BIOTECHNOLOGY INDUSTRY ORGANIZATION
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March 2, 2011

Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA–2011–N–0002: Advisory Committee for Pharmaceutical Science and Clinical Pharmacology; Notice of Meeting

Dear Sir/Madam:

On behalf of the Biotechnology Industry Organization (BIO), thank you for the opportunity to present our views regarding FDA policies to facilitate innovative approaches to the development of drugs for orphan and rare diseases. BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. Indeed, the mission of many biotech companies is to bring hope to and meet the needs of patients who suffer from rare diseases.

Our challenge today - that this meeting seeks to address - is to identify new or modified FDA approaches, policies, and processes that will further facilitate and eventually accelerate the development of the next generation of orphan products. Given the significant morbidity and mortality often associated with rare and orphan diseases, the unmet medical need, the societal costs, and the challenges of conducting trials in these patient populations, we believe that the current regulatory environment and FDA's review processes need to be re-evaluated and modified for orphan products. The regulatory approval pathway needs to be predictable, faster, and one that more clearly balances benefit/risk for these orphan disease patients and their families.

In general, small size of patient populations is a crucial factor in clinical study design and demands different, flexible approaches to FDA evaluation of trial design and statistical

analysis of results. Numbers of subjects for any orphan product study should be based on current disease situations. Additionally, given that these trials, especially registration studies requiring larger numbers of subjects, typically necessitate global recruitment, protocols should be able to satisfy institutional review boards and ethics committees internationally.

More specifically, we have five additional recommendations for consideration:

1. *Additional Guidance on Orphan Drug Development*

First, BIO urges FDA to publish further guidance regarding orphan drug development to improve understanding among both FDA reviewers and Sponsors regarding novel study approaches and non-traditional clinical development programs so that we may encourage flexibility and scientific judgment in FDA's review processes. For example, FDA guidance should address unique scientific consideration around study design; validation of novel efficacy endpoints in small patient populations; statistical analysis; development of patient-reported outcome tools; and challenges associated with post-market studies. Additionally, FDA guidance should provide interpretation of current orphan drug regulations including, what are acceptable subsets of disease to meet the prevalence requirement; what is a "major contribution to patient care; what is the definition of "reasonably likely to predict clinical benefit", and whether the sponsor of the original drug can also be a "subsequent sponsor."

2. *Consider Alternative Approaches to Demonstrating Efficacy*

Additionally, we urge that FDA review use of its standards for demonstrating efficacy of a rare disease product. Given the small patient populations involved, BIO urges FDA to consider alternatives to demonstrating efficacy including approval based on a single adequate and well controlled trial at a $p \leq 0.05$. In the many cases where it is not feasible or even may be unethical to conduct a placebo-controlled study, we urge FDA to consider use of other data including NIH-conducted studies using the same populations; use of consortia between government, academia and industry; and use of patient registries for rare diseases as part of efficacy considerations. We appreciate the comments from FDA staff today in support of case-by-case, science driven flexibility regarding approval standards for rare disease therapies, and we encourage additional adoption of these views across FDA review divisions.

3. *Greater Use of Surrogate Endpoints:*

Furthermore, we urge FDA to support the use of scientifically validated surrogate endpoints for product approval. Amazingly, in the past 20 years, only one drug for the treatment of a human genetic disease was approved under the "accelerated approval" provision of the FDA regulations. Timely approval with adequate follow-up should become the norm for such diseases - of course, understanding that it will have to be based on credible scientific rationale and will need to be assessed on a case by case basis.

We also encourage FDA to promote flexibility in the utilization of alternative surrogate endpoints and biomarkers. If data suggest that an alternate endpoint would be more

appropriate than the established surrogate marker, then FDA should be open to discussing its utilization.

4. Enhanced FDA-Sponsor Communication Processes

BIO believes FDA can improve communications processes for rare disease stakeholders. It is important that FDA encourage reviewers to establish more efficient communications processes that allow reviewers and sponsor researchers to discuss scientific issues based on real-time data. Additionally, there is no special priority given to rare disease products in current FDA practices regarding protocol assistance, informal communication with the agency, regulatory path, and other matters. Given the complexity and special challenges of developing rare disease products, this impedes development and approval. It is also important that FDA consult with other review offices and multi-disciplinary teams well in advance of meeting with the Sponsor so that all staff members are fully acquainted with the issue at hand.

5. Understanding and Accepting Appropriate Risk Tolerance

Finally, we need a better understanding of the risk/reward ratios for these rare diseases drugs. Currently, the required pre-clinical and clinical safety studies and risk assessments for the development and approval of life saving drugs for rare diseases are virtually the same as those for common, non-life threatening conditions. Addressing the tolerance for risk in drug development in the rare disease space is essential to advancing newer therapies. Along these same lines, the agency might consider having medical reviewers spend more time with rare disease patient organizations to learn from their leadership and members what they think and know of clinical trials, barriers to participation, and anticipated benefit, and tolerated risk.

Conclusion:

In conclusion, BIO companies believe that FDA has made great strides to make sure that safe and effective orphan products reach patients as soon as possible and we encourage additional progress to facilitate additional innovative approaches to orphan drug development. Thank you.

Sincerely,

/S/

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