accept designation requests submitted at a different time than that provided by statute as long as FDA receives the designation request before FDA has filed the NDA/BLA for the drug for the relevant indication. Although we will aim to respond to such requests in a timely manner, the 60-day response deadline does not apply. We will not accept requests for rare pediatric disease designation received after FDA has already filed the NDA/BLA for the drug for the relevant indication."	**pathway** designation before the enactment of FDASIA, or if for whatever reason they have no interest in submitting either such request but do want to submit a rare pediatric disease designation request. FDA is willing to accept designation requests submitted at a different time than that provided by statute as long as FDA receives the designation request before FDA has filed the NDA/BLA for the drug for the relevant indication. Although we will aim to respond to such requests in a timely manner, the 60-day response deadline does not apply. We will not accept requests for rare pediatric disease designation received after FDA has already filed the NDA/BLA for the drug for the relevant indication."
Lines 375-382	FDA states that it "is willing to accept designation requests submitted at a different time than that provided by statute as long as FDA receives the designation request before FDA has filed the NDA/BLA for the drug for the relevant indication," noting however that, with respect to these submissions, "the 60-day response deadline does not apply."	This flexibility in approach is greatly appreciated. BIO requests that the FDA provide some sense of the timeline for expected response, beyond "timely manner" would be helpful (e.g., not more than X days).
C. Requesting a Rare Pediatric Disease Priority Review Voucher		
D. Using and Transferring a Rare Pediatric Disease Priority Review Voucher		
Lines 669-671	In this section the FDA indicates that "The application using the priority review voucher must be submitted under section 505(b)(1) of the FD&C Act or section 351 of the PHS Act and is not limited to drugs for rare pediatric diseases," however there is no reference to indicate whether a voucher can be used for a supplement.	BIO requests that the FDA clearly indicate in the answer whether a voucher can be used for a 505(b)(2) application and/or a supplement. Currently, the answer simply refers to a previous footnote and that footnote only discusses the applicability of a voucher to a 505(b)(2) application. To avoid any confusion, we request that the FDA explicitly note in the answer the potential use of a voucher for a 505(b)(2) application and/or a supplement.

SECTION	ISSUE	PROPOSED CHANGE
E. Specific Eligibility Questions		
F. Relationship between Rare Pediatric Disease Designation and Orphan-Drug Designation		
Lines 749-758	To better convey the eligibility of combination products for priority review vouchers in addition to a drug-drug combination BIO recommends that the Agency should also discuss the eligibility of all combination products (i.e. drug-biologic, drug-device, biologic-device, biologic-biologic combinations) for a priority review voucher.	BIO requests the following edit: A combination drug, **also referred to as drug-biologic, drug-device, biologic-device, biologic-biologic combinations**, is eligible for a voucher if the combination product submitted under section 505(b) of the FD&C Act contains a drug substance or biologic that has not been approved in any other application under section 505(b) of the FD&C Act.
G. Agency's Responsibilities and Roles		