

# The Nanomedicine Revolution

## Part 3: Regulatory and Safety Challenges

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This is the last part of a three-part series about nanomedicine. Emerging concepts were discussed in the September issue of *P&T*, and current and future clinical applications were discussed in the October issue.

### Introduction

The number of nanomedical products being submitted to the FDA for approval is rapidly growing, and new applications are continuously being developed. However, the FDA's current approach to regulating nanomedicines has been questioned. Critics say that rather than adapting and applying existing regulations, the agency should establish regulatory guidelines that are specific to nanomedical products.<sup>1-3</sup> However, prior to doing so, additional data need to be gathered and appropriate testing criteria need to be established.<sup>4,5</sup> The FDA is currently laying the groundwork to establish formal regulatory guidelines that will specifically apply to nanomedical and other nanotechnology products.<sup>6</sup> Other U.S. government agencies are also collaborating with the FDA to coordinate policies and generate data to ensure the safety and efficacy of nanoproducts.<sup>6</sup>

### Need for Specific Regulatory Guidelines

#### Existing FDA Guidelines Have Been Adapted For Nanomedicines

Most FDA regulations were written before the advent of nanotechnology.<sup>5</sup> Nevertheless, the FDA currently uses the existing framework of regulatory standards and statutes to regulate nanomedical products.<sup>7,8</sup> The FDA does, however, recognize that it is "necessary for technical assessments to be product-specific, taking into account the effects of nanomaterials in the particular biological and mechanical context of each product and its intended use."<sup>8</sup> The agency also acknowledges that "because of some of their special properties, nanoscale materials may pose different safety issues than their larger or smaller (i.e., molecular) counterparts."<sup>5</sup>

According to federal regulations, an Investigational New Drug (IND) application must be submitted to the FDA before human clinical trials for a drug are conducted, whether it is nanomedical or conventional. While reviewing an IND, the FDA may request any additional information needed to support the application, ensure the adequacy of the study design, or protect the safety of the clinical trial participants.<sup>5</sup> For example, in reviewing the IND for a nanomedicine, the FDA might request particle size data if the agency considers it to be relevant to whether a drug is safe or effective.<sup>5</sup> If the FDA determines that particular information is needed for an entire class of drugs, it can issue guidance to industry recommending that the data be submitted in all INDs filed for that drug class.<sup>5</sup>

Federal regulations also require applicants to notify the FDA if any changes have been made to a drug after it has been approved.<sup>5</sup> When significant changes have occurred, a supplement to the original New Drug Application (NDA), Abbreviated New Drug Application (ANDA), or Biologics License Application (BLA) must be filed.<sup>5</sup> Significant changes include any modification to the drug ingredients, the production process, quality control, the equipment, or manufacturing facilities that might substantially or adversely affect the drug.<sup>5</sup> Changes to an approved drug that introduce nano-ingredients would therefore likely trigger a request for a "change notification chemistry supplement," which the FDA would then review prior to granting or denying approval of the revised formulation.<sup>5</sup> Depending on how significant the change is, it is possible that an altered product might be considered to be new.<sup>5</sup> In this case, a new application for approval would be required rather than just a supplement to a previously filed submission.<sup>5</sup>

Existing FDA regulations have similarly been adapted to evaluate medical devices with nanomaterial components. The FDA considers Class III devices to be the most complex and "high-risk" category for medical devices.<sup>5</sup> A Class III designation therefore requires a device manufacturer to submit a Premarket Approval Application (PMA) to the FDA.<sup>5</sup> In the PMA, manufacturers must provide detailed evidence that a device provides a "reasonable assurance of safety and effectiveness."<sup>5</sup> This evidence usually consists of data from preclinical testing and clinical trials.<sup>5</sup> Any modification to an FDA-approved Class III device or its method of manufacture that could affect safety or efficacy, such as the introduction of nanomaterials, would require FDA approval of a PMA supplement.<sup>5</sup>

The FDA considers medical devices "for which safety and effectiveness are generally well-established," as posing a lower risk, so they are classified as Class I or II devices.<sup>5</sup> Class II devices are more complex and carry a higher risk than Class I devices.<sup>5</sup> Manufacturers of Class I and II medical devices are usually required to submit only a 510(k) application for FDA approval rather than a PMA.<sup>5</sup> In this document, manufacturers have to submit data or other information showing only that the safety and efficacy of a product are "substantially equivalent" to a similar medical device that has already received FDA approval.<sup>5</sup>

Manufacturers of Class I or Class II medical devices can make modifications to FDA-approved products without being required to submit a new 510(k) application.<sup>5</sup> However, a new 510(k) application is required under certain circumstances, such as when the device is modified in a way that uses a "fundamentally different scientific technology" than the original approved device.<sup>5</sup> Manufacturers, therefore, do have to submit a new 510(k) application when the inclusion of nanomaterials is determined to qualify as a fundamentally different scientific technology.<sup>5</sup> A PMA could also be required if the FDA determines that the use of nanomaterials in a Class I or II device requires original clinical study data to determine safety and efficacy.<sup>5</sup>

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In summary, the FDA presently considers existing drug and medical device regulations to be sufficiently robust, flexible, and comprehensive to ensure the safety of nanomedical products.<sup>1,8</sup> When warranted, nanomedical products must undergo premarket testing and approval as new drugs or devices under the NDA or PMA process.<sup>1</sup> The FDA has defended its position by asserting that the clinical studies that existing regulations require would detect any toxicity due to the unique properties of nanomedicines.<sup>1</sup>

### FDA Policies for Regulating Nanomedicines Have Been Criticized

Critics consider the current FDA approach to nanoparticle regulation to be flawed because nanoparticles (NPs) aren't just smaller versions of larger molecules ("bulk counterparts") but often have fundamentally different properties.<sup>1</sup> For example, the pharmacokinetic profile of nanomedicines often changes (such as altered area-under-the-curve and peak plasma concentrations) compared with conventional versions. Therefore, some experts say that nanoformulations of existing drugs should be treated as new molecular entities (NMEs) and thus should require an entirely new application for FDA approval.<sup>9</sup>

Specific regulations for the oversight of nanomedical products are yet to be established, leading some commentators to question whether the FDA's current approach to regulating nanomedical products is adequate.<sup>1</sup> Some say that the pre-clinical and clinical trial requirements for the FDA's approval of conventional drugs and devices are insufficient to detect possible toxic effects from nanomedical products.<sup>1</sup> There have also been complaints about the FDA's approval of nanoparticle-based products in whole, or in part, on study data from tests that had previously been used only for larger-scale molecules.<sup>1</sup> These nanoparticle products were granted approval based on safety data from equivalent conventional versions without having gone through the full PMA or NDA process.<sup>1</sup>

Reflecting these concerns, in January 2008, the International Center for Technology Assessment (ICTA) and a coalition of 40 consumer, health, and environmental groups issued a report that called for strong, comprehensive FDA oversight of nanotechnology products.<sup>3</sup> In this report, the ICTA called for more specific laws regulating nanoparticle products, stating that "current legislation provides inadequate oversight of nanomaterials. A modified or *sui generis*, nanospecific regulatory regime must be an integral aspect of the development of nanotechnologies." In 2006, the ICTA coalition had also filed a legal petition challenging the FDA regulation of nanoparticle products. The petition requested (1) comprehensive nanospecific regulations, (2) new standards for nanomaterial toxicity testing, (3) classification of nanomaterials as new substances, and (4) the mandatory labeling of nanomaterials and nanoparticle products.<sup>2</sup>

### The Properties of Nanoparticles Differ From Those of Bulk Counterparts

It is well established that the properties of NPs and nanomaterials can differ from conventional substances.<sup>1</sup> When particle size decreases below 100 nm, a number of unusual physicochemical phenomena are observed.<sup>10</sup> These include enhanced plasticity; altered thermal, optical, and magnetic properties; enhanced reactivity and catalytic activity; faster electron/ion transport; modified structural integrity; increased

biological or chemical activity; and novel quantum mechanics.<sup>5,10</sup> Because these altered properties occur at the nanoscale level, NPs cannot be assumed to be biologically equivalent to larger "bulk counterparts."<sup>1</sup>

The properties and biological effects of a nanomaterial can also change when particle size is varied *within* the nanoscale.<sup>5</sup> For example, a compound that previously was not absorbed into systemic circulation when applied topically might be when particle size is further decreased below a certain threshold.<sup>5</sup> It is also possible that NPs below a certain size might be able to enter vital organs, which can lead to unique toxic responses.<sup>11</sup> These effects could be based on the impact of size on the filtering capacity of phagocytes, the transport effects of capillary structures, or adhesion to proteins or other molecules in biological fluids.<sup>5</sup> In some cases, these interactions can be predicted; in others, they are unexpected.<sup>5</sup> Data therefore need to be developed to better predict the biological interactivity of NPs, particularly with a focus on size dependency.<sup>5</sup> The FDA and the National Toxicology Program are currently collaborating to develop these data.<sup>5</sup>

Some laboratory studies have shown that rather than size, surface area per unit of volume or mass is a better determinant of NP toxicity.<sup>5</sup> Surface area can have a profound effect on the reactivity of NPs, since reactivity per unit mass increases with increased surface area.<sup>5</sup> Important biological effects are altered when NP surface area increases as the size of an NP decreases, even though the amount of a biologically active material remains constant.<sup>5</sup> For example, some NPs are believed to generate an increased amount of reactive oxygen species, or free radicals, as size decreases and surface area increases, leading to an increased inflammatory response.<sup>5</sup>

Other features, besides size and surface area, have also been shown to affect the properties of NPs, including charge, surface modifications, shape, and polarity.<sup>1</sup> For example, positively charged lipid NPs have been observed to induce cerebral edema, whereas neutral and low concentrations of negatively charged lipid NPs do not have this effect.<sup>5</sup> Studies have also shown that modifying the surface of nanoscale materials with surfactants or biocompatible polymers, such as polyethylene glycol (PEG), reduces the toxicity of some NPs *in vitro* and alters the half-life and tissue deposition *in vivo*.<sup>5</sup> In other cases, surface modification has been shown to be a more important determinant of biological interactivity than surface area.<sup>5</sup> Just as the configuration of a molecule can affect the interaction with cell receptors and compounds in the body, the location of surface modifications can affect the biological interactivity of NPs.<sup>5</sup>

### A Consensus That Further Research Is Necessary

Industry has requested that the FDA provide specific guidance to manufacturers about when the use of nanoscale ingredients might require additional data, change the product's regulatory status or pathway, or merit taking special steps to address potential safety or product quality issues.<sup>5</sup> However, the FDA can apply only the currently limited scientific understanding of nanomaterials to assess what additional data might be needed when reviewing nanoparticle products.<sup>5</sup> Therefore, the FDA has been unable to issue such specific guidelines; instead, it "encourages industry to consult early with the agency to address any questions related to the safety, effectiveness, or other attributes of

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products that contain nanomaterials, or about the regulatory status of such products.”<sup>8</sup>

The FDA needs to acquire a greater understanding of the toxicity and other properties of nanomaterials before it can establish new guidelines for nanoproducts.<sup>4,5</sup> More data are also needed to help the FDA determine what, if any, additional testing should be required during agency evaluation of products containing nanomaterials.<sup>5</sup> For example, the size boundary at which data regarding larger particles of a particular material become irrelevant to NPs is currently unknown.<sup>5</sup> In addition, only limited data are available regarding the metabolism and toxicity of NPs, including excretion, translocation, carcinogenicity, and immunological or genotoxic effects.<sup>4</sup> Such findings are relevant to evaluating toxicity, biocompatibility, and the potential distribution of NPs in the body.<sup>5</sup> Long-term toxicity data for many nanomaterials are also currently unavailable.<sup>5</sup> The biopersistence of inorganic NPs, which can build up in the body, must also be studied extensively in animals before they can be approved for use in human applications.<sup>4</sup>

Interestingly, the available data do not conclusively suggest that all NPs are inherently more hazardous than their bulk counterparts.<sup>5</sup> In fact, numerous histology and renal or hepatic marker analyses have demonstrated that certain NPs do not elicit toxic responses in animals.<sup>11</sup> However, a connection between magnetic NPs used in thermal ablation therapy and treatment-related adverse effects, resulting from retention in the urinary tract, has been reported.<sup>11</sup> The matter of NP toxicity remains controversial and therefore must be investigated.<sup>11</sup>

### The FDA Is Struggling to Accumulate Data and Establish Testing Criteria

NPs aren't necessarily intrinsically toxic, but they do have unique properties that bring safety into question.<sup>12</sup> Therefore, nanomedical products and other nanoproducts could be considered “new for safety evaluation purposes,” meriting careful FDA regulatory oversight both before and after entering the market.<sup>12</sup> However, validating every nanotherapeutic agent for safety and efficacy, whether drug, device, biologic, or combination product, presents an enormous challenge for the FDA, which is currently struggling to accumulate safety data and formulate testing criteria for this purpose.<sup>13,14</sup> The FDA faces numerous obstacles in its efforts to establish regulatory guidance for the evaluation of nanomedicines; among these are the limited availability of data that correlates the physicochemical properties of NPs to safety risks, a lack of validated preclinical screening tests and animal models to assess nanomedicines, and a lack of appropriate expertise.<sup>1,12</sup>

Regarding the availability of data, numerous publications do exist concerning the biological interactions of naturally occurring NPs, as well as for those released during industrial processes, such as combustion-related particulate matter, silica dust, and biological particles.<sup>5</sup> In 2002, there were 22,000 publications that discussed nanotechnology.<sup>5</sup> Although managing so much information is a formidable task, data mining these publications would likely yield a wealth of information that would be helpful to the FDA in determining the general properties of NPs.<sup>5</sup> However, because surface modifications can significantly affect NP properties, the value of existing data is likely limited.<sup>5</sup> Therefore, whenever possible, it is important

to supplement this information with data from hazard studies that focus on specific NPs.<sup>5</sup>

The development of a comprehensive database of information regarding NPs that utilizes standardized ontologies, or other means of integrating all available data, could also be very valuable to the FDA.<sup>5</sup> There has been a tendency within conventional pharmacological research to develop and organize information using physiologically based pharmacokinetic (PbPK) or quantitative structure activity relationship (QSAR) models.<sup>5</sup> Such models are useful in predicting the biological interactions of conventional molecules, and they may be equally useful in helping the FDA understand the behavior of NPs.<sup>5</sup> Categorizing information according to certain characteristics (material type, size, charge, surface modification) could be beneficial in understanding and predicting NP properties.<sup>5</sup> As the FDA and the scientific community become more familiar with different nanomaterials, it may be possible to predict, for example, that specific variations in NPs may cause them to react in a certain way, similar to how a specific functional group may influence the interactivity of a molecule.<sup>5</sup> Presently, the FDA has not established or applied comparable PbPK or QSAR models to nanomaterials.<sup>5</sup>

The lack of testing criteria to generate data regarding the toxicity of nanomaterials is also a concern.<sup>15</sup> The predictive value of existing testing approaches, when applied to assess the safety, efficacy, and the quality control of nanoproducts, has been questioned.<sup>5</sup> Appropriate endpoints for *in vitro* assays of nanomaterials can also be difficult to determine.<sup>5</sup> There are established *in vitro* and *in vivo* assays and predictive models that evaluate a variety of endpoints to establish hazard(s) and identify further testing needs.<sup>5</sup> However, many of these tests were developed for conventional materials.<sup>5</sup> Because nanomaterials often behave differently, whether these tests have the ability to detect biological effects or define further testing requirements is yet to be determined.<sup>5</sup>

Most toxicology tests are also short-term, thus leaving the long-term effects of nanomaterials unknown.<sup>5</sup> In some cases, it may therefore be necessary to develop information to evaluate whether current short-term tests provide sufficient predictive value regarding long-term toxicity.<sup>16</sup> Similarly, new testing methods may be necessary to gather data to support decisions regarding nanomaterials that may have novel biological responses over the long term.<sup>5</sup> To this end, the Nanotechnology Characterization Laboratory has developed an assay cascade protocol, lasting for approximately 1 year, to carefully characterize the physicochemical attributes, *in vitro* biological properties, and the *in vivo* compatibility of NPs using animal models.<sup>15</sup>

The complexities presented by some nanomedical products are likely to pose additional challenges and review issues for the FDA.<sup>1</sup> Nanotechnology is expected to produce many nanomedical products that have multiple functions.<sup>5</sup> These products are likely to include highly integrated combinations of drugs, biologics, and/or devices that have multiple applications.<sup>5</sup> The FDA traditionally uses mechanism of action, or operation, to classify conventional therapeutic products as drugs, devices, biologics, or combinations thereof.<sup>12</sup> The FDA then usually applies the appropriate regulatory requirements to each part of a “combination product.”<sup>12</sup> The FDA expects that many nanomedical products will span the regulatory boundaries between drugs,

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medical devices, and biologics. These would be regulated under the rules established for “combination products.”<sup>17</sup>

However, because of the ambiguous nature of nanomedical drug-delivery devices, these agents cannot truly be considered to fit into any of these categories.<sup>1,12</sup> In this case, the FDA is expected to view these products as nanomedical combination products that are “technologically overlapping.” The FDA acknowledges that “the adequacy of the current paradigm for selecting regulatory pathways for ‘combination products’ may need to be assessed to ensure predictable determinations of the most appropriate pathway for such highly integrated [nanomedical] combination products.”<sup>5</sup>

Rendering appropriate regulatory decisions also requires a staff that has the proper expertise, up-to-date training, and access to current information.<sup>5</sup> The ability of the FDA to fulfill its responsibility to evaluate nanomedical products depends, in part, on having staff members with expertise in areas such as pharmacology, materials science, biology, physics, chemistry, medicine, and toxicology.<sup>5</sup> Continuing agency efforts to gather staff across centers and divisions to share scientific knowledge on nanomedical topics and materials will be important to facilitate the ability to perform an informed regulatory review.<sup>5</sup> Because of the evolving nature of nanomedicine, it is also important to continuously distribute new information and provide ongoing training in order to conduct an FDA review process that is timely, informed, and based on the most current science.<sup>5</sup>

To meet these substantial challenges, the FDA asserts that it is working to access the information that is needed to oversee products that contain nanomaterials, stating that:<sup>7</sup>

[The] FDA has long encountered the combination of promise, risk, and uncertainty that accompanies emerging technologies. Nanotechnology is not unique in this regard. The very changes in biological, chemical and other properties that can make nanotechnology applications so exciting also may merit examination to determine any effects on product safety, effectiveness, or other attributes. Understanding nanotechnology remains a top FDA priority. [The] FDA is monitoring evolving science and has a robust research agenda to help assess the safety and effectiveness of products using nanotechnology.<sup>8</sup>

### The FDA Has Defined Important Regulatory Issues Regarding Nanotechnology

In 2006, the FDA convened a Nanotechnology Task Force to assist with the challenges that nanoparticle regulation presents.<sup>5</sup> This task force identified four important broad questions concerning the regulation of nanoparticles.<sup>5</sup> They are as follows:<sup>17</sup>

- Is the FDA able to determine whether a product incorporates NPs or nanomaterials?
- What is the scope of the FDA’s authority when evaluating the safety and efficacy of nanoparticles?
- Should the identification of nanomaterials be permitted or required in product labeling?
- Does the use of a nanomaterial in an FDA-regulated product raise any environmental issues covered by the National Environmental Policy Act (NEPA)?

These and other areas of concern are briefly discussed in the

following sections. Table 1 includes a detailed list of questions that the FDA needs to address.

### Determining Whether an FDA-Regulated Product Contains Nanomaterials

During June 2011, the FDA issued draft guidelines for industry on “Considering whether an FDA-Regulated Product Involves the Application of Nanotechnology.”<sup>18</sup> Specifically, the agency named certain characteristics—such as the size and properties of any nanomaterials used—that should be considered when attempting to identify whether a regulated product utilizes nanotechnology.<sup>5,6</sup>

However, in order to evaluate particle size, the FDA needs to develop standard particle-characterization methods.<sup>5</sup> Currently, the FDA’s ability to detect nanomaterials in regulated products is limited, and the development of appropriate analytical

**Table 1 Emerging Questions for the FDA Regarding the Regulation of Nanomedicines**

- What is the scope of the FDA’s authority when evaluating the safety and efficacy of nanoparticle products?
- Is the FDA able to determine whether a product incorporates NPs or nanomaterials?
- Should the FDA create a specific regulatory definition of “nanomedicines”? If so, should the FDA’s definition differ from that developed by other regulatory agencies?
- Are new, more specific regulations needed for all nanomedical products or only a subset of them?
- Should the FDA rely on manufacturers to determine and report whether medical products are nanoparticle products during the submission process?
- Do nanomedical products blur the distinctions between drugs and devices, making the existing regulatory system insufficient for proper classification and evaluation?
- Does reformulation of a drug into a nanoformulation change how the drug should be regulated? Is a supplemental new drug application sufficient? Is a nanomedicine ever therapeutically equivalent to a conventional version of the same drug?
- Should nanomedicines that treat cancer be approved through an accelerated approval process? Or, because the risk of nanomaterials is unknown, should the FDA require extra testing before the product is marketed?
- Should other agencies share the responsibility of regulating nanomedicines? Should there be a greater coordinated effort on the part of federal agencies to review, amend or create specific regulations concerning nanoparticle products when warranted?
- What implications do nanomedical products present with respect to the labeling and misbranding provisions of the Federal Food, Drug, and Cosmetic Act (FFDCA)? When should companies be permitted, required, or prohibited from labeling their products as nanoparticle products?
- Does the use of a nanomaterial in an FDA-regulated product raise any environmental issues covered by the National Environmental Policy Act (NEPA)?

Text based on content from Bawa R. *Curr Drug Deliv* 2011;8(3):227–234;<sup>1</sup> Paradise J. 2009;<sup>2</sup> and *Nanotechnology Task Force Report 2007*.<sup>5</sup>

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methods is expected to require substantial effort.<sup>5</sup> In addition, FDA reviewers are generally less familiar with new analytical methods that are used to characterize nanomaterials.<sup>5</sup> It is important to be knowledgeable about these methods because they may have different strengths and weaknesses when evaluating particle size and distribution, surface charge and properties, and particle interactions or aggregation. These features may have an impact on dose, stability, and other characteristics that could affect safety, efficacy, or product quality.<sup>5</sup>

### The FDA's Authority to Evaluate Nanoproducts

The FDA considers its authority to be adequate to meet the challenge of regulating nanomedical and other nanotechnology products. However, the agency acknowledges that due to the evolving nature of nanotechnology, a case-by-case approach is warranted to assess whether a product satisfies applicable statutory and regulatory standards.<sup>5</sup> Testing criteria also need to be evaluated to determine whether modifications need to be made to address nanomaterials.<sup>5</sup> The increased use of nanomaterials may present particular challenges, for example, testing for product stability or detecting potentially hazardous by-products.<sup>5</sup>

### Product Labeling

Consumer advocate groups and commentators have suggested that the FDA should seriously contemplate requiring labeling that identifies the presence of nanomaterials in the products that the agency regulates.<sup>1</sup> Whether the inclusion of nanomaterials must be specified in product labeling for FDA-regulated products, either as a requirement or voluntarily, is dependent upon the Federal Food, Drug, and Cosmetic Act (FFDCA).<sup>5</sup> Even when the FDA reviews a labeling claim, such as a structure, function, or health claim, it would not necessarily evaluate information on the use of nanomaterials.<sup>5</sup> The FDA would review such information only if a nanomaterial was relevant to a labeling claim and, if so, only in cases where such information was required (such as in a health claim petition) or voluntarily submitted for other types of claims.<sup>5</sup> If the FDA determines that a specific use of a particular nanomaterial is a material fact for a category of products, the FDA could amend its regulations to require that all members of a product category include labeling regarding the use of a nanomaterial.<sup>5</sup>

The FDA may also have to balance the desire for transparency with the possibility that the public might reject some beneficial products because they include nanomaterials.<sup>1</sup> In any case, it has been requested that nanoproducts for human consumption include product labeling.<sup>1</sup>

### Environmental Safety

There are already hundreds of nanoproducts on the market, yet little is known about the environmental risks that may be associated with them.<sup>1,19</sup> Nanomaterials may have environmental implications if they enter waterways during the manufacturing process or when they are disposed of, presenting a safety risk to the general public.<sup>20</sup> This problem is particularly worrisome, because NPs may have a greater intrinsic potential for toxicity due to the increased biological interactivity that occurs with increased surface area.<sup>1</sup> Nanomaterials might also present occupational hazards to personnel exposed to them during the manufacturing process.<sup>20</sup>

### Postmarketing Surveillance

It is well established that premarket drug testing cannot detect all potential adverse reactions. Therefore, it is essential that long-term surveillance of nanomaterials be conducted to gather additional safety data.<sup>1</sup> In this regard, an effective postmarketing risk research strategy needs to be devised to collect toxicity data specific to nanomaterials.<sup>1</sup> The FDA has stated that it is committed to gathering and sharing scientific knowledge, including the postmarketing surveillance of nanomedicines and other nanoproducts.<sup>5</sup>

### Information Gathering by the FDA And Other Governmental Agencies

#### The FDA Nanotechnology Task Force

In August 2006, the FDA established the Nanotechnology Task Force to address ways to evaluate FDA-regulated nanoproducts.<sup>6</sup> The responsibility of this task force is to determine regulatory approaches that encourage the continued development of innovative, safe, and effective nanoproducts.<sup>21</sup> In July 2007, the task force issued a report that recommended that the FDA issue guidelines to industry to address the potential risks and benefits of drugs, medical devices, cosmetics, and other nanoproducts.<sup>6,16,17</sup> The task force also held a public meeting in 2008 to gather information that would help the FDA implement the recommendations of the 2007 *Nanotechnology Task Force Report*.<sup>1</sup> The report recommended that the FDA:<sup>16</sup>

- provide guidance clarifying what information manufacturers need to submit to the agency and when the use of nanomaterials might change the regulatory status of a product.
- be contacted by manufacturers early in the product-development process.
- assess data needs for regulated nanoproducts, including for the biological effects and interactions of NPs.
- evaluate current testing approaches to assess the safety, effectiveness, and quality of nanomaterials.
- develop in-house expertise to ensure that new information on nanotechnology is properly considered as it becomes available.

Since the Nanotechnology Task Force issued its 2007 report, the FDA issued its first draft guidance on nanotechnology in June 2011, titled "Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology: Draft Guidance for Industry."<sup>16</sup> In April 2012, the task force issued additional draft guidelines, specifically for food and cosmetic manufacturers.<sup>6,8</sup> To date, the FDA has issued these draft guidance documents but has not yet established specific formal regulatory guidelines for any nanoproducts.<sup>1</sup> The task force continues to identify knowledge or policy gaps in an effort to enable the FDA to evaluate possible adverse health effects from products using nanomaterials.<sup>21</sup>

#### The Nanotechnology Interest Group

The FDA also formed the Nanotechnology Interest Group (NTIG), which is a committee composed of representatives from all of its regulatory centers.<sup>1</sup> The NTIG provides an open forum for networking and the exchange of information relevant

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to the development and commercialization of nanoproducts.<sup>22</sup> NTIG members meet quarterly to discuss the issues about nanotechnology that the regulatory centers are facing, what type of products they're reviewing, and the process they follow for evaluating those products.<sup>22</sup> The NTIG also invites representatives from industry to talk about their concerns and the development of nanoproducts.<sup>22</sup>

### The National Nanotechnology Initiative

The FDA is also working with other U.S. government agencies to focus on coordinating policies and generating data to ensure the safety and efficacy of nanoproducts.<sup>6</sup> To this end, the FDA and 24 other federal agencies formed the National Nanotechnology Initiative (NNI) (Table 2).<sup>16,23</sup> The NNI is a federal research and development program established to coordinate the efforts of government agencies involved in nanotechnology.<sup>5,16</sup> Participation in the NNI provides the FDA and the other governmental agencies the opportunity to define, coordinate, and pursue their research needs.<sup>5</sup> The goals of the NNI are to:<sup>5</sup>

- maintain a world-class research and development program with the aim of realizing the full potential of nanotechnology.
- encourage the inclusion of new technologies in products in order to facilitate economic growth, jobs, and other public benefits.
- develop the supporting infrastructure and tools needed to advance nanotechnology, including educational resources and a skilled workforce.
- promote the responsible development of nanotechnology.

### The Alliance for Nanotechnology in Cancer

In 2004, the National Cancer Institute (NCI) launched the Alliance for Nanotechnology in Cancer in 2004.<sup>15,24</sup> This group promotes the use of nanotechnology to advance the diagnosis, prevention, and treatment of cancer.<sup>24</sup> The alliance encompasses both the public and private sectors for the purpose of accelerating the application of nanotechnology to cancer.<sup>25</sup> Its goals are to develop:<sup>25</sup>

- tools to identify new biological targets for cancer treatment.
- agents to monitor molecular changes and prevent precancerous cells from becoming malignant.
- imaging agents and diagnostics to detect cancer in the earliest, most easily treatable, presymptomatic stage.
- multifunctional targeted nanodevices to deliver multiple therapeutic agents directly to cancer cells.
- systems that will provide real-time assessments of therapeutic and surgical efficacy.
- novel methods to diminish symptoms that reduce the quality of life for patients with cancer.

### Conclusion

Although the FDA's current approach to regulating nanomedical and other nanotechnology products has been challenged as lacking specificity, the FDA cannot develop more specific guidelines until it collects more data, establishes valid testing criteria, and answers important questions regarding the regulation of these products.<sup>1-5</sup> The FDA has not yet established formal guidelines for the regulation of nanomedical and other nanotechnology products; however, it has published several draft guidance documents on this topic.<sup>5,6</sup> The ideal outcome

**Table 2 Federal Agencies Participating in the National Nanotechnology Initiative During 2011**

#### Federal Agencies With Budgets Dedicated to Nanotechnology Research and Development

- Consumer Product Safety Commission (CPSC)
- Department of Defense (DOD)
- Department of Energy (DOE)
- Department of Homeland Security (DHS)
- Department of Justice (DOJ)
- Department of Transportation (DOT, including the Federal Highway Administration, FHWA)
- Environmental Protection Agency (EPA)
- Food and Drug Administration (FDA, Department of Health and Human Services)
- Forest Service (FS, Department of Agriculture)
- National Aeronautics and Space Administration (NASA)
- National Institute for Occupational Safety and Health (NIOSH, Department of Health and Human Services/Centers for Disease Control and Prevention)
- National Institute of Food and Agriculture (NIFA, Department of Agriculture)
- National Institute of Standards and Technology (NIST, Department of Commerce)
- National Institutes of Health (NIH, Department of Health and Human Services)
- National Science Foundation (NSF)

#### Other Participating Agencies

- Bureau of Industry and Security (BIS, Department of Commerce)
- Department of Education (DOED)
- Department of Labor (DOL, including the Occupational Safety and Health Administration, OSHA)
- Department of State (DOS)
- Department of the Treasury (DOTreas)
- Director of National Intelligence (DNI)
- Nuclear Regulatory Commission (NRC)
- U.S. Geological Survey (USGS, Department of the Interior)
- U.S. International Trade Commission (USITC)
- U.S. Patent and Trademark Office (ISPTO, Department of Commerce)

From the National Nanotechnology Initiative Supplement to the President's 2012 Budget, February 2011.<sup>23</sup>

with respect to regulating nanomedicines is a proper balance between "underregulation," which could cause inappropriate and possibly harmful product approvals, and overregulation, which could limit innovation.<sup>1</sup>

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