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August 15, 2011

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

Re: Docket No. FDA-2010-D-0530: Draft Guidance for Industry on Principles for Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the *Draft Guidance for Industry on Principles for Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology*.

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.

We are pleased that the Agency is providing its current thinking on whether FDA-regulated products contain nanomaterials or otherwise involve the application of nanotechnology. This is an important first step in defining the types of products considered to contain nanoscale materials. The main points of this document appear to be that:

a. A Sponsor would need to justify the application of nanotechnology in medical products and inform FDA of medical products that are based on nanotechnology.
b. FDA is particularly interested in the deliberate manipulation and control of particle size to produce specific properties, and in better understanding of the properties and behavior of products that are based on engineered nanomaterials or nanotechnology.

While the Draft Guidance will be helpful for Sponsors, we believe that additional comprehensive, science-based regulatory guidance specific to the development of nanomaterials is needed.

I. "Nanosized material" does not Imply Potential Harm or Risk

The science behind nanomaterials has been around for decades, though its application to medical products has been less common. It is important to consider that just because a product is considered to be "nanotechnology derived material" or "nanosized material" should not imply potential harm or risk. Therefore, we appreciate FDA's statement that nanotechnology is not intrinsically benign or harmful, and encourage the Agency to reinforce this point throughout the document:

> *The application of nanotechnology may result in product attributes that differ from those of conventionally-manufactured products, and thus may merit examination. However, FDA does not categorically judge all products containing nanomaterials or otherwise involving application of nanotechnology as intrinsically benign or harmful.* (lines 40-43, emphasis added)

However, it is unclear what the reference to meriting "examination" means in actual regulatory practice. While the draft document is not designed to provide guidance on how to conduct a risk assessment for products involving the application of nanotechnology, does the term "examination" refer to additional safety reviews or environmental or occupational safety and health assessments?

As with all drug and biologic products undergoing FDA approval, whether involving the application of nanotechnology or otherwise, safety risk assessments are conducted to determine product risk. Pharmaceutical products are already subject to extremely stringent toxicology and safety evaluation regardless of their size or method of manufacture. Safety and effectiveness measures to assure a pharmaceutical product meets quality attributes throughout its shelf-life are already covered by relevant FDA regulations and International Conference of Harmonisation (ICH) guidance. Unique properties of nanomaterials that are attributable to its nano-size will be one of the critical quality attributes and will be assured by specifications for particle size. "Examination" of products involving the application of nanotechnology should not duplicate or unnecessarily complicate existing regulatory pathways.

II. Clarity is Needed Regarding the Scope of Pharmaceutical Products Involving the Application of Nanotechnology

Second, it is not sufficiently clear what counts as a product involving the application of nanotechnology, and how the Draft Guidance should be interpreted with respect to pharmaceuticals in particular. In the pharmaceutical area, a variety of very different pharmaceutical systems or products such as (mixed) micelles, polymer systems (dendrimers), liposomes, (modified) therapeutic monoclonal antibodies, emulsions, suspensions, crystalline particles, *etc.*, contain nanoscale particles, but most are not considered to be "nanomaterials". Greater clarity on the scope of the guidance is essential for Sponsors.

For example, workable limits should be set for the proportion of the material meeting a nanoscale size specification. In case only an insignificant proportion of material is within the nanoscale range, applying additional requirements for nanomaterials would not be appropriate. The guidance should specify that operations commonly utilized in industry, such as jet milling, which can result in a certain percentage of particles in the nanoscale, should not result in the active pharmaceutical ingredient (API) product being categorized as a nanomaterial.

III. Bio-Persistence is a Significant Criteria for Evaluating Nanomaterials

A criterion to consider in evaluating a product containing nanomaterials is bio-persistence. While the guidance takes into account nanomaterial "properties or phenomena….that are attributable to its dimensions," it does not recognize the important difference between degradable engineered nanomaterials (*e.g.*, O_2, photo, or biodegradable) and nanomaterials that may persist in the environment. We recommend that FDA recognize this difference and incorporate it into a risk-based approach to FDA regulation of investigational and marketed medicinal products containing nanomaterials.

For example, materials produced by relatively simple wet milling processes of a single material or API are considered (according to the provided criteria) as products involving the application of nanotechnology. In case of APIs processed in this way, the sole purpose is the increase of oral bioavailability by increased dissolution rates. These particles will disappear via dissolution in biological environments within a very limited time (seconds, or minutes). On the other extreme, other nanomaterials (often based on inorganic materials) may not be soluble or biodegradable at all. Risk assessments of nanomaterials must recognize these differences.

Although it is suggested in some papers (see footnote 15 of Draft Guidance) not to use persistence as a prime element in the definition of nanomaterials, a material's bio-persistence as nanoscale may play a more important role with respect to its behavior or any potential risk than its pure dimensions or its way of preparation. In simpler terms, a rapidly dissolving nanoparticle no longer behaves as a nanoparticle.

IV. Additional Considerations Related to Nanotechnology:

To increase the usefulness of the current Draft Guidance, we recommend the document be revised to address several issues that could be critically important to evaluation of nanotechnology based products, including delivery route, particle size instrumentation, agglomerates and aggregates, and inert materials.

A. Agglomerates and Materials Up to One Micrometer:

The Draft Guidance also says that when considering whether an FDA-regulated product contains nanomaterials, FDA will ask whether an engineered material or end product exhibits properties or phenomena that are attributable to its dimensions, even if these dimensions fall outside the nanoscale range, up to one micrometer. For example, the Draft Guidance states that "Structures such as agglomerates and aggregates are of interest in this context…" (lines 138-139) We do not believe that the one micrometer size limit is helpful in addressing FDA's apparent concern that materials outside the nanoscale range may display nanoscale properties or phenomena. Instead, we suggest it would be more straightforward to address agglomerates or aggregates by keeping the upper limit of 100 nm specified in the Draft Guidance and providing additional guidance specifying the concern is directed to nanomaterials and nanomaterial formations larger than 100 nm that have properties or phenomena different from those of conventionally-scaled material.

It would also be helpful for FDA to provide guidance on what such properties or phenomena may be. For example, do they have to consist of (or need to disintegrate into) smaller nanoparticles? We note that if they do not, it should not be assumed (as the draft document appears to assume), that such agglomerates or aggregates behave similarly to nanoparticles in the 1-100 nm range.

B. Delivery Route:

Certain concerns associated with the administration of nanoparticles are related to the dosage form or delivery route. For example, toxicity and safety concerns are common to nanoparticles for parenteral use, but less so for oral applications. Further, nanoparticles for oral and parenteral routes encounter very different physiology in the body and thus would require correspondingly different characterization tools. We recommend that FDA consider when the delivery route for the nanoparticles has important implications, and in those situations provide different regulatory recommendations based on the intended delivery route.

C. Instrumentation to Determine Nanomaterial Size:

It is challenging to determine just "one dimension in the size range of approximately 1 to 100 nanometers" (lines 59-60), as most instrumentation routinely used to measure particle size gives overall size information, instead of any one dimension. We recommend that reference to any size specifications be based on measurement from a specific instrumentation (*e.g.*, hydrodynamic radius from dynamic light scattering, radius

of gyration from static light scattering, or mean particle size from size-exclusion chromatography (SEC)).

D. Inert Ingredients:

BIO also suggests that FDA should exempt from the scope of the guidance inert ingredients that meet the requirement of nanomaterials /nanotechnology, such as lubricants, binders, fillers (or diluents), disintegrants, colorants, buffering agents and coatings, etc. Many of these materials have been used for years and retrospective classification as nanomaterials or nanotechnology could lead to undue regulatory burden.

V. Conclusion

BIO appreciates this opportunity to comment on the Draft Guidance for Industry on Principles for Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology. 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)