March 10, 2014

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

Re: Docket No. FDA-2013-N-0985: Complex Issues in Developing Drug and Biological Products for Rare Diseases

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments to the docket regarding "Complex Issues in Developing Drug and Biologics Products for Rare Diseases." Comments are being provided in two areas; general comments on the challenges of rare disease drug development, and specific comments in response to the public workshop.

BIO represents more than 1,000 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, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

I. General Comments on the Challenges of Rare Disease Drug Development:

BIO appreciates FDA's efforts in convening its two day public workshop on January 6-7th entitled "Complex Issues in Developing Drug and Biological Products for Rare Diseases" as required by the *Food and Drug Administration Safety and Innovation Act of* 2012 (FDASIA) and opening a docket for public comment. BIO was pleased to be invited to participate in Day One "Complex Issues in Rare Disease Drug Development" to provide an industry perspective of rare disease development.

Rare diseases represent an area of substantial unmet medical need: many are serious or life-threatening, and for the vast majority there are no approved therapies available for their treatment. Product development programs face unique challenges in terms of small patient populations and often a high degree of variability and heterogeneity within these small populations. As such, there is no one-size-fits-all approach to rare disease drug development and, likewise, no one-size-fits-all regulatory approach. Thus, thinking creatively and acting flexibly are crucial for both developers and regulators to ensure patients get safe and effective treatments as quickly as possible. Furthermore, patients can play a critical role in the development of products for rare diseases and should be engaged throughout the drug discovery process. It is particularly critical for rare disease therapies that the FDA drug review process be grounded in a careful evaluation and balance of both benefits and risks made in the broader context of disease rarity and severity, patient perspectives, and the body of available scientific evidence.

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BIO believes FDA has taken some important first steps regarding its regulation of drugs for rare diseases and in implementing its FDASIA requirements. Below, we provide several questions and requests for FDA as the agency continues to move forward in this area and look forward to continuing to engage with FDA and other stakeholders.

A. Expedited Programs and Accelerated Approval for Rare Disease Products

BIO believes Accelerated Approval can be a powerful tool for expediting the development of therapies for rare conditions. We were pleased that provisions of FDASIA highlighted specific new ways that the Accelerated Approval approach could be applied and, in particular, included a consideration of the rarity of a disease as a key factor in determining when to apply it. To aid Sponsors in understanding various expedited review pathways, FDA released a Draft Guidance for Industry in June 2013 entitled "Expedited Programs for Serious Conditions—Drugs and Biologics." While this Draft Guidance is useful in explaining the procedures, eligibility criteria, and general features under each of the four expedited pathways—Accelerated Approval, Fast Track, Priority Review, and Breakthrough Therapies—it does not discuss the unique issues associated with rare diseases under the Accelerated Approval paradigm as directed by FDASIA.

To promote a common understanding of how Accelerated Approval will apply for rare diseases, we urge FDA to include this detail in the Final Guidance. In particular, we urge that the Final Guidance reference the specific inclusion, as directed by FDASIA, of the unique considerations for rare diseases in decisions about the use of the Accelerated Approval pathway. This includes, but is not limited to, the Agency's data requirements for rare disease products seeking Accelerated Approval and the feasibility of meeting those requirements given the inherent complexities of developing rare disease drugs and biologics. In particular, the Final Guidance should address how the Agency will apply flexibility in cases where small patient populations can benefit from the Accelerated Approval pathway, as well as other unique considerations for rare diseases. For example, in rare diseases that affect pediatrics, the loss of core functions is a critical event for the patient and his or her caregivers, which must be considered adequately in FDA's risk/benefit calculations and decisions to apply the Accelerated Approval pathway.

B. Evidentiary Standards for Endpoints

1. Use of Intermediate or Surrogate Endpoints

BIO believes intermediate clinical and surrogate endpoints such as biomarkers are integral in clinical development of a product, especially for rare diseases. However, a framework is needed to define the degree of evidence, and the robustness of data required, to justify whether the surrogate/biomarker or intermediate clinical endpoint is predictive of a clinical outcome. We request that FDA work with stakeholders to establish pragmatic evidentiary criteria or a framework correlating the surrogate/ intermediate clinical endpoints with clinical benefit, taking into account the rarity of the disease, so this does not continue to be an issue that delays or forestalls development programs.

Further, guidance is needed that clearly outlines the evidentiary standards needed for the acceptance of surrogate and intermediate clinical endpoints for the Accelerated Approval of drugs to treat rare diseases and other serious and life-threatening conditions. Often

biomarker validation is more challenging in rare diseases and in the case of Accelerated Approval, this should be taken into consideration and regulatory flexibility should prevail.

2. Novel Endpoints

We request that FDA develop a framework addressing development of novel endpoints in the rare disease setting and specifically acknowledging the challenges and providing potential options to overcome the complex rare disease issues. A more defined and achievable regulatory pathway for developing novel endpoints would also encourage and stimulate needed innovation.

We propose that the Agency work with industry Sponsors, specifically companies involved in the rare disease space, to develop a framework addressing the rare disease-specific challenges and defining the expectations for using novel endpoints in rare diseases, yet allowing the appropriate flexibility given disease heterogeneity and very small patient populations.

Early communication with Sponsors on endpoint selection and validation is crucially important in the development of drugs for rare diseases; FDA should establish a process for discussing and selecting endpoints earlier in drug development. As time is essential for these patients, FDA readiness to meet with Sponsors to establish clinical protocols can have significant and life-enhancing benefits.

C. Rare Disease Program

We note that the PDUFA V FY13 Performance Report states that "FDA drafted a staffing and implementation plan for the Rare Disease Program in CDER's Office of New Drugs and increased the staff capacity of the Rare Disease Program to include the five positions stipulated in the Commitment Letter."[1] However, to our knowledge this staffing and implementation plan has not yet been published and we encourage FDA to make it available to the public. Furthermore, in light of the hiring freeze that was in place during sequestration, it is unclear if the five new full time equivalent (FTE) positions mentioned represent new FDA staff hires or reallocated staff from within the Agency. We believe a greater understanding of the roles and responsibilities of the enhanced program is essential.

BIO would appreciate clarity surrounding the Program's mandate and how the Program interacts and coordinates within the Agency, including:

- The relationship between the Program, the Office of Orphan Product Development, and the review divisions;
- The Program's interactions with Sponsors;
- The role of the Program in the review process; and
- How and when the reviewer training agreed to under PDUFA V will take place.

In particular, BIO believes this training is a critical part of the Rare Disease Program's mission and should include educating reviewers about the unique features of applications for approval of a drug for a rare disease, design of clinical trials for rare diseases, application of statistical analyses appropriate for very small numbers of patients, and, in general,

[1] FY2013 Performance Report to the President and Congress for the Prescription Drug User Fee Act, page 14, http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/UCM384035.pdf

employing flexibility when conducting such reviews. BIO would also appreciate knowing the anticipated timeline for initiating this training.

II. Specific Comments in Response to the FDA Public Workshop:

In addition to our general comments above, we also have the following more specific and targeted comments regarding the topics of the meeting.

A. Endpoints

As mentioned above, BIO believes that clear evidentiary standards for endpoints, such as biomarkers for limited populations, are vital. It is important for FDA to recognize that the standards required for common diseases are not practical, nor feasible, for rare diseases. Although FDASIA amended the language for Accelerated Approval regarding the use of biomarkers, the scientific basis and context for use are not clear. In order for the benefits of these amendments to be realized fully, FDA clarification and guidance are crucial.

As biomarker qualification is time-consuming, it would be helpful if FDA would provide a separate process for this, outside the construct of the established clinical development Type C meetings. Such a process could bring biomarker developers together with the Agency in a timeframe conducive to achieving validation of a biomarker and agreement on a surrogate endpoint in time for development to proceed expeditiously.

The importance of novel endpoints to adequately capture the benefits of treatments for rare diseases was noted during the meeting. BIO appreciates the progress the Agency has made in the previous two years, including, for example, through its January 2014 Guidance on the Qualification Process for Drug Development Tools. However, there is still work to be done, specifically with regard to the current system that results in either a delay of a promising product to attempt to qualify a novel endpoint or employing an otherwise imperfectly suited existing endpoint. This is not ideal or efficient, and we feel contributes to the slower development of rare disease products in general.

An inability to qualify or validate novel surrogate endpoints or biomarkers, and the difficulty of completing large, randomized controlled confirmatory/verification studies, creates extraordinary hurdles that deter action on drugs for rare diseases. Additionally, in diseases that impact pediatric populations, the value of pathological data must be weighed alongside the vulnerability of these patients.

Further regulatory flexibility around primary and secondary endpoint selection is needed because of the difficulty of predetermining clinically meaningful primary and secondary endpoints for a rare disease (*e.g.,* it is important to consider how to employ creative strategies that identify clinically meaningful endpoints but factor in the outcome measures in selecting an appropriate primary and secondary endpoint).

B. Study Design, Conduct, and Analysis

In the area of trial design for rare disease products, there is a strong need for clearer policy on extrapolation to sub-populations within orphan indications, including pediatric sub-populations, given the impracticality of enrolling trials with such small populations. It is also

important to allow for creative bridging strategies from adult rare disease settings to pediatric rare disease settings.

Guidance is needed on the use and acceptability of data from non-traditional study designs—including observational data sources, natural history studies, the use of cross-sectional designs, and patient registries—to inform FDA benefit/risk decision making.

Flexibility should include a consideration of regulatory options that allow drugs for rare and ultra-rare diseases to reach the market earlier, especially for those diseases for which no current treatments are available and diseases in which patients tend to rapidly lose functional status.

There is a strong need to develop more robust guidance on how best to utilize Breakthrough Therapy Designation for rare disease products, given the challenges with unknown natural history and lack of clinical endpoints. For complex biological products, a crucial hurdle is the required substantial investment to speed up manufacturing and chemistry, manufacturing, and controls (CMC) activities. The inability to obtain such investment, in many cases, will prevent meeting shortened development timelines. It is also important for FDA and stakeholders to continue to discuss, beyond guidance, new scientific tools that can be leveraged to advance expedited approvals for rare disease products.

It is important to incorporate the patient view more fully into regulatory considerations and to broaden the range of patient input so regulators better understand the burden of the disease and the patient perspective on benefit versus risk. Many outcome measures evaluating the most important patient symptoms have not previously been used as primary endpoints. This brings particular challenges in evaluating a drug's effectiveness.

The two current FDA Guidances—*Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* and *Qualification for Drug Development Tools*—on developing and qualifying endpoints provide useful information, but are challenging to implement in the rare disease setting. Development of endpoints using the Patient Reported Outcome (PRO) Guidance is overly burdensome due to the guidance-specified sequential nature and number of patients required to establish a clinically meaningful change. In addition, it is challenging to meet the requirement that clinical endpoints must demonstrate a therapeutic effect in small patient populations having a slow progression of disease. A guidance on patient reported outcomes (PROs) as they pertain to rare disease drug development would be very helpful.

Sponsors and FDA need to consider ways to elucidate patient viewpoints at very early stages of the product development process. Specifically, it is critical for patients, FDA, and Sponsors to have an early understanding of patients' views regarding meaningful benefits and the level of risk patients are willing to assume to obtain these benefits. It is important in this regard to listen to all patients and seek alignment among patients, FDA, and Sponsors on benefit-risk assessment.

In rare diseases there are few experts who help define the field and knowledge in specific disease areas. As FDA considers applying flexible and expedited regulatory pathways, including Accelerated Approval, FDA scientists should have a way of engaging experts in the forefront of science and lead clinicians in order to solicit their expertise and gain insight into the disease state and risk tolerance of those being treated.

1. Responder analysis

FDA's preference to analyze patients meeting a predefined definition of responder for a specific symptom(s) is not realistic for small patient populations, most especially small patient populations with slowly progressing, heterogeneous diseases. Responder analysis raises three issues. First, there is the challenge of defining a responder in small heterogeneous diseases. Secondly, determining efficacy based on responders with a heterogeneous disease seems to run counter to FDA's current policy of investigating a drug's efficacy in as broad a spectrum of the patient population as possible. Finally, powering a study based on a responder analysis is not feasible for small patient populations. Heterogeneous disease is part-and-parcel of many rare diseases. Setting a predefined bar for a specific symptom would exclude enrollment of potentially a large segment of the patient population with other potentially equally debilitating symptoms. Instead of generating evidence of effectiveness based on responders based on a single outcome measure we should be evaluating the totality of evidence across all patients.

2. Disease Specific Meetings

We recommend that FDA collaborate with external stakeholders to increase the number of disease-specific meetings—in particular, meetings for diseases with no approved treatments—and use the information from these meetings to generate publications on best practices for developing drugs to treat those specific diseases.

3. Natural History Studies

Natural history studies are frequently initiated by patient organizations. It takes many years and considerable resources to generate longitudinal data. Cross sectional data also provides valuable information and should not be ignored. Robust cross sectional data from a well-designed study is more useful than longitudinal data from a poorly designed or executed study.

C. Foundational Science

There is a need for increased reliance on nonclinical data in the development of drugs for rare diseases, where clinical data would be highly impractical or impossible to obtain. Guidance regarding circumstances under which FDA would agree with this possibility may be warranted.

Guidance also is needed regarding the circumstances in which natural history studies may be useful and how they can be used toward approval of a drug for a rare disease.

It may be helpful to identify ways Sponsors can engage the Agency early (pre-IND or earlier) to discuss how increased utilization of nonclinical research tools *(e.g.,* from computational modeling, human induced pluripotent stem (iPS) cell and genetic animal models of disease) could be combined with limited knowledge of natural history to build a more robust pathophysiological map of the rare disease (from molecular characteristic to clinical outcomes) as the basis for designing a clinical development program.

D. Safety and Dosing

Preclinical safety assessment for some biological products intended for rare diseases can be challenging due to the often special nature of these products and the unavailability of animal models of some of these rare diseases. Often, toxicity concerns are not easily addressed in animals and surrogate systems have applicability restrictions and caveats. For animals or humans, it may also be difficult to develop pharmacokinetic and pharmacodynamic assays for such products. Thus, the traditional tools and methods for providing preclinical support to project the pharmacologically active dose and define the first-in-human dose may not apply. Therefore, it may be exceptionally difficult to define or to put dose into context. As a result, patient risk may not be as well defined.

Additionally, due to the small number of patients enrolled in clinical trials for rare disease and the heterogeneity of these patients, it may be difficult to assess safety and efficacy of multiple doses. As such, FDA guidance on dose evaluation in small populations would be helpful.

E. Pediatrics

We ask FDA to provide clearer guidance on the requirements for first-in-human trials in a pediatric rare disease indication for drugs and biologics, including standardizing approaches across review divisions. Clarity surrounding "reasonable enrollment period" and "due diligence" to identify patients for a study is needed to address recruitment and endpoint selection challenges. Again, the pressing need of this patient population and the risk tolerance of their families must be considered in trial implementation and trial size.

We also encourage FDA to continue to look for innovative ways to incentivize the development of new treatments over time. If a submitted Written Request is deemed inadequate, we encourage FDA to provide specific guidance to the Sponsor on ways to make their proposal acceptable.

We understand that FDA is currently developing draft guidance on Pediatric Rare Disease Priority Review Vouchers (PRV), which we think would be helpful in ensuring that the law is fully implemented as intended. As the guidance is being drafted, we request that the Agency consider establishing criteria for eligibility of a PRV, specifically, defining "primarily" in children based upon disease incidence, so that important disease areas that continue to be treatment challenges would not be excluded from the program and are sufficiently incentivized. In addition, we request clarification regarding the language in the statute "does not seek approval for an adult indication in the original rare pediatric disease product application" (Sec. 529 [360ff](a)(4)(E)), that is, we ask FDA to clarify that the Sponsor can submit an New Drug Application (NDA) or Biologics License Application (BLA) for an adult indication concurrently with an ongoing review of the rare pediatric disease filing. Lastly, if a Sponsor conducts a full pediatric development program, we believe that the Sponsor should still be awarded the PRV as they would for exclusivity under the Best Pharmaceuticals for Children Act (BPCA) of 2007, regardless of the results of the pivotal trials or ultimate filing of the rare pediatric disease application.

F. Layout and Organization of Meeting

BIO appreciates the efforts put forth to meet the FDASIA requirements ahead of schedule and commends FDA on a positive first step in organizing this event and initiating a more

structured dialogue with multiple stakeholders around this important, complex, and multi-faceted topic. We look forward to additional meetings in the near future. In the meantime, and in anticipation of such future events, we would like to take this opportunity to offer our comments on the structure of the Public Workshop itself as we believe that the way the discussion was structured impacts its outcomes and follow-up. Moving forward and for future such events, BIO recommends that FDA follow a similar model as was used for Day Two of the Workshop as a way to optimize stakeholder engagement and foster even more productive and substantive dialogue. We note specifically that for Day One, the breadth and depth of the topics envisioned for discussion within each of the four sessions lent themselves better to having individual experts for each session, per the Day Two model, versus having the same group of panelists for all four sessions. Following this model for future workshops would ensure a more effective use of expert panelists, better coordinated moderation, better facilitated patient/caregiver input, and increased audience interaction. This format in turn allows for a deeper, more well-rounded discussion of each of the diverse topics.

Additionally, we appreciate the Agency's efforts to communicate with stakeholders in advance of the meeting and believe there are additional opportunities for routinizing these communications, refining the information that is shared, and establishing realistic target timelines over which the information is communicated. This is especially important to ensure these dialogues are as productive and efficient as possible, and participants from all stakeholders, including the Agency, are available and prepared to discuss in detail relevant specific issues and potential resolutions.

Finally, we recognize that the technical and clinical discussions held during the sessions are an important consideration for rare disease development. We also feel that the regulatory and policy issues involved were not discussed as fully. We recommend that these topics be a focus of future meetings as these issues are also vital to the development of rare disease products.

CONCLUSION:

BIO appreciates this opportunity to submit comments to the docket regarding "Complex Issues in Developing Drug and Biologics Products for Rare Diseases." We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

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