BIOTECHNOLOGY INDUSTRY ORGANIZATION
1201 Maryland Avenue SW, Suite 900, Washington, DC 20024
202-962-9200, www.bio.org

January 17, 2012

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

Re: Docket No. FDA–2011-N-0583: Proposed Rule: Orphan Drug Regulations

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments on the "Proposed Rule: Orphan Drug Regulations." As an association with a significant portion of its membership committed to addressing unmet needs for the rare disease community, BIO appreciates and welcomes FDA's efforts to clarify and improve the 1992 Orphan Drug Regulations issued to implement the Orphan Drug Act (ODA).[1]

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. 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 of a century ago, Congress passed the ODA, which contained several incentives for biotechnology and pharmaceutical companies to develop products for rare

[1] Pub. L. 97-414 and related regulations at 21 CFR part 316.

diseases. It is widely recognized that the ODA has been an enormous success. In the decade prior to enactment of the ODA, fewer than ten products for rare diseases were approved for marketing by FDA. Since enactment of the ODA, FDA has approved 392 marketing applications for orphan drugs. These products have helped many thousands of patients in the US and around the world.

The biotechnology industry has made significant contributions to the rare disease space over the years. In fact, the mission of many biotech companies is to bring to market innovative products that address unmet medical needs, particularly the needs of patients suffering from rare diseases, disorders, and conditions. There remain, however, an estimated 6,000 – 7,000 rare diseases for which there is no treatment. These diseases afflict about 25 million patients in the US, as well as another 25-30 million patients in the European Union.

BIO believes that the critical 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 complex and require a commitment to innovative policy and regulatory solutions. As FDA is aware, because each rare disease affects a relatively small population, developing drugs and therapies to prevent, diagnose, and treat these conditions is extremely challenging. Difficulties include attracting public and commercial funding for research and development, recruiting sufficient numbers of research participants, designing sound clinical trial strategies for treatments for small populations or poorly-characterized diseases, and assessing the safety and efficacy of products before they are marketed.

In order to continue to encourage and facilitate the development of drugs for rare diseases and conditions, it is important that the regulatory framework provide the flexibility needed for the designation and review of medical products for the diagnosis, treatment, and prevention of rare disease. This includes recognizing that while market exclusivity of approved orphan products is a major incentive to the development of drugs for rare diseases, the other statutory incentives that arise from designation -- such as tax credits, research grants, and exemptions from the usual drug application user fees -- are equally important in securing and sustaining the necessary capital investments to develop orphan drugs.[2] BIO also encourages consideration of new incentive programs that would foster further creativity and innovation. In addition, we urge the FDA to support new regulatory pathways that would provide flexibility and encourage innovative approaches to the assessment and expeditious review of orphan products while appropriately balancing benefits and risks for unmet medical needs.

The challenges of developing orphan products are great and they require innovative policy and regulatory solutions. BIO applauds FDA's intent to clarify regulatory provisions and make minor improvements to address issues that have arisen since the Orphan Drug Regulations, as set forth in 21 CFR part 316, were issued in 1992. In regard to the thirteen proposed clarifications and minor improvements, we support eight of the proposals, but raise concerns about and seek clarification as to five of the proposals, specifically:

[2] For example, the last five drugs developed and approved to treat lysosomal storage diseases have cost more than $200 million each in research and development expenses alone to develop, while addressing populations in the US of children and adults of less than 3,000 patients.

- Demonstration of an "Orphan Subset" of a Disease or Condition
- Eligibility for Orphan-Drug Designation of a Drug that was Previously Approved for the Orphan Drug Indication
- Eligibility for Multiple Orphan-Drug Exclusive Approval
- Demonstration of Clinical Superiority
- Publication of Orphan-Drug Designations

Specific Comments

- ***Demonstration of an "Orphan Subset" of a Disease or Condition***

Currently, a sponsor may request orphan-drug designation of a drug for use in persons with a rare disease or condition, or in some special circumstances, a subset of persons with a disease or condition that may not otherwise be rare. In those special circumstances § 316.20(b)(6) stipulates that when a drug is to be developed only for a subset, the sponsor must provide "a demonstration that the subset is medically plausible." BIO agrees that this concept of "medically plausible" is confusing and subject to misinterpretation, especially because it has not been further clarified through regulations or guidance.

To limit confusion arising from the use of the term "medically plausible" FDA proposes to remove the term from § 316.20(b)(6) and instead provide a description of how an appropriate subset may be identified for the purpose of orphan-drug designation. BIO appreciates FDA's recognition of the confusion within the regulated community and the Agency's attempt to provide clarity and understanding. However, we are concerned that the proposed method of subset identification may be equally confusing and subject to misinterpretation.

Additionally, the proposed change seems to create an altogether different standard, rather than just clarify longstanding policy. Moreover, this new standard may actually be at odds with the purposes of the ODA. Under the proposed rule it appears that a designation may be declined because the drug might be used in patients beyond the identified subset. Given that the practice of medicine may encompass further exploration or use of any approved product, this seems to be a disincentive to development as it would speculatively limit the designation of potential orphan products due to other hypothetical subsets. In addition, to demonstrate that a population may not be a candidate for the drug may require more extensive study than would otherwise be necessary to demonstrate safety and efficacy for the population subset. This too may create a barrier to development.

We propose, that instead of removing the term "medically plausible" and providing a description of how an appropriate subset may be identified, the Agency provide a precise definition of "medically plausible," provide additional illustrative examples of what would or would not be considered "medically plausible," and indicate the types and extent of data that would support a "medically plausible" subset. In addition, a chart at the end of this document proposes additional language for the proposed definitions of "pharmacological property" and "previous clinical experience" to include wording on validated biomarkers.

Related to FDA's goal to reduce uncertainty about the requirements for orphan-drug designation (ODD), we propose that FDA's finding of the acceptability of the prevalence data should not be considered proprietary information, and thus should be made publicly available. This will allow sponsors to use prevalence data already assessed by FDA and thereby streamline the process for obtaining these data to complete applications.

- ***Eligibility for Orphan-Drug Designation of a Drug that was Previously Approved for the Orphan Drug Indication***

Currently, in the absence of a clinically superior hypothesis, the Agency does not interpret the orphan-drug regulations to permit orphan designation of a drug that is otherwise the same as a drug that is already approved for the orphan use, either where the already approved drug received orphan-drug exclusive approval (even after such drug's exclusivity period has run out) or where the approved drug was not previously designated as an orphan drug and thus did not receive orphan exclusive approval. The Agency raises several concerns, including that in such cases designation would be inappropriate because it would be inconsistent with the primary purpose of the ODA, and that permitting a subsequent orphan-drug designation where a drug is already approved for the orphan indication could permit inappropriate "evergreening" of exclusive approval periods. But these concerns unnecessarily link orphan designation and marketing approval exclusivity.

We are requesting that the Agency make a distinction between orphan designation and orphan exclusive approvals in its application of the clinical superiority threshold for drugs that are the "same" as an already approved drug. Under the ODA, designation is meant to encourage the development of rare disease treatments, not restrict development. This is especially true for certain therapies where clinical superiority presents a significant barrier to orphan designation, notwithstanding their sole indication to treat one or more rare diseases or conditions. Therefore, if clinical superiority needs to be addressed it should be done at the time of NDA/BLA review, and only related to whether a product is seeking to break or gain exclusivity.

The FDA has the authority to grant Orphan designation (ODD) after other "similar" products obtain exclusivity. In fact, the ODA conditions exclusivity solely on (1) a designation request being made and (2) that the drug for which the request is made be investigated for a rare disease or condition as defined by the statute. Such a grant of ODD would benefit public health by providing additional encouragement to development of alternative sources of drugs for orphan populations. These drugs could not be approved during the exclusivity period of the innovator, nor granted exclusivity upon approval, but the subsequent product would still benefit from exclusion from certain taxes and user fees. And patients with orphan conditions would benefit from having more sources of treatment for life saving therapies.

As discussed above, it is especially critical to differentiate designation from approval because designation is used increasingly to carve out therapies from a broader array of legislative obligations, including certain taxes and user fees. Accordingly, we urge FDA to re-evaluate its interpretation of the clinical superiority requirement and eliminate this requirement for orphan designation, while maintaining the requirement for orphan approval/exclusivity, as necessary.

This would better protect the value of orphan exclusivity and advances the overall intent of the ODA to stimulate development of rare disease therapies.

We also ask the Agency to confirm that (1) there are instances where it may be easily established that a drug is clinically superior based on safety but, that studies to establish safety would be ethically inappropriate and therefore would not be required as a condition of marketing approval; and (2) a sponsor who improves its own drug by demonstrating patient benefit is eligible for exclusivity for the improved drug, regardless of whether the first drug received exclusivity.

- ***Eligibility for Multiple Orphan-Drug Exclusive Approval***

In the case of approved drugs or biologics that obtained orphan designation for a subset of a rare disease or condition, FDA proposes to grant orphan exclusive approval to such a product for additional subsets of that rare disease or condition without requiring the sponsor or manufacturer to request and obtain orphan designation for these additional orphan subsets. In general, BIO has no immediate concern with the Agency's approach, as it appears to permit multiple orphan-drug exclusive approvals for multiple subsets of the same underlying disease or condition and therefore provides an important incentive for one or more sponsors to develop, or continue to develop, a potentially promising drug for use in all persons affected by a rare disease or condition. However, because of the many benefits afforded orphan designated drugs beyond the incentive of the seven years market exclusivity, we ask the Agency to ensure that the orphan designated drugs that obtain orphan exclusive approval for the additional subsets will be formally designated as orphan drugs for those new indications despite not formally requesting and obtaining orphan designation. We also ask the Agency to provide greater clarity by way of examples of how exactly the approach works under the various situations discussed in the proposed rule where the approach may apply.

- ***Demonstration of Clinical Superiority***

Under the proposed rule a drug may still be considered clinically superior without demonstrating greater effectiveness or safety if it makes a "major contribution to patient care". On its face, the proposal intends to make a finding of clinical superiority more, rather than less likely (*i.e.*, broaden the definition); however it is not clear what constitutes a "major contribution to patient care," and what level of evidence would be needed to sufficiently demonstrate "comparable" safety and effectiveness. Therefore, it is possible that the proposed change may actually result in fewer findings of clinical superiority – which on the one hand protects orphan drug exclusivity, but on the other hand further limits the availability to patients of an alternative to an existing treatment. We, instead, urge FDA to adopt an approach that would make both exclusivity and availability of alternative treatments to patients more broadly available.

The barrier to obtaining orphan designation for a "major contribution to patient care" has typically been unclear. Therefore, we seek greater clarity and guidance regarding the Agency's views on what may be considered as a "major contribution to patient care" beyond its statement that "such clinical superiority is meaningful only when the subsequent drug provides safety or effectiveness comparable to the approved drug."

BIO requests that FDA provide some examples of what may and may not constitute major contributions to patient care. Such clarification and guidance should also address how the Agency defines comparable safety under the proposed rule (*e.g.,* if a new dosage form, formulation, or route of administration eliminates an adverse side effect of infusion but creates a new adverse effect, how comparability would be determined). Clarification is particularly important because at the time of the orphan designation request, it is frequently too early in the drug product's development to speculate on whether it will have comparable efficacy and safety to an approved product unless such definitive data are already available. Comparable efficacy and safety to an approved product should therefore not be used as a criterion for orphan designation.

- ***Publication of Orphan-Drug Designations***

The ODA requires that notice respecting designation of a drug be made available to the public.[3] FDA currently makes available a cumulative list of all designated drugs to date and a cumulative list of designated drugs in the current year on its website. These lists are updated monthly. The proposed rule notes that the Agency is considering ways to make available to the public information about the status of development for designated orphan drugs, including whether to provide information to the public on whether a sponsor has submitted the required annual progress report.

BIO supports the Agency's efforts to ensure that notice is meaningful, such that patients, health care providers, sponsors, and other stakeholders can identify which drug has been designated an orphan drug. We believe it would be helpful if additional information was made publicly available, such as clarifying when orphan drug designations have been withdrawn. This information may encourage new sponsors to begin development. However, as to providing information on whether a sponsor has filed a progress report, we note that ClinicalTrials.gov offers a significantly better way for the public to get information about the progress of clinical trials, including the development of orphan drugs. Moreover, any added value of such publication (yes or no to filing a yearly report) is outweighed by the potential that this information may be misleading and misinterpreted since the submission or not of an annual report is not dispositive of a sponsor's continued development of a product, but could easily be misunderstood as abandonment or hold.

[3] See 21 U.S.C. 360bb(c).

CONCLUSION:

BIO appreciates this opportunity to comment on the "Proposed Rule: Orphan Drug Regulations." 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	Issue	Proposed Change
Demonstration of an "Orphan Subset" of a Disease or Condition	*"Pharmacological Property: The mechanism of action is a common principle for limiting the investigation and use of a drug to a subset of patients. For example, it is reasonable to expect that use of a monoclonal antibody directed against a specific surface antigen would be restricted to treatment of subtypes of tumors that possess that specific antigen, and not subtypes of tumors that lack the antigen."*	The definition in 316.20 does not include validated biomarkers as an option. We suggest including additional wording to the section on 'Pharmacological Property:' *"Pharmacological Property: The mechanism of action is a common principle for limiting the investigation and use of a drug to a subset of patients. For example, it is reasonable to expect that use of a monoclonal antibody directed against a specific surface antigen would be restricted to treatment of* patients with *subtypes of tumors that possess that specific antigen, and not* patients with *subtypes of tumors that lack the antigen.* Similarly, a biomarker may be used to identify the population of patients that are likely to be affected by a drug."
Demonstration of an "Orphan Subset" of a Disease or Condition	*Previous clinical experience: Information on the drug's activity available from completed trials or published clinical literature may be used to establish an orphan subset. If, for example, relevant data show that the drug has no significant activity in the remaining subset of patients with high-grade tumors, then patients with low-grade tumors may constitute an orphan subset."*	We also suggest making the following changes to the text on 'Previous Clinical Experience' to include wording on validated biomarkers: *Previous clinical experience: Information on the drug's activity available from completed trials or published clinical literature may be used to establish an orphan subset.* ~~*If, for example, relevant data show that the drug has no significant activity in the remaining subset of patients with high-grade tumors, then patients with low-grade tumors may constitute an orphan subset.*~~ Examples of meeting this criterion include: using data demonstrating that the

Section	Issue	Proposed Change
		drug has no significant activity in patients lacking a biomarker to identify the subset of patients with the biomarker as an orphan subset or utilizing data showing a lack of significant activity in patients with high-grade tumors, to establish patients with low-grade tumors as an orphan subset.”