Nanomedicines Alliance
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15 August 2011

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

Re: FDA-2010-D-0530-0002. Considering Whether an FDA Regulated Product Involves the Application of Nanotechnology

Dear Madam or Sir:

We submit these comments on the FDA draft guidance "*Considering Whether an FDA Regulated Product Involves the Application of Nanotechnology*"[1] on behalf of the Nanomedicines Alliance[2], a consortium of pharmaceutical and biotechnology companies that develop nanomedicines. Current members of the Alliance include CytImmune Sciences, Eli Lilly, NanoCarrier, NanoViricides, Pfizer and Roche. The following companies also endorse these comments: Cerulean Pharma Inc., NanoMedical Systems, Inc., NanoSpectra Biosciences, Alliance for NanoHealth, Leonardo Biosystems, and Calando Pharmaceuticals, Inc. The mission of the Nanomedicines Alliance is to promote and facilitate the scientific advancement, regulatory approval and public appreciation of nanotechnology-based medicines world-wide for the diagnosis, treatment and prevention of disease. The scope of the Nanomedicines Alliance includes nanomaterials and nanotechnologies involved in the discovery, research, development, testing, manufacturing, marketing and disposal of pharmaceuticals, biologics and medical devices, including imaging and diagnostics.

We recognize that FDA needs to inform the public about its views on FDA-regulated products, and to assure that appropriate characterization, testing and controls be applied to products using nano-scaled materials. Considering, however, that the range of FDA-regulated products is very broad, this draft guidance may create confusion rather than clarify this topic.

For example, foods, cosmetics and some devices do not require the Agency's pre-approval before entering the market, and are subject to relatively minimal regulation and testing requirements. By contrast, pharmaceutical and biotechnology products are subject to an extensive set of regulations and requirements spanning the entire product life cycle - from

[1] FDA-2010-D-0530-0002. Considering Whether an FDA Regulated Product Involves the Application of Nanotechnology (2011) http://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm

[2] http://www.nanomedicines-alliance.org/

investigational studies to toxicology, pharmacology, preclinical and clinical studies, chemistry and manufacturing controls, environmental assessments, and sometimes post-approval studies.

The Nanomedicines Alliance believes that for pharmaceutical and biotechnology products, the existing regulatory framework is sufficiently comprehensive and adequate to address nano-scaled materials without any further guidances. We would like to re-emphasize points we have previously offered on this topic.[3] In fact, many existing conventional medicines involve molecules (such as PEGylated proteins and peptides) and presentations (e.g., suspensions, micelles, etc.) that are inherently nano-scale size and employ "deliberate manipulation". Introducing a size-based definition of nanomaterials in this guidance without further discussing its consequences for the pharmaceutical and biotech products is counterproductive and confusing.

If in the long term, after extensive discussions with stakeholders, it is determined that an additional guidance for bio-pharmaceutical industry is needed to address nano-scaled materials, such guidance should ideally describe the specifics of FDA's expectations for nanomedicines that would go above and beyond the current requirements for medicinal products, e.g., specific labeling requirements, specific types of data or information that the sponsor needs to submit to FDA in addition to those already required for pharmaceutical and biotechnology products, and descriptions of how FDA review of such products may differ from that of other drug products and biologics. We recognize, however, that this is a complex area, and that it is difficult to write a Guidance sufficiently flexible yet comprehensive to achieve this aim. As an industry consortium, we would welcome dialogue with the Agency on this topic.

The "*Policy Principles for the U.S. Decision-Making Concerning Regulation and Oversight of Applications of Nanotechnology and Nanomaterials"*[4] advocates a risk-based approach and use of current scientific information when establishing regulations. That position has been clearly articulated by FDA and is supported by the Nanomedicines Alliance. We recommend this aspect be strengthened in a revised guidance.

The Nanomedicines Alliance appreciates FDA's continuous efforts to update the pharmaceutical and biotechnology industry regarding the Agency's current thinking on nanomedicines through published documents, public meetings and other forums. The general information provided by these sources, as well as specific existing guidelines regarding drug and biological product development and characterization, combined with the valuable direct FDA/CDER and CBER input on a case-by-case basis during meetings with sponsors, which are

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[3] *Comments On FDA Questions Regarding Nano Scale Materials*. Submitted to Docket No. FDA-2008-N-0416 on 10 February 2009 in response to the Request for Comments, Consideration of FDA Regulated Products That May Contain Nanoscale Materials [Vol. 73, No. 153 Federal Register, Page 46022 (August 7, 2008)] http://www.regulations.gov/#!documentDetail;D=FDA-2008-N-0416-0042 – for your convenience, a copy of those comments is attached.

[4] *"Policy Principles for the U.S. Decision-Making Concerning Regulation and Oversight of Applications of Nanotechnology and Nanomaterials"* issued on June 9, 2011, jointly by the Office of Science and Technology Policy, Office of Management and Budget, and the United States Trade Representative http://www.whitehouse.gov/sites/default/files/omb/inforeg/for-agencies/nanotechnology-regulation-and-oversight-principles.pdf

held as part of the typical medicinal product development and application process, have been demonstrated to provide sufficient guidance to the industry. For the pharmaceutical and biotechnology industry, therefore, this draft guidance does not provide any new insights, and is not needed, unless it is significantly revised, as suggested above.

In light of this view of the members and partners of the Nanomedicines Alliance, we are not providing any specific detailed comments on the draft guidance.

The members of the Nanomedicines Alliance remain committed to advancing the science of nanomedicines through collaboration with one another, with FDA and with other stakeholders and regulatory agencies, both global and domestic.

Thank you for this opportunity to provide comments. Please do not hesitate to contact us with any questions.

Sincerely,

Mary Devlin Capizzi

Mary Devlin Capizzi
Nanomedicines Alliance Secretariat

Attachment: A copy of previously submitted comments (see footnote 3 of the letter)

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Re: Docket No. FDA-2008-N-0416; Request for comments, Consideration of FDA-Regulated Products That May Contain Nanoscale Materials *[Vol. 73, No. 153 Federal Register, Page 46022 (August 7, 2008)]*]

COMMENTS ON FDA QUESTIONS REGARDING NANO SCALE MATERIALS

PREAMBLE

We submit these comments on behalf of the following companies: AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Pfizer and Roche in response to the questions published in the U.S. Food and Drug Administration (FDA) Federal Register notice (Docket No. 2008-N-0416) on August 7, 2008 [1] and discussed at the FDA public meeting on September 8, 2008.[2] We support the FDA efforts in facilitating public discussions on nanoscale materials in FDA-regulated products and appreciate the opportunity to provide comments on this issue.

Among the range of FDA-regulated products, pharmaceutical products and innovative medical devices are unique in that they require thorough preclinical and clinical testing and an extensive regulatory review to obtain marketing approval. Other FDA-regulated products (food, supplements, cosmetics) do not require pre-market approval. Our comments are limited to FDA-regulated pharmaceutical products and medical devices that require pre-market approval. We believe that the use of nanoscale materials and nanotechnologies in the research, discovery, manufacturing, testing, and disposal of pharmaceutical products and medical devices is an important area that may deliver

[1] http://edocket.access.gpo.gov/2008/E8-18132.htm)

[2] http://www.fda.gov/nanotechnology2008/

improved health outcomes for patients and deserves continuing scientific and regulatory inquiry. The pharmaceutical and medical device industries will continue to embrace and pragmatically apply on-going and emerging advances in bionanotechnology in terms of poly-functionality, multi-component composition and controlled self-assembly. The current U.S. regulatory framework for development, review and approval of new pharmaceutical products and medical devices is sufficiently comprehensive to accommodate nanoscale materials. Forthcoming advances in nanotechnology and nanomaterials, especially those that cannot be foreseen today, may stimulate development of new tools and approaches in the future.

RESPONSES TO FDA QUESTIONS

1. What characteristics of nanoscale materials in FDA-regulated products should be identified and evaluated to ensure the safety and, where relevant, effectiveness of these products?

Characterization of nanoscale materials for safety and effectiveness in the context of evaluating safety and effectiveness of finished pharmaceutical products and medical devices is ensured by customary procedures established and observed by the pharmaceutical industry for all new substances, and are in compliance with requirements issued by regulatory authorities. Likewise, occupational safety for nanoscale materials used in discovery, research, testing or manufacturing, is ensured by the same mechanisms.

The safety of novel pharmaceutical products and medical devices has been promulgated by relevant FDA guidances and by the guidelines prepared by The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). These guidance documents will be utilized for evaluation of nanotechnology based products. Safety assessment would include such tests as:

- genotoxicity;
- general toxicity (acute, sub-chronic and chronic);
- developmental and reproductive toxicity;
- absorption, distribution, metabolism and elimination (ADME);
- phototoxicty;
- carcinogenicity; and
- tissue compatibility.

Similarly, the assessment of effectiveness of novel pharmaceutical products and medical devices is governed by globally accepted good clinical practices, which will be utilized to demonstrate objective benefits of nanotechnology based products.

The reasons for using nanoscale materials in finished products may be varied and unique to each product or device. The nanoscale-specific characteristics that should be evaluated

as part of the established processes, will, as always, depend on the particular product or device.

All pharmaceutical products and devices, regardless of whether they include nanoscale materials or not, are subject to characterization tests and controls to measure critical quality attributes (CQAs). Appropriate tests and controls should be employed for nanoscale materials and may differ when compared to more traditional products. These tests may address such CQAs as:

- delivery efficiency and accuracy;
- composition and purity;
- dissolution;
- particle size distribution;
- re-suspension characteristics;
- particle shape, crystalline form, surface morphology, and surface charge;
- physical and chemical stability upon storage; and
- *in vivo* performance (absorption, distribution, metabolism and elimination).

2. What assessment tools are available (including test methods and standards) for evaluating the characteristics of nanoscale materials that may affect the safety, effectiveness, and quality of FDA-regulated products? How reliable are these tools? How widely available are these tools? Are these tools practical for regulatory use or do they have aspects that render them impractical? What additional tools should FDA and industry consider developing to evaluate the characteristics of nanoscale materials?

A large number of standards and test methods for characterization of materials used in pharmaceutical products and medical devices have been promulgated by relevant FDA Centers [Center for Drug Evaluation and Research (CDER), Center for Devices and Radiological Health (CDRH) and Center for Biologics Evaluation and Research (CBER)], as well as by other national and international standard-setting bodies [e.g., United States Pharmacopeia (USP), International Organization for Standardization (ISO)], and these standards and test methods are applicable to nanoscale materials as well. For example, for particle characterization, techniques such as light scattering, dynamic light scattering, scanning electron microscopy and Zeta potential measurements may be used. For particle sizing, polystyrene latex beads standards are available. Most of these tools are reliable, readily available, routinely applied and practical for regulatory use.

In addition to traditional *in vitro* and *in vivo* methods, *in silico* simulations and genetic testing may prove to serve as valuable tools for evaluation and characterization of all new materials used in medical products and devices, including those involving nanomaterials and nanotechnologies.

New tools that may be required specifically for novel nanoscale materials will be product- and process-specific and will depend on the composition of the product or device, method of manufacturing, recommended storage conditions, and intended use.

3. Are there unique features of the manufacturing process for products containing nanoscale materials? If so, how should these features be evaluated? Is the manufacturing process for nanoscale materials different from that of conventional materials? If so, how? What parameters are critical when manufacturing products containing nanoscale materials? What unique challenges are there for ``scale-up'' of manufacturing for products using nanoscale materials? How do potentially unique features of nanoscale materials, such as particle size, shape, and surface charge, affect what should be considered in the development of controls, standards, and specifications for manufacturing?

Unique features of the manufacturing process would be product- and process-specific. For products containing nanoscale materials, conventional pharmaceutical industry techniques (such as homogenization, milling, and solvent-antisolvent processes) may be utilized. As for many conventional pharmaceutical products, producing a consistent particle size distribution and maintaining it throughout shelf-life are critical. Any "scale-up" should preserve the unique characteristics of the employed nanoscale material, and therefore the challenges will be product- and process-specific.

For all pharmaceutical products , the principles of Pharmaceutical Development, Quality Risk Management and Pharmaceutical Quality System set forth in the Q8, Q9 and Q10 ICH guidelines of , as well as the principles of Quality by Design (QbD) promulgated by the U.S. FDA, are useful to guide development of controls and specifications. This valuable framework is applicable to and should be employed for nanoscale products and devices as well, as it provides a guide for developing appropriate criteria for particle size and other critical quality parameters identified during product development. Risk management principles should be employed in conjunction with safety and efficacy data from pivotal clinical studies.

As companies study nanoscale materials in medicinal products and devices, they may recognize novel properties requiring additional studies during development, just as may happen with any new technology or chemical entity. The quality of these materials, however, will be ensured through thorough physico-chemical characterization; and their safety will be assessed in pre-clinical and clinical studies before these products are brought to the market.

4. Are there particular aspects of product formulation, processing, or storage that can affect the quality, safety, or effectiveness of products containing nanoscale materials, including as excipients?

The unique formulation, processing, and storage aspects will be specific to the product and manufacturing process.

5. What has been your experience with products containing nanoscale materials? Have you avoided these products due to specific concerns about aspects of development, characterization, or manufacturing?

Nanoscale materials have been used in pharmaceutical products for decades, so the collective experience of the pharmaceutical industry already encompasses a broad range of nanoscale materials. The size of many biological molecules and of aggregates or agglomerates of chemical molecules is measured on the 1 to 100 nm scale defined as "nanoscale". Unique features observed in nanoparticles but not observed in particles on the micron scale or sub-nanometer scale, will be product specific, and as such duly characterized and evaluated during established processes applied to all new molecular entities (NMEs).

6. What additional questions focusing on characterization (including stability) and manufacturing aspects of products containing nanoscale materials should be addressed in this forum or otherwise brought to the attention of FDA?

The environmental impacts of nanoscale materials should be evaluated, just as the environmental impact of pharmaceutical products in general is required to be evaluated during product development. Specific requirements may differ by product type. For example, biodegradable and biocompatible nanomaterials may need to be evaluated differently than other types of nanomaterials.

CONCLUDING REMARKS

We are encouraged by the FDA's thoughtful attention to the issue of appropriate regulatory oversight of nanoscale materials in FDA-regulated products. As described above, pharmaceutical products and medical devices are subject to extensive pre-market studies to characterize safety, effectiveness and quality, to regulatory approval for commercialization, and to thorough ongoing testing and post—approval pharmacovigilance activities. We strongly believe that the existing regulatory framework is sufficiently robust to meet any challenges posed by nanoscale materials. This framework has been employed successfully to products as diverse as pen injectors, transdermal patches, sustained release tablets and other complex dosage forms.

Considering the global nature of the pharmaceutical industry, it will be important to engage in processes that can facilitate international harmonization of approaches to nanoscale materials.

We look forward to further dialogue with the FDA on these important issues and will be pleased to meet with the Agency to pursue these discussions.

Very truly yours,

Mary Devlin Capizzi

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