Regulating Nanomedicine – Can the FDA Handle It?

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Abstract: There is enormous excitement and expectation surrounding the multidisciplinary field of nanomedicine – the application of nanotechnology to healthcare – which is already influencing the pharmaceutical industry. This is especially true in the design, formulation and delivery of therapeutics. Currently, nanomedicine is poised at a critical stage. However, regulatory guidance in this area is generally lacking and critically needed to provide clarity and legal certainty to manufacturers, policymakers, healthcare providers as well as the public. There are hundreds, if not thousands, of nanoproducts on the market for human use but little is known of their health risks, safety data and toxicity profiles. Less is known of nanoproducts that are released into the environment and that come in contact with humans. These nanoproducts, whether they are a drug, device, biologic or combination of any of these, are creating challenges for the Food and Drug Administration (FDA), as regulators struggle to accumulate data and formulate testing criteria to ensure development of safe and efficacious nanoproducts (products incorporating nanoscale technologies). Evidence continues to mount that many nanoproducts inherently possess novel size-based properties and toxicity profiles. Yet, this scientific fact has been generally ignored by the FDA and the agency continues to adopt a precautionary approach to the issue in hopes of countering future potential negative public opinion. As a result, the FDA has simply maintained the *status quo* with regard to its regulatory policies pertaining to nanomedicine. Therefore, there are no specific laws or mechanisms in place for oversight of nanomedicine and the FDA continues to treat nanoproducts as substantially equivalent ("bioequivalent") to their bulk counterparts. So, for now, nanoproducts submitted for FDA review will continue to be subjected to an uncertain regulatory pathway. Such regulatory uncertainty could negatively impact venture funding, stifle nanomedicine research and development (R&D) and erode public acceptance of nanoproducts. The end-result of this could be a delay or loss of commercialized nanoproducts. Whether the FDA eventually creates new regulations, tweaks existing ones or establishes a new regulatory center to handle nanoproducts, for the time being it should at least look at nanoproducts on a case-by-case basis. The FDA should not attempt regulation of nanomedicine by applying existing statutes alone, especially where scientific evidence suggests otherwise. Incorporating nanomedicine regulation into the current regulatory scheme is a poor idea. Regulation of nanomedicine must balance innovation and R&D with the principle of ensuring maximum public health protection and safety.

Keywords: Nanomedicine, nanotechnology, Food and Drug Administration, FDA, regulation, nanoparticles, nanotherapeutics, nanoproduct, bioequivalence, National Nanotechnology Initiative, nanoscale technologies, combination products, patents, Patent and Trademark Office, PTO, National Institutes of Health, NIH, safety, efficacy, commercialization.

1. DEFINING NANOTECHNOLOGY AND NANOMEDICINE

The term nanotechnology is very much in vogue. But what does it mean? A nanometer (Greek, *nanos*, dwarf) is one billionth of a meter, or 1/75,000th the size of a human hair. An atom is about one third of a nanometer in width. Nanotechnology is a misnomer since it is not one technology but encompasses many technical and scientific fields such as medicine, chemistry, physics, engineering, biology, etc. One can view it as an umbrella term used to define the products, processes and properties at the nano/micro scale.

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One of the major problems regulators and lawyers continue to face regarding nanotechnology is the confusion and disagreement about its definition [1, 2]. There are numerous definitions of nanotechnology. One often used – yet clearly wrong – definition of nanotechnology was proposed by the US National Nanotechnology Initiative (NNI) – a federal R&D program established by the US government to coordinate the efforts of government agencies involved in nanotechnology. It simply limits nanotechnology to "about 1 to 100 nanometers" [3]. Various US government agencies, including the Food and Drug Administration (FDA) and the Patent and Trademark Office (PTO) continue to use this vague definition based on a sub-100nm size. Although the FDA is part of the NNI and participated in the development of this narrow definition, it has yet to officially adopt the NNI's definition for its own regulatory purposes or establish a "formal" definition.

The NNI nanotechnology definition presents numerous difficulties. For example, although the sub-100nm size range may be important to a nanophotonic company (e.g., a quantum dot's size dictates the color of light emitted therefrom),

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this size limitation is not critical to a drug company from a formulation, delivery or efficacy perspective because the desired property (e.g., improved bioavailability, reduced toxicity, lower dose, enhanced solubility, etc.) may be achieved in a size range greater than 100nm. Moreover, this NNI definition excludes numerous devices and materials of micrometer dimensions (or of dimensions less than 1 nanometer), a scale that is included within the definition of nanotechnology by many nanoscientists. Therefore, experts have cautioned against an overly rigid definition, based on a sub-100 nm size, emphasizing instead the continuum of scale from the "nano" to "micro."

Add to this confusion the fact that nanotechnology is nothing new. For example, nanoscale carbon particles ("high-tech soot nanoparticles") have been used as a reinforcing additive in tires for over a century. Another example is that of protein vaccines – they squarely fall within the definition of nanotechnology. In fact, many biomolecules are in the nanoscale. Peptides are similar in size to quantum dots and some viruses are in the size range of nanoparticles. Hence, most of molecular medicine and biotechnology can be classified as nanotechnology.

Technically speaking, biologists have been studying all these nanoscale biomolecules long before the term "nanotechnology" became fashionable. Even though the National Institutes of Health (NIH) concurs that while much of biology is grounded in nanoscale phenomena, it has not reclassified most of its basic research portfolio as nanotechnology. In this regard, NIH identifies three broad areas that it considers nanotechnology:

1) studies that use nanotechnology tools and concepts to study biology;
2) the engineering of biological molecules toward functions very different from those they have in nature; or
3) manipulation of biological systems by methods more precise than can be done by standard molecular biological, synthetic chemical or biochemical approaches.

In light of this confusion, the following practical definition of nanotechnology, unconstrained by an arbitrary size limitation, has been developed by the author [1, 2]:

"The design, characterization, production, and application of structures, devices, and systems by controlled manipulation of size and shape at the nanometer scale (atomic, molecular, and macromolecular scale) that produces structures, devices, and systems with at least one novel/superior characteristic or property."

Naturally, disagreements over the definition of nanotechnology carry over to the definition of nanomedicine. At present, there is no uniform, internationally accepted definition for nanomedicine either. One definition, not constrained by size, yet correctly emphasizing that controlled manipulation at the nanoscale results in medical improvements and/or significant medical changes, comes from the European Science Foundation [4]:

"The science and technology of diagnosing, treating and preventing disease and traumatic injury, of relieving pain, and of preserving and improving human health, using molecular tools and molecular knowledge of the human body."

Hence, the size limitation imposed in NNI's definition must be abandoned, especially when discussing nanopharmaceuticals or nanomedicine. The phrase "small technology" may be more appropriate to accurately encompass both nanotechnologies and micro-technologies. An internationally acceptable definition and nomenclature of nanotechnology should be promptly developed.

2. ADVENT OF NANOMEDICINE

Commercial nanomedicine, although at a nascent stage of development, is already a reality. While many sought-after innovations are decades away, there are hundreds, possibly thousands, of nanotech-based consumer products in the marketplace today. According to most experts, the market potential for medically-oriented new nanotechnologies – such as nanopharmaceuticals – will become increasingly significant in the future. Obviously, development is progressing more rapidly in certain sectors of nanomedicine. The most active areas of product development are drug delivery and *in vivo* imaging. However, it is impossible to gauge an accurate picture of the full commercialization potential for nanomedicine. This is partly due to the extremely rapid development of healthcare products in a fragmented marketplace, an explosion of nanopatents and the unpredictable nature of the research and development (R&D) process itself. Still harder to predict is what precise course nanomedicine will take in years to come. Will this relatively nascent area make small yet valuable contributions to medicine, or will it become a driving force that catalyzes a vast healthcare revolution? Many believe that "nano" is here to stay, and it will generate both evolutionary as well as revolutionary products. As evidence, one can look beyond current challenges and point to governments around the world that continue to be impressed by nano's potential and are staking their claims by doling out billions of dollars, Euros and Yen for R&D. From a business point-of-view, nanoproducts offer the ability to extend the economic life of proprietary compounds and create additional revenue streams, thereby significantly affecting the commercialization landscape. For instance, nanopharmaceuticals offer potential solutions to fundamental problems in the drug industry ranging from poor water solubility of compounds to a lack of target specificity [5, 6]. Eventually, "nano" should reduce the cost of drug discovery, design and R&D.

3. FDA EXAMINES NANOMEDICINE

There is growing evidence that various nanoproducts marketed for direct and indirect human consumption may be unsafe [7, 8]. These products could present unexpected human toxicity effects due to: (a) an increased reactivity compared to their "bulk" counterparts (discussed later); and (b) an increased potential to transverse biological barriers/membranes and reach/accumulate in tissues and cells due to their smaller size [9, 10]. In addition, there are concerns about the occupational and environmental risks associated with the manufacture and disposal of nanoproducts [11, 12].

Common sense warrants that some sort of guidance, oversight or regulation by the FDA is in order, but so far it has chosen to regulate nanomedicine and nanoproducts solely by regulations already on the books. This decision is

similar to that made a few decades ago with respect to biotechnology [13]. Obviously, regulating nanoproducts – whether they are a drug, device, biologic or combination of any of the above – is creating challenges for FDA regulators as they struggle to accumulate data and formulate testing criteria to ensure development of safe and efficacious nanoproducts [14].

To facilitate the regulation of nanoproducts, the FDA has formed an internal NanoTechnology Interest Group ("NTIG") composed of representatives from all its regulatory centers. In addition to the NTIG, the FDA has formed a Nanotechnology Task Force which, in 2007, issued an FDA Task Force Report [15]. However, as of March 2011, no clear guidelines or regulations have been proposed by this Task Force, whose mandate appears to be to simply encourage the continued development of innovative, safe and efficacious FDA-regulated products incorporating/involving nanotechnology. In fact, via this Report [15], the Task Force concluded that existing regulations are sufficiently comprehensive to ensure the safety of nanoproducts because these products would undergo pre-market testing and approval either as new drugs under the New Drug Application ("NDA") process, or in the case of medical devices, under the Class III Pre-market Approval ("PMA") process [15, 16]:

"FDA's authority over products subject to premarket authorization 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."

This conclusion by the FDA is based on the assumption that current regulatory requirements would detect any toxicity via the required clinical studies even if nanoproducts present size-related unique "nano" properties. Many experts have criticized this inaccurate extrapolation, especially since most FDA approved nanoproducts have obtained approval based in whole or in part on studies of non-nanoversions (i.e., based on their bulk counterparts). In other words, the approvals were granted based on safety data of equivalent non-nanoversions; the nanoproducts did not undergo the full PMA or NDA.

Clearly, the current scope of FDA's regulatory authority is limited. The guiding principle here is that the FDA regulates end-products, not any technology *per se*. The agency does not regulate nanomaterials or manufacturing processes, but the end-products. In other words, the FDA only regulates nanoproducts (i.e., products that incorporate nanotechnology) and not nanotechnology *per se* [17].

The Task Force Report does, however, allude to the need for regulatory oversight of some nanoproducts but offers no regulatory remedy or framework [15]:

"In some cases, the presence of nanoscale materials may change the regulatory status/regulatory pathway of products. The Task Force believes it is important that manufacturers and sponsors be aware of the issues raised by nanoscale materials and the possible change in the regulatory status/ pathway when products contain nanoscale materials."

Experts continue to criticize the FDA's rather lax and uncoordinated effort when it comes to regulating nanomedicine. All in all, US governmental regulatory agencies are in disarray over the regulation of nanomedicine. The situation is not much different at regulatory agencies in other countries either. As nanoproducts move out of the laboratory and into the clinic, US federal agencies like the FDA [12-14, 17-19] and the PTO [1, 2, 20] continue to struggle to encourage the development of nanomedicine while imposing some sort of order. Numerous challenges confront the FDA as important unanswered questions linger (Table **1**). All the while a steady stream of nanoproducts continue to reach the marketplace. Given this backdrop, investors have been cautious and confused as to what route, if any, the FDA will take in regulating nanomedicine. Additionally, FDA's delay in addressing nano-regulation could have a chilling effect on public confidence and commercialization efforts [19].

Table 1. Critical Questions for the FDA Regarding Nanomedicine

• Why has nanomedicine not gained prominence on the FDA's regulatory agenda?
• Are nanomaterials inherently toxic?
• Are bionanomaterials inherently safe?
• Is science and technology moving too fast for proper review to take place to formulate appropriate laws by federal agencies?
• Has the FDA kept pace with emerging advances in nanomedicine R&D?
• Who in addition to the FDA should be given the responsibility to regulate nanomedicine?
• Can regulations truly tame the vastness encompassed by nanomedicine?
• Can nanomedicine be regulated under existing regulations and authorities?
• Are new regulations needed for all nanomedical products or only a subset of products containing nanomaterials?
• Has the delayed and uncoordinated effort by the FDA regarding nanomedicine hurt venture and commercialization activities?
• What is the "official" position of the FDA regarding the definition of nanotechnology and nanomedicine?
• Should there be a greater coordinated effort on the part of federal agencies to review, amend or create nano-regulations where appropriate and warranted?

So far, the process of converting basic research in nanomedicine into commercially viable products has been difficult. Securing valid, defensible patent protection from the PTO [1, 2, 20] along with clear regulatory/safety guidelines from the FDA [12-14, 17-19] is critical to any commercialization effort. In spite of the above-mentioned bottlenecks, a large number of FDA-approved nanodrugs have been launched and many more are poised to receive regulatory approval [5, 6]. Furthermore, there are currently hundreds of unregulated and unlabeled nanoproducts on the market that incorporate engineered nanoparticles and nanomaterials. Tons of these continue to be produced and recycled annually.

4. FDA's REGULATION OF NANOPRODUCTS – CURRENT POSITION

As stated above, under the current regulatory regime, it continues to be the FDA's position that particle size is immaterial and that the safety of large particle versions (i.e., bulk counterparts) of an active ingredient can be used to predict the safety of the nanoscale versions of the same ingredient. Put differently, according to the FDA if large particle versions of a product are considered to be safe, then it can be presumed that the nanoversions are safe as well. Furthermore, nano-ingredients (e.g., nanoparticles) are presumed by the FDA to be "bioequivalent" to their bulk counterparts. Thus, currently, manufacturers of nanoproducts are neither required to obtain premarket approval from the FDA nor required to list nano-ingredients on product labels. According to the FDA, the existing health and safety tests that it uses to assess the safety of normal size materials (i.e., "traditional bulk counterparts") are generally considered adequate to assess the health effects of nanoproducts [14-16].

This is simply *not* true and various scientific studies contradict this hypothesis proposed by the FDA. These studies establish that the FDA's presumption of bioequivalence is scientifically flawed. In fact, not all nanoscale materials are created equal and their toxicities depend upon various factors like size, charge, shape, polarity, etc. in addition to the specific material. Although nanoparticle toxicity is complex, it is a well established scientific fact that nanoscale products and particles, such as nanomedicines, *often* have fundamentally different properties as compared to the same material in bulk form (i.e., their larger counterparts) [5, 6]. Put differently, "nanoscale" does not just mean that a product is smaller, it often means that the particle is fundamentally different. Surprisingly, given its current stance, the FDA has admitted this point [21]:*"such differences include altered magnetic properties, altered electrical or optical activity, increased structural integrity, and increased chemical and biological activity."*

Specifically, as the size of a particle decreases, a greater proportion of its atoms are located on the surface relative to its core, often rendering the particle more reactive over its conventional "bulk counterpart" (this could correspond to a reduction in required dose, thereby improving toxicity profiles and patient compliance). Not only can it be more reactive, its dissolution rate and saturation solubility may increase and, if the particle is a drug, this frequently correlates to improved *in vivo* performance. In addition, as the particle size decreases, its total surface area increases exponentially, again often making it more water soluble and imparting to it an enhanced bioavailability. Finally, nanoparticles have a greater potential for biological interaction and the intrinsic toxicity of any given mass of nanoparticles is greater than the same mass of larger particles. Basically, from the FDA's perspective, it is currently unresolved whether nanoproducts present unique risks (as compared to their bulk counterparts) that warrant regulatory oversight, and what specific toxicity testing is needed to demonstrate their safety. However, the FDA has made the following contradictory statement in the past regarding safety being an issue for nanoscale products [22]:

"Due to their small size and extremely high ratio of surface area to volume, nanotechnology materials often have chemical or physical properties that are different from those of their larger counterparts because of some of their special properties, they may pose different safety issues than their larger counterparts."

Given this, there are serious public health concerns and toxicological risks with FDA's dated position on bioequivalence. This position implies that the safety of bulk counterparts is predictive of the safety of the nanoscale versions and that these are *not* more hazardous than their bulk counterparts. This is scientifically incorrect. Moreover, this position of the FDA is rather surprising given that the US Environmental Protection Agency (EPA) and other scientific authorities [23, 24] concur that nanoparticles can have toxicological properties that often differ from their bulk counterparts. In addition, preexisting FDA regulations allow marketing without any form of risk/benefit analysis and, in some instances, lack of labeling requirements (for example, for certain cosmetics) are creating confusion and health concerns. For now, all nanotech products are being regulated by the FDA in the same manner as their bulk counterparts.

The FDA's Task Force Report of 2007 [15] and a Public Meeting held in 2008 [25] to *"gather information that will assist the Agency in implementing the recommendations of the Nanotechnology Task Force Report"* have not resulted in any nano-specific regulatory action. The FDA's Report concluded:

"The available information does not suggest that all materials with nanoscale dimensions will be hazardous. Furthermore, if all nanoscale materials are compared to all non-nanoscale materials, whether larger or smaller, it is not apparent that the nanoscale materials as a group would have more inherent hazard. However, consideration of the basic science of how materials interact with biological systems does indicate that a material's properties can change when size is increased or decreased into, or varied within, the nanoscale range."

So far the FDA has failed to follow through on its promise [11] that it would later "issue additional guidance to provide greater predictability of the pathways to market and for ensuring the protection of public health." In fact, the FDA has no intention to issue any guidance documents any time soon as was evident from the presentation of Dr. Nakissa Sadrieh from the FDA at the American Society for Nanomedicine conference in October 2010 [26]:

"There's no need right now to issue guidance documents specifically for nanomaterials The existing framework can accommodate the kind of nanoparticle therapeutics under development. We're viewing nanoparticle-containing drugs as just new drugs."

Many had hoped that this critical issue would be addressed by the Obama administration. In fact, his FDA commissioner, Dr. Margaret Hamburg, had stressed regulatory science as a discipline in a speech delivered in Philadelphia in the fall of 2009 [27]:

"Just as biomedical research has evolved in the past decades, regulatory science -- the science and tools we use to assess and evaluate product safety, efficacy, potency, quality and performance -- must also evolve. Our efforts will be seriously compromised if we don't significantly increase the sophistication of our regulatory science soon. A strong and robust field of regulatory science is essential to the work of FDA, and I believe it represents an important driver of our nation's health. The goal is to place the emerging, very promising areas in science and technology, such as genomics and personalized medicine, the development of stem cell therapies and therapies that harness the power of nanotechnology fully at the service of public health. We cannot afford to have a muscular investment in fundamental research and discovery with only a scrawny counterpart in regulatory capacity."

An FDA document dated October 2010 "outlines a broad vision for advancing regulatory science and unleashing its potential to improve public health" [28]:

"Although developments in science and technology hold great potential, the ways in which new therapies are developed and tested remain underdeveloped and underappreciated while the world of drug discovery and development has undergone revolutionary change-shifting from cellular to molecular and gene-based approaches-FDA's evaluation methods have remained largely unchanged over the last half-century. Without advances in regulatory science, promising medical therapies may be discarded during the developmental process simply because we lack the tools to recognize their potential, or outdated evaluation methods may unnecessarily delay their approval. Conversely, countless dollars and years may be wasted assessing a novel therapy that is later shown to be unsafe or ineffective. With creative advances in regulatory science, we can change the landscape entirely. We can modernize product development and develop new tools, standards, assays, disease models and science based pathways to improve the speed, efficiency, predictability, capacity and quality of the entire process, from development to evaluation to manufacturing."

While speeches and documents are helpful, it is action that will eventually carry the day. In the meantime, stakeholders, government, industry, academia and the public at large have offered various proposals to regulate nanomedicine. These include [29]: (a) creating new laws and regulations, (b) revising/modifying existing laws and regulations to cover nanomedicine, (c) designing new non-regulatory governance approaches such as voluntary industry standards, and (d) revising/modifying existing non-regulatory approaches.

5. NANOPRODUCTS AS COMBINATION PRODUCTS

According to the US Code of Federal Regulation, 21 CFR Section 310.3 (g): *"New drug substance means any substance that when used in the manufacture, processing, or packing of a drug, causes that drug to be a new drug, but does not include intermediates used in the synthesis of such substance."* Therefore, nanoformulations (e.g., "nanopharmaceuticals") of existing therapeutics are considered new formulations but not necessarily new molecular entities (NMEs).

As stated earlier, all nanopharmaceuticals currently on the market have been approved by the FDA according to preexisting laws and without any special testing (e.g., with respect to pharmacokinetic profiles). However, approval of new "nanoformulations" has challenged the FDA's regulatory framework. Products, including some that may contain nanomaterials or involve nanomedicine, submitted to the FDA for market approval are evaluated on a category-based system in one of the nine centers that focus on a specific area of regulation. For example, a drug, biologic, or device would be assigned for evaluation respectively to the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), or the Center for Devices and Radiological Health (CDRH). Obviously, categorizing nanoproducts according to this legal FDA classification is critical due to the widely divergent regulatory approval standards employed by the FDA [13, 29]. However, certain therapeutics are "combination products," which consist of two or more regulated components (drug, biologic, or device) that are physically, chemically or otherwise combined or mixed to produce a single entity [30]. Here, the FDA's category-based approval process has resulted in inconsistency [31].

It is difficult to predict how nanoproducts will be regulated. Size changes within the nanoscale and the potential unpredictability therefrom are likely to add complexity to the FDA review process. The traditional product-by-product regulatory model that the FDA currently employs may not be effective for all nanoproducts because it may be difficult to classify them into one of the available traditional classifications (i.e., drug, device, biological or combination product). However, in many cases, the FDA may view nanoproducts as technologically overlapping (miniaturization will blur distinctions between different categories) from a review perspective, and therefore, consider them as highly integrated nanomedical combination products. These complexities are likely to pose additional challenges and review issues for the FDA [32].

According to the FD&C Act of 1938, the scope of FDA's authority varies from category to category, with the strongest authority being over new drugs and devices and the weakest authority being over cosmetics and whole foods [14].

As a result of these variations in the extent of FDA's regulatory authority, its ability to effectively regulate nanomedicine will depend largely on the category under which the product seeking approval falls.

6. RECOMMENDATIONS TO THE FDA

There are numerous challenges confronting federal agencies like the FDA regarding reform of regulatory guidance

for nano-toxicological evaluation. Among these are limited availability of information correlating physicochemical properties of nanomaterials to risks, and a lack of validated preclinical screens and animal models for the assessment of nanomaterials [33]. The toxicity of many nanoscale materials will not be fully apparent until they are widely distributed and their exposure is felt by a diverse population. Therefore, post-market tracking or a surveillance system must be adopted (along with any proposed legislation) to assist in product recalls. Although toxicological testing for health risks of nanoparticles is not currently a complete science [34], it is crucial to monitor their unique properties (if any) that may lead to serious adverse effects and toxicity. Because it is well established that premarket testing of drugs will not detect all adverse reactions [35], it is essential that the long-term testing of nanoscale materials be in place for safety testing. In this regard, toxicity data specific to nanomaterials needs to be collected and an effective risk research strategy devised. However, none of this will be possible if sufficient funding is not allocated to federal agencies such as the FDA.

Although the FDA has downplayed nanoproduct safety issues [36] and the need for modification of the current regulatory regime, it is begining to recognize that there are knowledge gaps and a lack of scientific expertise in these areas [15]. The FDA is also encountering problems in applying its current regulations to all nanoproducts as well as placing these into its present classification scheme. These issues are compounded by the fact that the agency is confronted with serious deficiencies in general (Table **2**).

Table 2. Challenges Confronting the FDA

• Chronic under funding
• Complexity of new products and claims submitted
• Globalization of industries regulated
• Inability to attract and retain qualified experts
• Insufficient capacity in modeling risk assessment and analysis
• Inefficient regulatory structure
• Lack of expertise in some technology areas
• Growing reviewer case loads
• Public's generally negative perception
• Numerous high profile public relation disasters and recalls (e.g., medical device recalls linked to a lax approval process)

However, if the FDA plans properly now to mitigate foreseeable problems, it will help insure that scientific, ethical, commercialization and legal obstacles are overcome in future. In any case, regulating these products will require greater cooperation between drug companies, policymakers and the FDA. In light of these challenges, a multidisciplinary team of experienced regulators from the drug, biologic and device areas of the FDA (working with a scientific panel of experts) should be formed to assist across the board. Table **3** lists recommendations for the FDA to consider as it tackles the regulatory framework for nanomedicine.

7. FUTURE PROSPECTS AND CONCLUSIONS

While considering nanomedicine regulation a one-size-fits all approach is undesirable. Regulating nanomedicine, via preexisting regulations or by promulgation of new laws, must be based on sound scientific evidence. As nano begins to appear in a wide variety of products, its safety and effectiveness will warrant careful review. To date, no formal regulations for nanotechnology have been drafted. Whether the FDA eventually creates new regulations or establishes a new center to handle its regulation, at the moment it should at least look at nanoproducts on a case-by-case basis to determine if general trends or themes can be identified and whether new regulatory procedures are needed. The FDA should not attempt regulation of nanomedicine by applying existing statutes; incorporating them into the current regulatory scheme is a poor idea. It would be best if the FDA acknowledge that some nanomaterial-containing formulations (or "nanoformulations") are indeed NMEs. When warranted, nanoversions of active ingredients should be treated by the FDA as NMEs. This will ensure that drugs, biologicals, etc. that have been previously approved by the FDA, but later modified as nanoverisons will undergo a new and rigorous round of safety testing in order to obtain premarket approval.

Currently, there are few reliable means to identify marketed nano-containing products and consumers are unable to judge for themselves as to which ones may be toxic. Given this, the FDA should seriously contemplate nano-ingredient labeling in certain cases, balancing the public's desire for such labeling with the likelihood that the public may shy away from some beneficial products given the negative image of certain nanoscale ingredients. In any case, certain nanoproducts for human consumption, product labeling should be considered so that a consumer can feel safe while purchasing the product, knowing that toxicological studies have revealed no negative effects.

While leveraging its current regulatory authority, the FDA must recognize and publically admit that the existing regulatory framework is inadequate to address all of nanomedicine. Many consider that current laws for regulating nanomedical products are inadequate to regulate their manufacturing and distribution. Clearly, the FDA needs to "update" in some fashion its rigid regulatory regime to accommodate nanotech products intended for human consumption, especially those that have been clearly shown to possess novel nanoscale-related properties. Certain nanoproducts could be regulated under the preexisting rules of established regulatory authority for combination products while others will require new legislation to be passed (or current laws amended) to address certain unique size-related properties. Obviously, the ultimate goal here must be to protect health while supporting innovation. If the FDA does not adequately address nanomedicine safety issues, it could stifle research and commercialization efforts by blocking market access to innovative products. Eventually this could erode public confidence and acceptance of nanomedical products – all negatively impacting public health. Public perception is critical and the FDA should aggressively engage the public and keep it abreast of policy considerations and regulatory proposals. Public acceptance may be even more important than regulatory acceptance for certain sectors of nanomedicine because public acceptance often acts as a "hidden regulator" [37]. This is evident from certain biotechnology products like Calgene's Flavr Savr Tomato which was approved by the

Table 3. Regulating Nanomedicine - Recommendations for the FDA and Industry

❖ Identify unique safety issues associated with nanoproducts.
❖ Correlate physiochemical properties with *in vivo* biological behavior and therapeutic outcome.
❖ Develop research strategies that involve adsorption, distribution, metabolism and excretion (ADME) studies.
❖ Develop toxicology tests and conduct physicochemical characterization (PCC) studies for nanomaterials.
❖ Improve understanding of mass transport across membranes and body compartments.
❖ Determine accurate bio-distribution profiles following systemic administration via any route.
❖ Develop standards that correlate bio-distribution of various nanoparticles to safety/efficacy by using parameters like size, surface charge, stability, surface characteristics, solubility, crystallinity, density, etc.
❖ Create a databank relating the interactions between nanomaterials and biological systems.
❖ Require manufacturers to undertake post-market monitoring of their nanoproducts.
❖ Require "nanoversions" of pioneer therapeutics to undergo the full New Drug Application (NDA) process and not merely the current Abbreviated New Drug Application (ANDA) process.
❖ Abandon the flawed definition of "substantially equivalent" as it pertains to nanoversions of a pioneer therapeutic.
❖ Adapt existing methodologies as well as develop new paradigms for evaluating data pertaining to safety and efficacy of nanoproducts.
❖ Develop guidance documents/statutory requirements that provide specifics as to what kind of safety and efficacy data is needed.
❖ Evaluate evolving information from FDA submissions and amend guidance documents/statutory requirements accordingly.
❖ Aggressively seek and gather pre- and post-market data. Share such data in an internationally harmonized environment with strong public involvement.
❖ Develop consensus testing protocols to provide benchmarks for the creation of classes of nanomaterials.
❖ Undertake a comprehensive risk assessment of select "reference nanoproducts" within "reference classes" and obtain input from various stakeholders (organizations, professional societies, public) in this regard.
❖ Involve standard-setting organizations such as the International Standards Organization ("ISO") and ASTM International.
❖ Create uniform standards and/or working definitions of nanomaterials.
❖ Define nanotechnology and nanomedicine for the purpose of nanoproduct regulation. Discard the flawed NNI definition of nanotechnology.
❖ Explore international harmonization efforts and formal treaties that may impact nanotechnology.
❖ Assist in developing unique tools and techniques to characterize nanoscale materials.
❖ Develop imaging modalities for visualizing bio-distribution.
❖ Develop mathematical and computer models for risk/benefit analysis.
❖ Reevaluate the current FDA classification scheme. Develop a classification based on (a) function or (b) risk of potential harm.

FDA but later withdrawn from the US market under public pressure [38].

Under-regulation could result in inappropriate approvals, some of which could be harmful to public health, while over-regulation could limit innovation or promote "black market" research activities. Therefore, it is hoped that the FDA will strike an appropriate balance and, where appropriate, promulgate nanomedicine-specific regulations – undertakings that should expand the burgeoning field of nanomedicine. Regulatory oversight must evolve in concert with newer generations of nanomedical products. The need for this is sooner, rather than later.

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STATEMENT OF DISCLOSURE/CONFLICTS OF INTEREST

The author declares that he has no conflict of interest and has no affiliation or financial involvement with any organization or entity discussed in the manuscript. This includes employment, consultancies, honoraria, grants, stock ownership or options, expert testimony, patents (received or pending) or royalties. No writing assistance was utilized in the production of this manuscript and the author has received no payment for preparation of this manuscript.

The findings and conclusions in this paper reflect the current views of the author. They should not be attributed, in whole or in part, to the organizations with which he is affiliated, nor should they be considered as expressing an opinion with regard to the merits of any particular company or product discussed herein. Nothing contained herein is to be considered as the rendering of legal advice.

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