BIOTECHNOLOGY
INDUSTRY ORGANIZATION
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May 31, 2010

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

**Re: FDA–2010– N–0218:** Considerations Regarding Food and Drug Administration Review and Regulation of Articles for the Treatment of Rare Diseases; Public Hearing

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on *Considerations Regarding Food and Drug Administration Review and Regulation of Articles for the Treatment of Rare Diseases*.

BIO represents more than 1,200 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.

## GENERAL COMMENTS

More than a quarter-century ago, Congress passed the Orphan Drug Act (ODA), which contained several incentives for biotechnology and pharmaceutical companies to develop products for rare diseases. The ODA has been an enormous success. In the decade prior to enactment of the ODA fewer than ten products for rare diseases came to market. Today, according to FDA, there have been 357 applications for orphan indications approved for marketing. These products have helped millions of people in the US and around the world.

The biotechnology industry has made a significant contribution to this field over the years. Indeed, the mission of many biotech companies is to bring hope to the patients who suffer from rare diseases. Despite our successes over the years, though, there are still an estimated 6,000-7,000 rare diseases for which there is no treatment. These diseases afflict about 25 million people

in the US, as well as another 25-30 million in the EU. Many of these diseases are serious or life threatening.

BIO believes that the lesson we can learn from the ODA is that government policies can effectively foster research and development of products for rare diseases. The challenges of developing orphan products are great and they require innovative policy and regulatory solutions. Further, many rare diseases affect far fewer patients than the 200,000 threshold in the ODA. For these diseases, the challenges are even more daunting.

Below are BIO's thoughts about policies that will complement the ODA and facilitate the development of the next generation of orphan products. BIO's ideas include: policies specifically designed to support or incentivize research and development and improvements in FDA regulatory policy.

The ODA created a grant program administered by the FDA to fund companies for development of orphan products. It's called the Orphan Drug Grant Program. This program has not had increases in funding commensurate with inflation for many years. BIO urges increased funding for the Orphan Drug Grant Program. We also note that in Europe, orphan products receive 10 years of market exclusivity, while only receiving 7 years of exclusivity in the US. Given its importance, we urge consideration of a longer US exclusivity period to coincide with Europe.

In addition, the National Institutes of Health (NIH) launched the new $24 million Therapeutics for Rare and Neglected Disease (TRND) program last year. Though just getting off the ground, the TRND program has the potential to help companies bring promising products forward. Many of these products stall in development because biotech companies lack the financing to advance them. The TRND program could fill some of these funding gaps. BIO is encouraged by this effort. We pledge to work with the NIH on intellectual property concerns, technology transfer rules, and other matters to make sure the program accomplishes its goals.

BIO companies believe that FDA has made great strides to make sure that safe and effective orphan products reach patients as soon as possible. For example, we applaud the FDA Office of Orphan Products Development for their sponsorship of the training program for reviewers on statistical methods for small patient populations. In addition, the "Build an Orphan" – designed to help companies properly submit the application for orphan drug designation in a timely fashion – holds promise. But more must be done.

Similar to what FDA has done through its Critical Path initiative, we believe the agency needs to take affirmative steps to spur drug development for rare diseases. The regulatory approval pathway simply must be more predictable. For example, during the most recent negotiations surrounding enactment of the Prescription Drug User Fee Act (PDUFA), the FDA committed to developing a series of guidances regarding clinical trial design; adaptive clinical trials; and new methods of statistical analysis. These would be valuable for developers of rare disease products. While we appreciate the publication of the adaptive clinical trial guidance earlier this year, the other guidances still have not been published.

In addition, we urge FDA to publish additional guidance regarding orphan drug development that provides interpretation of current regulations including: what are acceptable subsets of disease to meet the prevalence requirement; what is a "major contribution to patient care" that allows a drug to be found "clinically superior" even if it has the same active moiety of a previously approved drug; and whether the sponsor of the original drug can also be a "subsequent sponsor".

Other regulatory changes should be pursued as well. For example, we urge that FDA review use of its standards for demonstrating efficacy of a rare disease product. The requirement for sponsors to use two adequate and well-controlled studies is the same standard used by the agency for other drugs and biologicals. However, it is significantly harder to develop those studies for rare disease products because of the small patient populations available. This is particularly true for very rare diseases. BIO urges FDA to consider alternatives that include: approval based on a single adequate and well controlled trial at a $p \leq .05$, if there have been 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.

In addition, we urge FDA to support greater use of surrogate endpoints for product approval, either for full approval or accelerated approval purposes. Although they currently can be used during the accelerated approval process, more guidance from the agency is needed on use of surrogate endpoints for registration.

Moreover, BIO believes FDA can improve communications processes for rare disease stakeholders. For example, once orphan designation has been granted, there is no communication policy for sponsors as the review divisions take over. This often makes interaction with the agency difficult. And, there is no special priority given to rare disease products in current FDA practices regarding protocol assistance, communication with the agency and other matters. Given the complexity and special challenges of developing rare disease products, these communication gaps impede development and approval.

Other regulatory changes should be pursued as well, such as greater transparency at the agency including more meeting opportunities, and greater consistency among FDA's review divisions. The challenges of developing rare disease products require new regulatory approaches.

In addition, many patients suffering from rare diseases are treated by products that are labeled for another indication. Companies looking to get FDA approval for the rare disease indication are often either prohibited or severely restricted from performing a placebo-controlled trial for that indication because the commercially available (off label) product has become the clinical standard of care. In such situations, FDA should allow non-placebo controlled trials such as historical control or open label trials.

Regarding FDA's approval of medical devices for rare diseases, the use of different threshold numbers for defining rare (“orphan”) disease for medical device (4,000) versus drugs and biologics (200,000) is illogical. The device regulations should be changed, as it is the disease incidence not the therapy that should define the population.

## CONCLUSION

BIO companies' mission is to develop innovative products to meet unmet medical needs. Many of these products are for patients suffering from rare diseases. Despite our progress, far too many patients with these diseases still have no treatments.

Thank you for this opportunity to comment on *Considerations Regarding Food and Drug Administration Review and Regulation of Articles for the Treatment of Rare Diseases*. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/s/

Sara Radcliffe
Executive Vice President, Health
BIO