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The Role of FDA in the Regulation of Manufactured Nanomaterials

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The marketplace for intentionally engineered (manufactured) nanoscale materials (MNMs) has grown exponentially in the last decade and will continue to see impressive growth well into the next decade. In five to ten years, by 2014, the market for nanomaterials, nanotools, and nanodevices could be worth anywhere from $25 billion to over $2 trillion.[1] The touted benefits resulting from greater application of nanotechnologies are vast and varied, with promises of cleaner soil and water, cheaper energy, improved and more effective consumer products and industrial tools, and potentially revolutionary medical tools and devices including new more effective approaches to treating cancer.

The use of nanotechnologies in medicine holds great promise for revolutionizing certain current therapies. For example, researchers from UCLA recently demonstrated the ability of mesoporous silica nanoparticles to not only store and deliver chemotherapeutic drugs used in cancer treatment, but to suppress breast and pancreatic tumors in mice.[2] The use of these nanoparticles showed excellent ability to accumulate only within tumors (which can potentially reduce undesirable side effects) and were expelled from the body within a few days (reducing worries of effects from repeat exposures, as necessary in chemotherapy). In order to bring life-saving applications of nanotechnologies like this to the public, the U.S. Food & Drug Administration (FDA) can help the federal government surmount some current obstacles to regulation and play a key role in the development of practical and protective approaches to safety assessment of manufactured nanomaterials (MNMs). This article provides background on FDA regulation of MNMs and highlights areas where FDA can provide federal leadership.

FDA Jurisdiction

FDA regulates a number of food and drug products that touch many lives every day, including biological products (vaccines, blood products, tissues), cosmetics, medical devices, foods and food additives, dietary supplements, and drugs (human and animal).

The Agency's website lists a number of applications where nanotechnology is being used in medical and consumer products today, including burn and wound dressings, dental-bonding agents, sunscreens, and protective coatings for eyeglasses. As reflected in the cancer treatment example, FDA predicts MNMs may be used to provide new drugs able to reach sites in the body more effectively and at safer doses, and to create tiny sensors that detect diseases in the body far earlier than existing diagnostic tools. It is also anticipated that many of the FDA-regulated nanotechnology products will span the boundaries between drugs, medical

devices, and biologics, which would be regulated under the rules established for "combination products". Like existing products, future applications of MNMs, such as applications of silver nanoparticles claiming antibacterial activity, may require joint approval by FDA and the U.S. Environmental Protection Agency (EPA).

FDA has vast experience with animal and human data as well as more recent experience with in vitro and in silico data to support the safety assessment of products. (In the broadest sense, in silico data refers to the output of the computer-based integration of bioinformatics and genomics.) FDA's expertise with toxicological data sets, modern approaches to data analysis, and regulatory applications of toxicological data is of crucial importance. FDA also has jurisdiction and/or knowledge of a large proportion of MNM products on the U.S. market today. A quick snapshot of the Woodrow Wilson Center Project on Emerging Nanotechnologies consumer product database (as of August 2009) reveals that more than half (340 of 540) of the products on the U.S. market fell into the "cosmetics" or "health and fitness" categories and roughly half of these products (259 out of 540) use nanosilver.[3] This latter fact is important from a regulatory perspective as silver is a very effective antimicrobial agent, and as such, may be subject to regulation by EPA under authority given by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). (Regulatory approval from both agencies for silver products claiming antimicrobial activity is not uncommon.)

Currently, FDA believes its existing requirements are adequate for most nanotechnology products it regulates. The rationale for this view is based on two observations: the FDA's decades of experience regulating products in the same size-range as nanoscale materials, such as cells, proteins, and molecules; and that, to date, FDA has no knowledge of adverse health effects related to the use of MNMs in drug or medical device products.[4]

Nanotechnology Task Force Findings

The current approach at FDA to regulating MNMs was largely shaped by its Nanotechnology Task Force, which issued an important report in 2007. A general finding of the Task Force is that the use of nanoscale materials presents regulatory challenges similar to other emerging technologies.[5] The Task Force also recognized that nanotechnologies can present unique challenges from a scientific and regulatory perspective because they can be used to make any FDA-regulated product in whole or in part, and that the safety and effectiveness of these materials is dependent on a number of characteristics, for example, size, shape, and surface treatment, which can vary under different conditions.[6] Furthermore, the rapid pace of product development and applications emphasizes the need for FDA to stay on top of the science and to issue guidance both on data requirements and their "triggers" based on the use of nanoscale materials in regulated products and the potential for exposure.

Another finding of the Task Force was that FDA authority for products subject to premarket authorization requirements, such as drugs, biological products, devices, and food and color additives, is comprehensive and generally adequate regarding the use of MNMs in regulated products.[7] Existing premarket authorities give FDA the ability to obtain detailed scientific information needed to review the safety and effectiveness of products. However, the Agency's oversight capacity is limited for products not subject to premarket requirements, such as dietary supplements, cosmetics, and food ingredients that are generally recognized as safe (GRAS)..

FDA Guidance and Leadership

To date, FDA has not posted any specific guidance documents for industry on data requirements for MNMs; however, an indication of the kinds of information FDA is interested in can be found in the

June 2010 Office of Pharmaceutical Science's "Reporting Format for Nanotechnology-Related Information in CMC Review."[8] This policy manual provides the framework by which relevant information about MNM-containing drugs will be captured in scientific reviews of drug application submissions. Examples of the kinds of information FDA believes are helpful in evaluating this type of drug application include: the type of nanomaterial (for example, dendrimers, liposomes, nanocrystals, metal colloids); average particle size or size range, and whether this property changes with different formulations; techniques used to assess particle size; solubility in aqueous media; and other properties, such as surface charge and how this property was measured.

Past FDA experience with more modern data (like genomic data and computational toxicity data) has demonstrated "outside the box" thinking that could be of extreme value to regulation of MNMs. One such example is the 2004 program to allow the regulated community to submit exploratory genomic data from the drug discovery process without regulatory impact, captured in the March 2005 Guidance for Industry: Pharmacogenomic Data Submissions. FDA has transformed this "safe harbor" idea from concept to a successful and unique opportunity for scientific exchange over the last decade. FDA has received 40 submissions of "voluntary exploratory data submissions" in the program's first 5 years, which has resulted in improving the content of later "official" data submissions, increasing the number of FDA consultations for "unofficial" review and demonstrating that "the industry is successfully integrating novel biomarker data in drug development."[9] This approach could be adopted by agencies in different forms for MNM-related data. Discussion of nanomaterial characterization data early in the discovery process could be crucial in the success of later data submissions and could help inform fate and transport of MNMs across the entire life cycle to enable more comprehensive quantitative risk assessment.

Some other major areas where FDA can provide leadership based on current capacity and past expertise include a federal-wide general regulatory definition of MNMs, the regulatory use of in vivo (animal and human) and in vitro toxicological data, the development of methods and protocols to leverage a priori knowledge and existing data (including the use of in silico data), development of integrated testing strategies to develop risk assessment data that minimize reliance on animal studies, and development of quantitative risk assessment guidance and/or risk-based frameworks for decision making.

Defining Manufactured Nanomaterials

With regard to a general definition, a major concern of virtually all stakeholders is how to define MNMs in a regulatory context. Different regulatory agencies have different needs for defining what falls under their purview and so a "generic" definition may not meet the needs of all agencies. The collective effect of many different definitions, however, is that they "counteract the power and strength of each individual definition" and provide a "source of ambiguity and confusion" for regulators, industry and the public.[10] Multiple regulatory definitions can also confuse product classification in existing regulatory frameworks, leading to misunderstanding across various scientific and technical disciplines due to a lack of shared understanding and consistent international terminology.[11]

The coordinating body for the federal-wide approach to nanotechnology in the U.S. is the National Nanotechnology Initiative (NNI), which is located in the Office of Science and Technology Policy in the Executive Office of the President. There are more than 20 different agencies and offices within agencies represented in NNI, with roughly half of these coming from the Departments of Defense and Energy. (*See* http://www.nano.gov for a list of these agencies as well as other useful information.)

The NNI refers to "nanotechnology" as:

> Nanotechnology is the understanding and control of matter at dimensions between approximately 1 and 100 nanometers, where unique phenomena enable novel applications. Encompassing nanoscale science, engineering, and technology, nanotechnology involves imaging, measuring, modeling, and manipulating matter at this length scale.

While the use of 100 nanometers (nm) has been a common upper bound until now, the California Department of Toxic Substance Control (DTSC) announced in a June 2010 green chemistry report that it would adopt a definition similar to that in OPS (2010) "with at least one dimension smaller than 1,000 nm."[12] Besides FDA and DTSC, the European Commission is contemplating using a 500 nm cut-off (after the French delegation suggested use of 400 nm) and the German government has initiated a registry of products using 500 nm as its initial cut-off. While FDA (2010) states that it adheres to the NNI definition,[13] the FDA Office of Pharmaceutical Science's working definition is for materials "with at least one dimension smaller than 1,000 nm," highlighting the need not only for intra- and interagency coordination on terminology but also harmonization with other international bodies where possible.[14]

A series of differing definitions like this will likely require manufacturers to meet the most stringent requirement (currently, the California and FDA definitions) in order to market products in the broadest way. Differing definitions will also lead to industry uncertainty because one jurisdiction may not consider a substance to meet its definition of nanoscale, while another could require expensive data packages for approval of the same substance.

The FDA Use of Toxicity Data

Early consideration of the hazards posed by MNMs focused entirely on the effects of size and its relationship to toxicity; however, it is now becoming clearer that structure, function and intent matter just as much as the actual length, width or diameter of the nanostructure.[15] Many of these same researchers are now calling for alternative approaches to exposure and dose metrics that focus more on particle number or surface area as opposed to particle diameter. Another sizeable data gap exists for the behavior of nanoparticles in the air, which can result in potential inhalation exposures to users of products, such as aerosolized sunscreens. FDA can play a significant role in developing meaningful dose metrics from inhaled nanoparticles.

While FDA has the most experience with animal and human data, it also has robust capacity with in vitro data and quantitative structure-activity relationships (QSAR, an in silico technique that predicts chemical toxicity from molecular structure) with drugs as a preliminary step in the tiered process of determining the nanomaterial's mode of action for regulatory purposes. FDA also has expertise in "bridging" to existing data, which has been suggested for nanomaterials,[16] whereby existing data and other a priori knowledge is used as much as possible in order to target in vivo animal testing to specific regulatory data needs. This concept is at the heart of the "21st century" toxicology (Tox21) vision embraced by FDA, EPA and others.[17] Finally, the FDA concept of comparison to "predicate devices" can also be of use to the development of a framework to leverage existing information where possible to avoid use of animals in experimentation and to reduce the burden on both the regulator and the regulated community.

Looking forward, FDA's expertise in conducting and interpreting animal data will be important as ongoing federal research efforts bear fruit. According to the most recent annual report from

the National Toxicology Program, testing was ongoing or planned for the neurotoxicity of silver nanoparticles, subchronic inhalation toxicity and genotoxicity of fullerenes, and metabolism/disposition studies of fullerenes, quantum dots, and nanoscale titanium dioxide.[18]

Risk Assessment and Management

The last major area where FDA can bring its experience to bear is in risk assessment and risk management. Risk assessment is perhaps in need of the greatest consideration given the need for government to continue to make decisions on product safety in the face of incomplete information. The biggest obstacle to this is uncertainty, particularly the "extreme uncertainty" that pervades all aspects of modern risk-based safety evaluation methods in regard to their application to MNMs.[19] This uncertainty is not limited to physicochemical characteristics that influence toxicity; environmental fate and transport of the myriad of known nanostructures, relevant routes of exposure (for regulatory purposes), metrics by which exposure and dose should be measured, the appropriateness and adequacy of testing procedures and analytical instrumentation, and basic molecular mechanisms of toxicity that lead to disease are largely unknown for MNMs.[20]

All of these knowledge gaps would have to be filled for a complete quantitative human health risk assessment, yet there are reportedly more than 1,000 products using nanotechnologies on the market with more coming every day. While no formal agency risk assessments for nanomaterials have been identified, two prominent researchers have applied the "3Rs approach" (Replace, Refine, Reduce the use of animals) to a cerium oxide nanoparticle using only in vitro data and computer modeling.[21] While much work still needs to be done for regulators to accept this approach to risk assessment, this strategy includes useful concepts, such as the use of a priori knowledge and bridging to existing data, non-traditional applications of in vitro data to satisfy existing regulatory data needs, and development of a "pathogenic sequence" linking health effects research with molecular mechanism of disease (a "bottom up" method to link molecular events with human disease, consistent with the Tox 21 approach). FDA expertise with in vitro testing systems and the regulatory application of these data may be crucial in the development of newer approaches to risk assessment, based on existing literature. In addition, FDA experience with microbial risk assessment (as done by the Center for Food Safety and Nutrition) could be instrumental in cross-agency interactions for MNM products claiming antibacterial activity.

FDA Can Provide Leadership, Knowledge and Experience

FDA is uniquely poised to demonstrate leadership among the federal agencies with regard to the safety assessment of MNMs and can play a leading role in developing a regulatory definition of MNMs. However, this definition needs to serve the needs of all relevant agencies, be simple yet enforceable, and should consider the needs of the international marketplace (Lovestam et al. 2010.)

Many devices and drugs are likely to have some MNM component and some of these products may also involve antibacterial properties and/or claims. FDA can provide a leading role in the safety assessment of such products and coordinate its approach with other relevant agencies, such as EPA and the U.S. Consumer Product Safety Commission.

FDA can play an instrumental role in conducting animal and human health effects research not only on currently known nanostructures and their applications but on future "standard reference nanomaterials" as they become available. In addition, FDA can participate in steering certain federally-conducted research to fill data gaps for basic understanding and/or regulatory purposes. The Agency has considerable knowledge and

experience in the interpretation and regulatory application of in vivo (animal), in vitro (cellular), and in silico (quantitative structure-activity relationships, or QSARs) data, often in novel ways, such as "bridging" to existing data where possible and relying on models such as QSAR prior to animal testing - consistent with the Tox21 vision.

Despite the lack of widely accepted regulatory definitions and extreme uncertainty that pervades all aspects of modern risk-based safety evaluation methods with regard to MNMs, responsible government must provide new approaches to bringing nanotechnologies to market while ensuring the public trust. All stakeholders involved have "little choice but to think about nanotechnology within the frameworks and worldviews already available to them" as they consider the "long-term future of [this] novel and nascent field of science and technology." [22] For the many reasons cited in this article, FDA can and should play a key role in establishing practical and protective approaches to nanotechnology regulation.

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