Biotechnology Industry Organization

February 13, 2015

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

Re: Docket No. FDA-2014-D-1461: Rare Pediatric Disease Priority Review Vouchers

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the Draft Guidance for Industry entitled "Rare Pediatric Disease Priority Review Vouchers."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 members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products.

GENERAL COMMENTS:

BIO appreciates FDA's implementation of the rare pediatric disease priority review voucher (PRV) in a manner that stimulates new drug development of new therapies for devastating childhood diseases and serious conditions through additional incentive mechanisms. On the whole, we believe that the Draft Guidance is well written, clear, and will clarify the process of seeking the rare pediatric disease designation and rare pediatric disease priority review vouchers.

A. Definition of Rare Pediatric Disease

BIO would like to ensure that FDA guidance on the rare disease PRV program, including in this Q&A document, is reflective of Congressional intent in passing Section 529 of the *Food and Drug Administration Safety and Innovation Act of 2012* (FDASIA). For instances, in Section 529 a rare pediatric disease is defined as a disease that "primarily affects individuals aged from birth to 18 years…" We note that in question one of the Q&A, FDA states that it has interpreted this Congressional language to mean that a rare pediatric disease is one in which "greater than 50% of the affected population in the U.S. is aged 0 through 18 years." In passing Section 529, Congress intended to incentivize development of new drug for rare pediatric diseases such as childhood cancers and

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

sickle cell disease.[1] However, it is unclear whether FDA's interpretation as currently stated would be inclusive of such diseases. BIO asks that FDA review its interpretation of Section 529 to ensure consistency with Congressional intent and to clarify this consistency to the public.

Additionally, we note that it is not just the age of patients that makes a disease a pediatric one. As treatments for pediatric diseases increase the lifespan of those affected into adulthood, the majority of interventions and other issues dealt with by patients still occur and have the greatest impact during pediatric years. Such diseases do not stop being pediatric diseases when patients begin to live into adulthood. It is critically important for such diseases that progress in treatments and increase of lifespans into adulthood does not affect the ability of these diseases to be recognized as pediatric diseases and benefit from this incentive. One way to ensure such diseases meet both the Congressional intent of Section 529 and take into account successful treatment of disease into adulthood is to interpret the definition for rare pediatric disease using a population-based rate, in which a disease would quality as "primarily affecting" the 0-18 year olds if the prevalence of the disease in that 0-18 year old group was higher than the prevalence of the disease in patients > 18 years old.

B. Priority Review Voucher Program Cap

We also note that the pediatric rare disease PRV program was initially limited to roughly three PRVs and that FDA may not award any priority review vouchers after the last day of the 1-year period that begins on the date that the FDA awards the third rare pediatric disease priority voucher. Congress also instructed the Government Accountability Office to publish a study on the program, which is required to be submitted one year after the issuance of the third PRV.

Given the market interest in pediatric PRVs and their potential value, we believe that the arbitrary cap on rare disease PRVs should be lifted. The limitation of three vouchers introduces significant uncertainty and unpredictability for sponsors who are considering the risky, long, and costly investment into a clinical development program for rare pediatric condition, especially if the three vouchers have been exhausted by the time of FDA filing. BIO looks forward to working with Congress to make the program permanent, similar to the tropical disease PRV program.

While lifting the statutory PRV cap that is beyond the scope of this particular guidance, BIO does believe it is important for FDA to implement a mechanism for notifying the public and industry when the third PRV has been issued and the clock has begun ticking on the final year of the program. This recommendation is consistent with the statutory requirement under §529(f)(1)(B) that FDA notice in the Federal Register when each PRV has been issued. This will allow industry to make any necessary course corrections in

[1] 112th Congress, 2nd Session, Vol. 158, No. 94, pages H3825-H3868 https://www.congress.gov/congressional-record/2012/06/20/house-section/article/H3825-1

their development program to facilitate potential submissions within the one-year window.

C. Additional Comments:

In addition to ensuring legislative intent is reflected in FDA policies and guidances, we request clarification on the below items in this Q&A:

- The Draft Guidance is unclear on whether or not a drug that is a New Chemical Entity, but has the same mechanism of action as a previously approved drug, qualifies for a rare pediatric disease PRV. We believe clarification on this point would be beneficial to Sponsors.

- We ask FDA to clarify what is meant by the term "active ingredient" in the Draft Guidance. We feel it is unclear whether the term refers to "active moiety" or to some other definition. "Active ingredient" and "active moiety" do not have the same definition under regulations. We believe that the Draft Guidance may refer to the definition of new chemical entity under 21 CFR 314.108 but it is unclear.

- The Draft Guidance describes how drugs and biologics in rare pediatric diseases might qualify for pediatric PRV, but we would welcome additional clarification on whether drug-device combinations might qualify for a pediatric priority review voucher. In BIO's view, a combination product where the primary mode of action is a drug or biologic should be considered eligible for a PRV.

- We would appreciate clarity on whether clinical data in all pediatric age groups affected by the rare disease is required in the original application in order to be eligible for a pediatric PRV, or if clinical data in at least one pediatric age group at the time of the original application would be sufficient.

- BIO requests additional clarity that the status of a PRV would not be affected if a Sponsor pursues a New Chemical Entity for a second non-pediatric indication simultaneously, but does not submit for marketing authorization or approval of that subsequent indication.

- While the Draft Guidance discusses whether a company can obtain a PRV for a later indication of an already marketed drug in Q&A 26, it does not address whether a company that obtained a PRV for a drug use the voucher for another indication of the same drug. BIO believes that the PRV could be used for a later indication of the same drug, but we believe a Q&A on the subject would be helpful to Sponsors.

- The Draft Guidance discusses the process for transferring a pediatric PRV from the original party which filed for and received approval of the pediatric rare disease product ("transferor") to another party ("transferee"). The Statute states in §529(e)(1) that "The Secretary may revoke any priority review voucher

awarded under subsection (b) if the rare pediatric disease product for which such voucher was awarded is not marketed in the United Sates within the 365-day period beginning on the date of the approval of such drug…" However, if a PRV has been transferred or sold to another party and the transferor does not market the original product within the 365-day window required by law, the implications to the transferee of the priority review voucher are unclear. BIO believes that to ensure confidence in the PRV system and market the PRV under the control of the transferee should not be affected if the transferor does not fulfill their obligations.

- Finally, BIO would like confirmation that a PRV does not have an expiration date.

CONCLUSION:

BIO appreciates this opportunity to comment on the "Rare Pediatric Disease Priority Review Vouchers" Draft Guidance. Specific, detailed comments are included in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Andrew J. Emmett
Managing Director, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)

SPECIFIC COMMENTS

SECTION	COMMENT WITH RATIONALE	PROPOSED CHANGE
I. INTRODUCTION		
II. BACKGROUND AND OVERVIEW		
III. DEFINITIONS, POLICIES, AND PROCEDURES – QUESTIONS AND ANSWERS		
A. RARE PEDIATRIC DISEASE PRODUCT APPLICATIONS		
Page 5, Question 3	We believe that the wording of the response to Question 3 could lead the reader to believe that dose ranging and efficacy studies must both be conducted in the same pediatric population for which a sponsor requests approval. There are instances in which dose ranging may be conducted in a pediatric population in an indication(s) that will provide sufficient PK data for advancement into later stage studies and in labelling though the indications studied may vary (*i.e.* in pediatric oncology, where dose ranging is frequently conducted in patients with a variety of solid tumors or hematologic tumors in a single study).	BIO suggests editing the text as follows: "As noted in the response to Question 2, an applicant cannot receive a rare pediatric disease priority review voucher unless, among other things, the application '[r]elies on clinical data derived from studies examining a pediatric population and dosages of the drug intended for that population or a related relevant pediatric population.' We interpret this clause to mean that, to be eligible for a voucher, the approved product…"
Page 5, Question 3	The Draft Guidance states "It is important that applicants seeking a voucher submit data adequate for labeling the drug for use by the full range of affected pediatric patients (*i.e.,* all pediatric patient age ranges that are affected by the disease)."	We believe it would be helpful to know if a population PK approach with limited covariate analysis due to the small sample size is acceptable to evaluate differences in the PK between adult and pediatric populations based on a single trial which include both adult and pediatric populations.

SECTION	COMMENT WITH RATIONALE	PROPOSED CHANGE
	This statement suggests data is required from all pediatric age ranges. However, there are instances when a disease or condition may be present across all age ranges, but the necessary studies are impossible or highly impractical for a particular age group. Additionally, the overall number of subjects may be limited to allow for characterization of pharmacokinetics using frequent sampling approach.	As such, BIO suggests editing the text to include a caveat that studies may be impossible or highly impracticable for certain age ranges: "It is important that applicants seeking a voucher submit data adequate for labeling the drug for use by the full range of relevant affected pediatric patients (i.e., all pediatric patient age ranges that are affected by the disease)."
B. REQUESTING RARE PEDIATRIC DISEASE DESIGNATION		
Page 9, first full paragraph	The Draft Guidance states "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."	BIO requests that FDA respond to a designation request submitted prior to the filing of the NDA/BLA within 90 days as companies need a reliable timeline for a response.
Pages 9-10, Question 8	Section 7(i) describes the documentation required to demonstrate that a drug is being studied in a rare pediatric disease.	We believe further detail would be helpful to understand what are considered "authoritative references" to support estimated prevalence and meet definition of "orphan subset". As such, we ask FDA to clarify what is meant by

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		"authoritative references", possibly including examples.
Page 10, Question 8	The Draft Guidance states "Documentation, with appended authoritative references, to demonstrate that (a) the estimated prevalence of the affected patient population in the U.S…" For rare pediatric diseases, there are likely very few literature citations available for reference. When designating an Orphan Drug and Biological Product, FDA has accepted other sources of information beyond referenced texts and journals when there is limited data on prevalence.	As there are often very few literature citations available when dealing with rare pediatric diseases, BIO suggests including a caveat of other methods that could be used to demonstrate prevalence when data is not readily available in literature due to rarity of the disease. Additionally, we request that the FDA provide examples of what would be acceptable if relevant literature is not readily available.
Page 11, Question 9	Sponsors often submit Orphan Drug Designation requests electronically (*e.g.,* via CD-ROM). It is unclear if this method would be acceptable for a Rare Pediatric Disease Designation request as well.	BIO suggests editing the text to read: "Sponsors should submit two copies, with at least one hard copy, of the completed, dated, and signed rare pediatric disease designation requests or an electronic version of the designation request (*e.g.,* via CD-ROM), with the information specified in response to Question 8, to the Office of Orphan Products Development…"
Page 12, Question 10	The response to this question states that "…prevalence estimates generally will not be reevaluated at the time of NDA/BLA submission…" The response to Question 14 states that	In order to ensure alignment with the responses in Question 10, Question 14, and with the regulations regarding Orphan Drug Designation we suggest editing the text as follows: "If FDA designates the drug as a drug for a "rare pediatric

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	"Sponsors who have received rare pediatric disease designation for the drug and conditional designation for the application should include that designation letter with the voucher request and need not re-analyze prevalence estimates at the time of NDA/BLA submission." Per 21 CFR 316.29(c), "Where a drug has been designated as an orphan drug because the prevalence of a disease or condition (or, in the case of vaccines, diagnostic drugs, or preventive drugs, the target population) is under 200,000 in the United States at the time of designation, its designation will not be revoked on the ground that the prevalence of the disease or condition (or the target population) becomes more than 200,000 persons."	disease," these prevalence estimates ~~generally~~ will not be reevaluated at the time of NDA/BLA submission, but FDA will evaluate the remaining eligibility criteria to determine whether the NDA/BLA is eligible for a priority review voucher (see Question 2)." We also suggest deleting footnote 32: ~~Footnote 32 FDA does reserve the right to revisit a decision on prevalence estimates if it becomes apparent that information relevant to that question and available at the time of the submitted request for designation was not provided to FDA or known by FDA at the time of designation decision.~~
Page 14, Footnote 33	The information regarding how the FDA would request prevalence information from a Sponsor if the FDA determines the application could be eligible for a rare pediatric disease designation is important information that gets lost as a footnote.	We recommend moving this statement from footnote 33 to the main body of the document within "Section II. Background and Overview."
C. REQUESTING A RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER		
Page 14, Question 13	This question and answer in the Draft Guidance discusses requesting a voucher.	We believe the Draft Guidance is unclear on where in an NDA/BLA a rare pediatric disease priority review voucher should be requested. As such, we ask FDA to provide

SECTION	COMMENT WITH RATIONALE	PROPOSED CHANGE
		guidance about the location in an NDA/BLA for a request of a rare pediatric disease priority review voucher.
D. USING AND TRANSFERRING A RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER		
Pages 16-18, Questions 18 & 21	The Draft Guidance states, "If a sponsor does not submit the application on the intended submission date, the sponsor should inform FDA as soon as possible of the new intended submission date. If the sponsor decides not to use the voucher for the application described in the notification, the sponsor should withdraw the notification from FDA. The sponsor should submit a new notification informing FDA, at least 90 days before application submission, of its intent to submit a different human drug application with a priority review voucher and include the intended submission date."	We understand that the additional user fee is due when a Sponsor informs FDA of its intention to redeem it. We ask FDA to clarify whether the Sponsor can request a refund of the user fee if the Sponsor decides to not use the voucher for the application described in the notification and withdraws the notification from the Agency.
E. SPECIFIC ELIGIBILITY QUESTIONS		
F. RELATIONSHIP BETWEEN RARE PEDIATRIC DISEASE DESIGNATION AND ORPHAN-DRUG DESIGNATION		
G. AGENCY'S RESPONSIBILITIES AND ROLES		