Biotechnology Innovation Organization

February 16, 2018

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

**Re: Docket No. FDA-2017-D-6380: Clarification of Orphan Designation of Drugs and Biologics for Pediatric Subpopulations of Common Diseases**

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments regarding FDA's Draft Guidance, Clarification of Orphan Designation of Drugs and Biologics for Pediatric Subpopulations of Common Diseases.

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. Specifically, BIO and its member companies are committed to conducting pediatric studies that lead not only to innovative therapies for children, but also provide important pediatric labeling information on efficacy, safety, and dosing. As FDA notes in the Draft Guidance, the Best Pharmaceutical for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) are responsible for the addition of new pediatric information in labeling for over 600 products.

BIO appreciates the FDA's efforts to clarify and provide notice of an FDA policy change intended, as stated in the Draft Guidance, to enable FDA to apply the Orphan Drug Law (ODA) and PREA to non-rare adult indications that correspond to orphan-designated pediatric subpopulations. However, in the paragraphs that follow, BIO details several general concerns and specific line edits regarding the draft guidance and policy changes:

**General Comments:**
We recognize that FDA's interpretation and application of the ODA to grant Orphan Drug Designation (ODD) to drugs for use in pediatric populations based on prevalence/incidence alone preceded BPCA and PREA. As such, it may have inadvertently created a regulatory scenario in which PREA-required pediatric studies could be exempt by virtue of the designation. However, there are many examples of products that have been designated and are either being studied or have been approved for pediatric indications, reflecting that the regulatory scenario that may have been created has not kept innovator companies from investing in pediatric drug development for rare pediatric sub-population of a common disease. However, the terminology used by the FDA in the draft guidance implies that sponsors are acting inappropriately by taking advantage of a "loophole". BIO respectfully disagrees and requests that the FDA adjust this

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language within the guidance to reflect that it has been FDA's legal interpretation of the PREA that has allowed for such designations to be granted.[1]

Throughout the Draft Guidance, the FDA references the terms "*pediatric subpopulation(s)*" and "*pediatric-subpopulation designation(s)*" as common lexicon, however, these terms have not been previously defined or described within Title 21: Food and Drugs PART 316—ORPHAN DRUGS, nor, have the terms been used in past FDA orphan drug guidance, or the associated FAQs on the FDA web-site.[2] Specifically, these terms have not been described in question 14 of the FAQs, defining an "*orphan subset*". To this end, BIO requests that the above terminology be more clearly defined within the text of the Draft Guidance. Additionally, to more clearly demonstrate the FDA's thinking, BIO also requests that the FDA provide, in the Draft Guidance, specific examples as to what would constitute an "orphan subset" as defined by molecular characteristics, safety profile, and empirical evidence. BIO also asks for clarification of the term "different disease", included in bullet two of FDA's criteria for determining whether a product may receive orphan designation for a pediatric subpopulation (Draft Guidance, page 4). We also ask that specific examples be provided indicating what is meant by "different disease" as defined by endpoints, biomarkers, or other measures.

For clarity, we ask the FDA to revise references to prevalence to state the following:

- Orphan or rare diseases: less than 200,000 patients
- Common diseases or conditions: 200,000 or greater patients

BIO appreciates this opportunity to submit comments regarding FDA's Draft Guidance, Clarification of Orphan Designation of Drugs and Biologics for Pediatric Subpopulations of Common Diseases. In addition to the comments above and the line edits include in the attached table, BIO strongly believes that multiple incentives work in tandem towards broader public health outcomes, and this is particularly true in the case for rare disease drug development. BIO asks the FDA to continue to strive towards an appropriate balance of incentives to encourage rare disease drug development. We would be pleased to provide further input or clarification of our comments, as needed.

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

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[1] *See* FDA, Summary Review of NDA 22205, at 16 ("OCC interpreted the Act to mean that PREA does not apply to adult approvals in which the same indication has orphan designation in pediatrics.").

[2] Food and Drug Administration FAQs, https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm240819.htm

**Specific Comments:**

| SECTION | ISSUE | PROPOSED CHANGE |
|---|---|---|
| **I. INTRODUCTION** | | |
| **Lines** | In Section I (Introduction) the Draft Guidance states: "*The Food and Drug Administration (FDA) no longer intends to grant orphan drug designation to drugs for pediatric subpopulations of common diseases (i.e., diseases or conditions with an overall prevalence of over 200,000), unless the use of the drug in the pediatric subpopulation meets the regulatory criteria for an orphan subset,*[2] *or unless the disease in the pediatric subpopulation is considered a different disease from the disease in the adult population.*"<br><br>A similar statement is repeated in Section III (Discussion), without any additional detail with regard to the effect of implementation of this guidance on the status of orphan drug designations that have:<br>1. Already been granted but the product has been approved for the adult indication<br>2. Already been granted but the product hasn't been approved for the adult indication<br>3. The orphan drug designation request has been submitted to FDA or is already under review/consideration prior to the Draft Guidance being finalized | BIO interprets the wording "no longer intends" as being *only prospective in nature* and that finalization of the guidance will not affect regulatory actions already taken (e.g., products that have been granted ODD) or applications under review (e.g., ODD requests that have been submitted or are under review by FDA). Furthermore, it is BIO's interpretation that revoking existing designations would need to occur in a manner consistent with 21 CRF 316.29.[3]<br><br>BIO, therefore, recommends that FDA edit the Draft Guidance to expand on and clarify the prospective effect of the final guidance on orphan drug designation requests that have been submitted, are under review as well as on designations that have been granted, regardless of whether the product has been approved. |

[3] Code of Federal Regulations, Section 316.29 Revocation of orphan-drug designation

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| | BIO believes that the Draft Guidance would benefit from this type of information to reduce uncertainty associated with the impact of change in policy. | |
| **II. BACKGROUND** | | |
| **Lines** | | |
| **III. Discussion** | | |
| **1st Line/Page 3** | It is unclear which statutory provisions are referenced in the opening statement in Section III. | We ask the FDA to please clarify which statutory provisions are being referenced. |
| **1st Paragraph/ Page 3** | The inclusion of the FDARA cancer provisions within the Draft Guidance is confusing. The cancer provisions within FDARA indicate that the molecular target, not the disease, defines the pediatric population. Bullets 1 and 2 on Page 4 would imply that the majority of pediatric cancer populations would likely qualify as a valid orphan designation because of their clear genetic epigenetic variability from the adult disease. Therefore, inclusion of these FDARA provisions in this 'clarification' guidance seem counter-intuitive. | BIO suggests removing the inclusion of this text from the Draft Guidance. |
| **1st Sentence/3rd Paragraph/Page 4** | We do not believe that this statement as written reflects what is intended by the FDA as per other statements in the Background and Discussion sections of the Draft Guidance. Under the new guidance, the FDA will still be granting an orphan designation to qualified pediatric sub-populations of an over-arching non-orphan disease when they meet the requirements laid out in bullets 1 and 2 at the bottom of page 4. The FDA will not be granting an orphan designation to a pediatric sub-population of | We ask the FDA to clarify this statement. |

| SECTION | ISSUE | PROPOSED CHANGE |
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| | an over-arching non-orphan disease based on the pediatric prevalence alone. | |
| **2nd Paragraph/Page 3** | The inclusion of the FDASIA Rare Pediatric Disease Priority Review Voucher provisions are counter-intuitive as the pediatric populations, by definition of the law would qualify as a "rare pediatric disease". | BIO suggests removing the inclusion of this text from the Draft Guidance. |
| **Bullet 2/Page 4 and 5** | It is unclear whether the FDA is referring to full extrapolation, partial extrapolation, or both. Linking of an orphan designation for a pediatric subpopulation to the inappropriateness of pediatric extrapolation of efficacy seems possible, but this inappropriateness may be difficult to validate and it may have unintended consequences whenever pediatric studies require some adaptations (e.g. endpoints, background treatment) compared to adult studies in the same disease. Attempts at pediatric extrapolation with unexpected findings may not establish that efficacy cannot at all be extrapolated to children. | We ask the FDA to provide greater detail regarding the definition of extrapolation in bullet 2. BIO requests that in exception 2, the definition of extrapolation should include full or partial extrapolation. |