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Regulation of Nanomaterials Today and Tomorrow

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"If nanotechnology is a racehorse, then industry is a jockey whipping it along to market at a breakneck pace. The regulatory community is a poor old trainer limping along in the backstretch, pleading to wrap the horse's legs for safety" (Houston Chronicle, 2007).

This quote from the June 25, 2007 edition of the *Houston Chronicle* summarizes what many still see as the current state of affairs regarding the regulation of nanotechnology and nanomaterials in the marketplace. Recent figures provided by the Project on Emerging Nanotechnologies appear to support this contention (**PEN, 2011**). As of March 2011, the Project's inventory of nanotechnology-based consumer products included 1,317 products or product lines, representing a more than 24-fold increase since the inventory's inception in 2006. Health and fitness products represented the largest product category with 738 items, including 143 cosmetics and 33 sunscreens. Given that this inventory is for consumer products (i.e., those that are not subject to pre-market authorization), a major question is: Who is ensuring the safety of these products and the nanomaterials they contain, and how is this being accomplished? Similarly, how are nanotechnology-enabled products that do require pre-market authorization being evaluated and regulated?

Regulating an Unknown

The regulation of products of nanotechnology is a dynamic and evolving activity, due largely to the wide spectrum of nanomaterials, nano-enabled products, and applications that are being developed and the uncertainties that are associated with defining, characterizing, and appropriately testing for efficacy and safety. Government agencies and other organizations worldwide are formulating means by which to categorize and catalogue nanomaterials (or products containing nanomaterials), assess their safety, understand the potential risks associated with their manufacture and use, and ultimately ensure that appropriate measures are taken to protect humans and the environment from any potential deleterious effects. However, there are a number of factors that contribute to the difficulty in establishing regulatory practices for nanomaterials. These factors include, but are not limited to, defining and establishing a universal nomenclature system, characterizing hazards, assessing exposure, determining environmental fate and persistence, and measuring, sampling and monitoring nanomaterials in different media.

While efforts are underway to address all of these variables, arguably the greatest challenge associated with regulating the use of nanomaterials is their potential risks are largely unknown. It is well established that risk is a function of hazard and exposure. In the case of nanomaterials, however, it is extremely difficult to assess risk, and thereby establish regulatory guidelines based on risk, because hazards and potential exposures to nanomaterials have not been adequately characterized.

Regional Approaches to Regulating Nanomaterials

United States

FDA regulates drugs, drug delivery systems, cosmetics, medical devices, vaccines and food products on a "product-by-product" basis and, as such, does not regulate nanotechnology or nanomaterials per se.

Rather, the stage at which FDA becomes involved in the regulation of nanotechnology-derived products depends on the actual product as opposed to its component materials or method of manufacture. Some nanotechnology-based products are likely to span regulatory boundaries between drugs, medical devices

and biological—although there are established pathways to regulate such combination products. In this regard, the primary mode of action of the nanotechnology-derived product will determine the regulatory framework (e.g., drug, medical device or biological product).

In 2006, FDA formed a Nanotechnology Task Force that was charged with determining regulatory approaches that encourage the continued development of innovative, safe and effective FDA-regulated products that use nanotechnology materials. The Nanotechnology Task Force issued a **report** in 2007 stating FDA's authority over products subject to premarket authorization (e.g., drugs, biological products, devices, and food and color additives) is comprehensive and provides FDA with the ability to obtain detailed scientific information needed to assess the safety and, as applicable, effectiveness of products, including relevant effects of nanoscale materials (FDA, 2007). For products not subject to premarket authorization (e.g., dietary supplements, cosmetics and food ingredients that are GRAS [generally recognized as safe]), FDA is encouraged to work with manufacturers of these products and assist them in identifying data to substantiate the safety of products containing nanoscale materials, including chronic toxicity and other long-term toxicity data as appropriate. The Nanotechnology Task Force also noted "nanoscale materials present regulatory challenges similar to those posed by products using other emerging technologies. However, these challenges may be magnified both because nanotechnology can be used in, or to make, any FDA-regulated product, and because, at this scale, properties of a material relevant to the safety and (as applicable) effectiveness of FDA-regulated products might change repeatedly as size enters into or varies within the nanoscale range" (FDA, 2007).

With specific reference to drug products, FDA's **Center for Drug Evaluation and Research** recently issued a Manual of Policies and Procedures describing what elements of nanomaterials to look for when reviewing drug applications relevant to nanotechnology (FDA, 2010). This is intended to help reviewers document in their reviews relevant information related to chemistry, manufacturing and controls when an application is for a drug product containing nanomaterials. The manual indicates that a nanotechnology drug product database will be generated that will "ultimately be used to develop policy regarding these products".

With regard to consumer products, as with other compounds that are incorporated into consumer products, the U.S. Consumer Product Safety Commission (CPSC) has stated that potential safety and health risks of nanomaterials can be assessed under existing CPSC statutes, regulations and guidelines (**U.S. CPSC, 2005**). Neither the Consumer Product Safety Act (CPSA) nor the Federal Hazardous Substances Act (FHSA) requires the pre-market registration or approval of products. As such, the CPSC generally does not evaluate a product's potential risk to the public until after it has been distributed in commerce. With regard to potential safety effects, the reporting obligation of manufacturers, retailers and distributors of products composed of or containing nanomaterials are the same as those of other products, namely to report to the CPSC immediately if information is obtained that reasonably supports the conclusion that a product "fails to comply with an applicable consumer product safety rule, contains a defect that could create a substantial product hazard, or creates an unreasonable risk of serious injury or death" (**U.S. CPSC, 2005**).

Canada

Health Canada is using existing legislative and regulatory frameworks to regulate applications of nanotechnology but recognizes that new approaches may be necessary in the future to keep pace with the advances in this area, particularly given there currently is inadequate information on risks associated with nanomaterials (**Health Canada, 2010**). Various Acts (and regulations contained therein) are envisioned by Health Canada to be applicable to nanomaterials, including the Food and Drugs Act, the Canadian Environmental Protection Act 1999, the Hazardous Products Act and the Pest Control Products Act.

Health Canada has indicated that in order to identify and assess potential risks and benefits (where applicable) of nanomaterials, the following types of information may be required to be submitted for review:

1. Intended use of the nanomaterial, including any end product it will be used;
2. Characterization of the nanomaterial, including manufacturing methods, identity and purity;
3. Physicochemical properties and toxicological, eco-toxicological, metabolism and environmental fate data that may be both generic and specific to the nanomaterial if applicable; and
4. Risk assessment and risk management strategies, if considered or implemented.

Health Canada has noted future guidance specific to different program areas, and legislative and regulatory authorities will be developed in a manner that promotes a consistent set of approaches (**Health Canada, 2010**).

Europe

Regulation (EC) No. 1223/2009, published in December 2009, represents a major overhaul of the regulatory process for cosmetics in the EU (**EC, 2009**). All cosmetic products must be in compliance with the Regulation by July 11, 2013. Article 16 of the Regulation pertains specifically to nanomaterials, including information on the timing and required content of notifications. Cosmetic products containing nanomaterials that are on the market prior to Jan. 11, 2013, must be notified to the European Commission between Jan. 11, 2013 and July 11, 2013. Cosmetic products containing nanomaterials that are not on the market by Jan. 11, 2013, must be notified six months prior to being placed on the market (this differs from products that do not contain nanomaterials for which notification can be made at the time of placing them on the market) unless the nanomaterials conform with the conditions set out in Annex III of the Regulation. In any instance, the information notified to the Commission must contain at least the following:

1. Identification of the nanomaterial, including its chemical name (IUPAC) and other descriptors;
2. Specification of the nanomaterial (physicochemical properties);
3. Estimate of the quantity of the nanomaterial contained in products intended to be placed on the market per year;
4. The toxicological profile of the nanomaterial;
5. Safety data of the nanomaterial relating to the category of cosmetic product, as used in such products; and
6. Reasonably foreseeable exposure conditions.

The European Medicines Agency (EMA) is applying current regulatory frameworks to assess products of nanotechnology. As stated by EMA in a reflection paper on nanotechnology-based medicinal products for human use: "It is important to point out that in the EU the evaluation and prevention of potential hazards related to the use of any given nanomedicinal product is already foreseen under the existing pharmaceutical legislation. As for any medicinal product, the EU competent authorities will evaluate any application to place a nanomedicinal product on the market, utilizing established principles of benefit/risk analysis, rather than solely on the basis of the technology per se" (**EMA, 2006**). However, EMA acknowledges regulating nanotechnology-based products will be challenging and may require additional specialized expertise for the evaluation of the quality, safety, efficacy and risk management of such products (**EMA, 2006**).

The European Food Safety Authority (EFSA) considers the risk assessment paradigm (hazard identification, hazard characterization, exposure assessment and risk characterization) applicable to nanomaterials, but suggests risk assessment of nanomaterials in the food and feed area take into consideration specific properties of nanomaterials in addition to those common to the equivalent non-nanoforms. EFSA suggests different types of nanomaterials likely vary, as do their toxicological properties, and notes the available data on oral exposure to specific nanomaterials and any consequent toxicity are extremely limited. Thus, the risk assessment of nanomaterials has to be performed on a case-by-case basis (**EFSA, 2009**).

Overarching Issues

Seemingly simple tasks such as defining what a nanomaterial is have proved more difficult than anticipated, but progress is being made in this and other areas of nanotechnology regulation so that uniform standards can be established and applied. That said, by recognizing adaptation will be instrumental to the overall process, regulatory authorities in various regions are building on experience to revise and enhance review and authorization processes for different product categories. While this certainly is no small effort, it is anticipated that it will better address the needs of the cosmetic, food, pharmaceutical and other industries; and, most importantly, protect the safety of the end users of the myriad nanotechnology-based products that have and will be developed in the coming years.

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