41 FDA and Nanotech: Baby Steps Lead to Regulatory Uncertainty

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41.1 Introduction

Emerging technologies bring with them concerns and uncertainties about how they should be regulated [1]. Clearly, when these technologies relate to human healthcare, regulation in some form is warranted. But what if the regulatory agencies lack the expertise or will to fully understand these technologies? This is one of the critical issues facing regulatory agencies globally. For over a decade, this challenge has continued to haunt the US Food and Drug Administration (FDA) as it struggles to handle the issue of nanogovernance. The "baby steps" this federal agency has taken over the past decade are generally inadequate and have contributed to regulatory uncertainty.

The FDA is a critically important regulatory agency of the US government. The breadth of products that it regulates represent about 20% of US consumer products worth billions of dollars. Employing various laws and regulatory mechanisms (and depending on the particular product class (Section 41.3)), the FDA conducts specific premarket and/or post-market oversight. The mission of the FDA is to ensure that drugs, medical devices, vaccines, veterinary products, and tobacco products reaching the consumer are both safe and effective. It is also responsible for the safety of foods (including dietary supplements and food additives), dyes and cosmetics. Obviously, many of these products utilize nanotechnologies or contain nanomaterials. Should these products be regulated? If so, how and to what degree? These are some of the questions the FDA is grappling with in relation to "nanogovernance" (Box 41.1).

Internationally, regulatory guidance for nanotechnology is generally lacking. In fact, regulatory agencies around the world continue to struggle in their efforts to develop new, meaningful regulatory definitions and balance them with policies that are already in place (Section 41.3). However, guidance is critically needed to provide clarity and legal certainty to manufacturers, policymakers, healthcare providers, and the consumer. 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 nanomedicines and nanoproducts solely via what is

Bio-Nanotechnology: A Revolution in Food, Biomedical and Health Sciences, First Edition. Edited by Debasis Bagchi, Manashi Bagchi, Hiroyoshi Moriyama, and Fereidoon Shahidi.

Box 41.1 Questions for the FDA to consider regarding nanogovernance as it fulfills its mission of safeguarding public health.

- When will nanotech take prominence on the FDA's regulatory agenda?
- It is likely that various marketed nanoproducts (e.g., sunscreens containing zinc oxide and titanium dioxide) warrant some sort of safety labeling to alert the unsuspecting consumer. Are most nanomaterials used in nanoproducts inherently toxic?
- Are nanoscience and nanotechnology moving too fast for meaningful FDA review to take place? Can regulations truly tame the vastness encompassed by "nano"?
- As a general rule, should industry input drive the formulation of appropriate rules and regulations by federal agencies?
- It is clear that the FDA is pushing industry to provide the agency with product-specific data for areas like cosmetics, where the FDA lacks statutory pre-market review authority. Are such voluntary industry measures enough?
- Is the "broadly inclusive approach" of considering whether FDA-regulated products containing nanomaterials or involving nanotechnolgy appropriate or sufficient?
- It does not appear that the present nanotech-specific review process/regulatory framework at the FDA is appropriately based on current science. Has the FDA kept pace with emerging advances in nanotech R&D with respect to predicting, defining, measuring and monitoring potential "nanotoxicities"?
- Should there be a wider coordinated effort on the part of federal agencies to review, amend, or create nanoregulations where appropriate and warranted? Who in addition to the FDA should be given the key responsibility to regulate nanomedical products for human use?
- Can nanotech, as applied to public health, be solely regulated under existing regulations and authorities?
- Are new regulations needed for all FDA-regulated products containing nanomaterials or involving nanotechnology or should they be limited to only a subset of products containing nanomaterials?
- It appears to this author that there is a general lack of strategic planning, effective collaboration and cohesion among federal agencies with respect to a nanogovernance framework. In fact, in 2012, the President's Council of Advisors on Science and Technology (PCAST) concluded that "individual agency contributions" to the NNI strategic plan "lack the cohesion of an overarching framework." Has this delayed and uncoordinated effort hurt venture and commercialization activities in the US?
- To date, the FDA has not officially embraced the narrow definition of nanotechnology proposed by the NNI (Section 41.2). What is the "official" position of the FDA regarding the definition of nanotechnology, nanoscale, nanomaterials, and nanomedicine?

already on the books. There are hundreds, if not thousands, of nanoproducts in the market for human use, but little is known of their health risks, safety data, or toxicity profiles. Even less is known of nanoproducts that are released into the environment that can potentially contact humans. Then, there are products such as cosmetics that are flooding the market but are not even subject to any pre-market review by the FDA. Under the current regulatory regime, it continues to be the FDA's position that nano-ingredients (e.g., nanoparticles) are presumed to be "bioequivalent" to their bulk counterparts (Section 41.3). Thus, manufacturers of nanoproducts are neither required to obtain premarket approval from the FDA nor required to list nano-ingredients on product labels at this time. These nanoproducts, whether they are a drug, device, biologic, or combination of any of these, are creating challenges for the FDA regulators as they struggle to accumulate data and formulate testing criteria to ensure the development of safe and efficacious nanoproducts.

In 2011, the FDA reopened a dialog on nanotech regulation when it published proposed guidelines on how the agency will identify whether nanomaterials have been used in FDA-regulated products. However, since these guidelines were published, there has been no concrete movement on this issue. Meanwhile, evidence continues to mount that many (if not most) nanoproducts inherently possess novel size-based properties and toxicity profiles. This scientific fact has been largely ignored by the FDA, and the agency continues to adopt a precautionary approach to the issue in hopes of countering negative publicity. The FDA has simply maintained the status quo with regard to its regulatory policies pertaining to nanotech. As a result, it has been criticized for having a one-size-fits-all approach to nanogovernance.

41.2 Defining nanotechnology in the context of medicine – Does size matter?

One of the major problems that regulators, policy-makers, researchers, and lawyers continue to face regarding nanotechnology is the confusion about its definition [2, 3]. Although the term is widely used, there is no internationally acceptable definition or nomenclature for it. In fact, nanotechnology is a misnomer, since it is not one technology but encompasses many technical and scientific fields like medicine, materials science, chemistry, physics, engineering, and biology. One can view it as an umbrella term used to define products, processes, and properties at the nano/microscale. In this chapter, conforming to convention, the applications and products of nanotechnology as they relate to medicine or pharma will be referred to as nanomedicines. Alternate analogous terminology used in the scientific literature or in patents includes nanobiotechnology and medical nanotechnology. Nanomedicines include drugs, therapeutics, vaccines, and biologicals that are intended to remedy a medical condition or disease.

Numerous definitions of nanotechnology have sprung up over the years. One often cited, yet clearly incorrect, definition is that proposed in the 1990s 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" [4]. Various US government agencies and offices, including the FDA and the US Patent and Trademark Office (PTO), continue to use this definition based on a sub-100 nm size. This overly rigid NNI definition presents numerous difficulties. For example, although the sub-100 nm size range may be important for nanomaterials where quantum effects are critical, this size limitation is not critical to a drug company from a formulation, delivery, or efficacy perspective because the desired or novel physiochemical properties (e.g., improved bioavailability, reduced toxicities, lower dose, or enhanced solubility) may be achieved in a size range greater than 100 nm. For example, the plasmon-resonance in gold nanoshells that imparts their unique property as anticancer thermal agents is due to the fact that their size is around 150 nm and not less than 100 nm. Similarly, the enhanced permeability and retention (EPR) effect, that makes nanoparticle anticancer drug delivery an attractive option, typically operates in a range of 100–400 nm. Liposomes in a size range of 150–200 nm have been shown to have a greater blood residence time than those with a size below 70 nm. Phagocytosis of nanoparticles via macrophage can also be accomplished in ranges beyond the arbitrary cut-off of 100 nm. Moreover, the NNI definition excludes numerous devices and materials of micrometer dimensions (and also of dimensions less than 1 nm), a scale that is included within the definition of nanotechnology by many nanoscientists.

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 range. For example, various peptides are similar in size to quantum dots and some viruses are in the size range of engineered-nanoparticles. Hence, most of molecular medicine and biotechnology can be classified as nanotechnology. Technically speaking, biologists were studying all these nanoscale biomolecules long before the term "nanotechnology" became fashionable. The tendency of numerous nanomaterials to aggregate may also blur the line as to what is truly nanoscale. What if the the size of these aggregated nanomaterials lies outside of the NNI definition but their characteristics and properties are identical to their nanoscale counterparts from which they arose?

Although the FDA is part of the NNI and participated in the development of the narrow definition of nanotechnology, it has not adopted the NNI's definition for its own regulatory purposes. Neither has it established a formal regulatory definition of nanomaterials, nanoscale, nanotechnology or nanomedicine. Instead, as of 2012, the agency is taking a broadly inclusive approach by determining whether FDA-regulated products contain nanomaterials or whether they involve nanotechnology (Section 41.3). We will have to wait and see if this uncertain proposal is an optimal one.

While the 1–100 nm real-estate is where much of nanomedicine operates, having an arbitrary cut-off of 100 nm excludes much of the field. In this context,

a size range is irrelevant and has no significance to nanomedicine. In light of this confusing background, the following practical definition of nanotechnology, unconstrained by an arbitrary size limitation, has been developed by the author [2, 3]:

> 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.

41.3 FDA confronts nanotech

Professor Gregory N. Mandel, a noted scholar on intellectual property law, has highlighted the inherent limitations of and opportunities for regulating nanotech [5]:

> Regulatory systems are designed to handle the technology in place when the regulatory system is adopted. New technologies place stress on and disrupt these systems. It is not surprising that an advance as transformative as nanotechnology raises substantial problems for the existing, mature (some would say "ossified") regulatory regime. This disruption, however, can provide an opportunity to illuminate problems with the existing system and to rethink how emergent technologies are governed. For the first time in history, there is the opportunity to develop a governance system simultaneously with an emerging technology.

There is growing evidence that various nanoproducts marketed for direct and indirect human consumption may be unsafe [6, 7]. These products could present unexpected human toxicity effects due to (i) increased reactivity compared with their "bulk" counterparts, and (ii) an increased potential to traverse biological barriers or membranes and reach or accumulate in tissues and cells owing to their smaller size [8, 9]. In addition, there are concerns about the occupational and environmental risks associated with the manufacture and disposal of nanoproducts [10, 11].

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 the development of safe and efficacious nanoproducts [12, 13]. To facilitate the regulation of nanoproducts, the FDA has formed a Nanotechnology Task Force, which issued an FDA Task Force Report in 2007 [14]. It concluded that existing regulations were sufficiently comprehensive to ensure the safety of nanoproducts because these products would undergo premarket 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 Premarket Approval ("PMA") process [14, 15]:

> 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 in 2007 was erroneously based on the assumption that regulatory requirements in place would detect any and all toxicity via the required clinical studies, even if nanoproducts presented size-related unique "nano" properties. Many experts criticized this inaccurate extrapolation, especially since most FDA-approved nanoproducts obtained approval based in-whole or in-part on studies of "non-nanoversions" (i.e., approval was based on their bulk counterparts). In other words, the approvals were granted based on safety data for equivalent non-nanoversions and the nanoproducts did not undergo the full PMA process or NDA process.

It has been the view of the FDA that existing health and safety tests that it uses to assess the safety of normal-size materials (i.e., non-nanoversions or bulk counterparts) are generally considered adequate to assess the health effects of nanoproducts [12–15]. However, studies have established that not all nanoscale materials are created equal. Some nanomaterials or products that incorporate nanotechnology may be toxic and their toxicities depend upon various factors that are material-specific (charge, polarity, chemical residues) and/or geometry-specific (size, shape, nanoscale features). Although nanoparticle toxicity

is complex, it is well-established that nanoscale products and particles *often* have fundamentally different properties as compared to their larger bulk counterparts [16, 17]. Put differently, "nanoscale" does not just mean that a product is smaller; it often means that it is fundamentally different, and one cannot presume that it will be safe or "bioequivalent" to its larger bulk counterpart.

Let us elaborate this point scientifically. It is a fact that materials with a large surface-area-to-volume ratio are more reactive than "monolithic" materials. Given this, as the size of a drug particle decreases (e.g., from "micro" to "nano"), a greater proportion of the atoms of the smaller drug particle are located on the surface relative to its core, often rendering the smaller drug particle more reactive than its conventional "bulk" or monolithic counterpart. In a clinical-setting, this could correspond to a reduction in required dose, thereby improving toxicity profiles and patient compliance. Not only can this render the drug particle more reactive, but its dissolution rate, water solubility and saturation solubility may also increase. This frequently correlates with enhanced *in vivo* bioperformance. Furthermore, as we granulate a drug particle into smaller particles, the total surface area of the smaller particles becomes much greater, again, often making it more water-soluble and increasing its bioavailability. Finally, nanoparticles have a greater potential for interaction with biological tissues, and the intrinsic toxicity of any given mass of nanoparticles is greater than that of the same mass of larger particles.

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 [18]. Given this, there are serious public health concerns and toxicological risks with the FDA's position. The FDA Task Force Report of 2007 does, however, allude to the need for more oversight of some nanoproducts, but it offers no regulatory remedy or framework [14]:

> 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.

In 2011, the FDA reopened the dialog on nanotech regulation by publishing proposed guidelines on how the agency will identify whether nanomaterials have been used in FDA-regulated products. The guidelines were published in the Federal Register in 2011 [19]. Their purpose was to help industry and developers identify when to consider the possible regulatory status, safety, effectiveness, or health issues that could arise from the use of nanomaterials or nanotech in FDA-regulated products. Specifically, this document asks industry to consider (i) whether an engineered material or end-product has at least one dimension in the nanoscale range (about 1–100 nm), or (ii) whether an engineered material or end-product exhibits properties or phenomena (including physical/chemical properties or biological effects) that are attributable to its dimensions, even outside of the nanoscale range (up to 1 μm). Also in 2011, the FDA commissioner, Dr. Margaret Hamburg, emphasized science-based nanoregulation [21]:

> Our goal is to regulate these products using the best possible science . . . Understanding nanotechnology remains a top priority within the agency's regulatory science initiative and, in doing so, we will be prepared to usher science, public health, and FDA into a new, more innovative era.

Recently in 2012, the FDA commissioner summarized in general terms a "broadly inclusive initial approach" with respect to nanogovernance in a two-page policy paper published in *Science* [21]:

> [The] FDA does not categorically judge all products containing nanomaterials or otherwise involving the application of nanotechnology as intrinsically benign or harmful. As with other emerging technologies, advances in both basic and applied nanotechnology science may be unpredictable, rapid, and unevenly distributed across product applications and risk management tools. Therefore, the optimal regulatory approach is *iterative, adaptive, and flexible* . . . It is iterative by developing and delivering incremental components of a regulatory system, such

> as guidances specific to product areas, each as warranted and when ready. It is adaptive by providing a mechanism, within statutory constraints, to change the rules, presumptions, or pathways for these regulatory components, in light of new information gained from research or from experience in regulating earlier products. And it is flexible by using all available means, ranging from workshops to consultations to guidances to rules, in order to match the burden of regulation to its need. (citations removed, emphasis added)

In spite of these "baby steps" by the FDA regarding nanoregulation, most experts continue to criticize its rather lax and uncoordinated effort. As of November 2012, no clear guidelines or regulations have been proposed by the FDA. The "broadly inclusive initial approach" needs to be expanded into real-world regulatory guidelines that can be depended upon by industry and consumers alike.

All in all, US regulatory agencies are in disarray over nanotech (Box 41.1). The situation is not much different at regulatory agencies in other countries either [22–27]. As numerous nanoproducts move out of the laboratory and into the clinic, US federal agencies such as the FDA [11–14, 18–19, 27, 28] and the PTO [1, 2, 20] continue to struggle to encourage the development of nanoproducts while imposing some sort of order. Numerous challenges confront the FDA as important unanswered questions linger (Box 41.1). All the while, a steady stream of nanoproducts, particularly nanomedicines (Table 41.1), continue to be approved by the FDA under preexisting regulations. A large number of these approved nanomedicines have already reached the marketplace.

Given this backdrop, investors have been cautious and confused as to what route, if any, the FDA will take in regulating nanotechnologies, and to what degree. Additionally, the FDA's delay in addressing nano-regulation could have a chilling effect on public confidence and commercialization efforts [13, 17, 27]. Meanwhile, various stakeholders – government, industry, academia, and the public at large – have offered various proposals to regulate nanomedicine. These include [29]:

- creating new laws and regulations;
- revising/modifying existing laws and regulations to cover nanomedicine;
- designing new nonregulatory governance approaches such as voluntary industry standards;
- revising/modifying existing nonregulatory approaches.

41.4 Nanoproducts as combination products?

Products submitted to the FDA for market approval, including some that may contain nanomaterials or involve nanomedicine, are evaluated according to 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 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), respectively. Obviously, categorizing nanoproducts according to this legal FDA classification is critical owing to the widely divergent regulatory approval standards employed by the FDA [29, 30]. According to the Federal Food, Drug and Cosmetic Act of 1938, the scope of the 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 [12]. As a result of these variations, the FDA's ability to regulate nanoproducts effectively will depend largely on the category into which the product seeking approval falls.

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 [31, 32]. In such cases, the FDA determines the "primary mode of action (PMOA)" of the product, which is "the single mode of action of a combination product that provides the most important therapeutic action." This process is frequently imprecise as it is not always possible to clearly elucidate a combination product's PMOA. This is because, at the time of an investigational application, it is not clear which mode of action provides the most important therapeutic action or because the product has two different equally critical modes of action. Determining which framework will apply to any combination product is the task of the Office of

Table 41.1 Selected FDA-approved nanomedicines.*

Drug Product/ Tradename in US	Active Agent(s) and/or Nanotherapeutic Class	Delivery Route	Manufacturer/ Alliance/Marketer	Indication(s)	FDA Approval Date
Doxil	Pegylated doxorubicin (Adriamycin) liposomes (80–90 nm)	IV	Johnson & Johnson	Metastatic ovarian or breast cancer; AIDS-related Kaposi's sarcoma	November 1995
Abraxane	Paclitaxel (Taxol) bound albumin nanoparticles (~120 nm)	IV	Abraxis BioScience AstraZeneca	Various cancers	January 2005
AmBisome	Amphotericin B liposomes (~45–80 nm)	IV	Astellas Pharma	Fungal infections	August 1997
Rapamune	Nanocrystalline sirolimus	Oral solution Oral tablet	Elan Corp. Pfizer	Immunosuppressant	September 1999
TriCor	Nanocrystal fenofibrate	Oral tablet	Elan Corp. Abbot Labs	Primary hypercholesteremia, mixed lipidemia, hypertriglyceridemia	November 2004
Emend	Nanocrystal aprepitant	Oral capsule IV	Elan Corp. Merck	Nausea in chemotherapy patients	March 2003
Diprivan	Propofol liposomes	IV	Astra Zeneca Pharmaceuticals	Anesthetic	October 1989
Renagel	Crosslinked poly(allylamine) resin (sevelamer hydrochloride)	Oral tablet	Genzyme Corp.	Control of serum phosphorus in patients with chronic kidney disease on dialysis	October 1998
Triglide	Nanocrystalline fenofibrate	Oral tablets	SkyePharma First Horizon	Lipid disorders; reduces elevated plasma concentrations of triglycerides, LDL, and total cholesterol and raises abnormally low levels of HDL	May 2005
DepoCyt	Sustained release cytarabine liposomes	IV	SkyePharma Enzon	Lymphomatous meningitis	April 1999
Daunoxome	Encapsulated daunorubicin citrate liposomes	IV	Galen Ltd.	Kaposi's sarcoma	April 1996
Estrasorb	Estradiol hemihydrate micellar nanoparticles (emulsion)	Transdermal	Novavax Allergan	Reduction of vasomotor symptoms, such as hot flushes and night sweats in menopausal women	October 2003
Macugen	Pegylated anti-VEGF aptamer	Intravitreal	OSI Pharmaceuticals Nektar Therapeutics	Neovascular age-related macular degeneration	December 2004

Table 41.1 (*Continued*)

Drug Product/ Tradename in US	Active Agent(s) and/or Nanotherapeutic Class	Delivery Route	Manufacturer/ Alliance/Marketer	Indication(s)	FDA Approval Date
DepoDur	Morphine sulfate extended-release liposomes	IV, epidural at lumbar level	Pacira EKR Therapeutics	pain following major surgery	May 2004
Megace	Megestrol acetate	Oral suspension	Elan Corp Par Pharma	Anorexia, cachexia	September 1993
Marqibo	Vincristine sulfate encapsulated-liposomes	IV	Talon	Ph(-) acute lymphoblastic leukemia	August 2012
Visudyne	Verteporfin	IV	QLT Novartis	Age-related macular degeneration	April 2000
Ontak	Denileukin diflitox nanoparticles	IV	Seragen	Cutaneous T-cell lymphoma	February 1999
Abelcet	Amphotericin B phospholipid complex	IV	Sigma-Tau Pharma	Invasive fungal infections in patients who are refractory to or intolerant of conventional Amphotericin B therapy	November 1995
Adagen	Pegylated adenosine deaminase	IV	Enzon	Enzyme replacement therapy for patients with severe combined immunodeficiency disease; adenosine deaminase deficiency	March 1990
Pegasys	Peginterferon alfa-2a	SQ	Nektar Hoffmann-La Roche	Chronic hepatitis C virus infection	October 2002
Somavert	Pegvisomant (PEG-hGH)	SQ	Nektar Pfizer	Acromegaly	March 2003
Neulasta	PEG-G-CSF or pegfilgrastim (covalent conjugate of recombinant methionyl human G-CSF (Filgrastim) and monomethoxypolyethylene glycol)	SQ	Amgen	Febrile neutropenia	January 2002
Copaxone	Glatiramer acetate (copolymer of L-glutamic acid, L-alanine, L-tyrosine, and L-lysine)	SQ	Teva Pharma	Relapsing-remitting multiple sclerosis	December 1996

(*Continued*)

Table 41.1 (*Continued*)

Drug Product/ Tradename in US	Active Agent(s) and/or Nanotherapeutic Class	Delivery Route	Manufacturer/ Alliance/Marketer	Indication(s)	FDA Approval Date
Amphotec	Colloidal suspension of lipid-based Amphotericin B (~115 nm)	SQ	Sequus	Invasive aspergillosis in patients who are refractory to or intolerant of conventional Amphotericin B	November 1996
PEG-Intron	Peginterferon alfa-2b	SQ	Nektar	Chronic hepatitis C	January 2001
Oncaspar	Pegasparginase	SQ	Sigma-Tau Pharma	Lymphoblastic leukemia	February 1994
Elestrin	Estradiol gel (0.06%) incorporating calcium phosphate nanoparticles	Transdermal	BioSanté	Moderate to severe hot flushes in menopausal women	December 2006

*To highlight the nanomedicine landscape, this table only lists FDA-approved nanomedicines. Nanomaterials are not included here unless they serve as nanomedicines *per se*. FDA-approved imaging or diagnostic agents are omitted from the table. The table also excludes nanomedicines that are (i) in various phases of clinical trials; or (ii) in pre-clinical research, including basic research, bench-science, early animal testing, etc.; or (iii) futuristic nanomedicines that offer revolutionary benefits that are impossible to confirm. A vast majority of these excluded nanomedicines will never be approved by the FDA, let alone commercialized. Note that therapeutic approval by FDA does not necessarily indicate that the nanomedicine is commercially available to consumers. Various factors, in addition to FDA approval, impact the commercialization of nanomedicines. Abbreviations used in table: AIDS, acquired immunodeficiency syndrome; HDL, high-density lipoprotein; IV, intravenous; LDL, low-density lipoprotein; PEG, polyethylene glycol; PEG-G-CSF, pegylated granulocyte colony-stimulating factor; PEG-hGH, pegylated human growth hormone; SQ, subcutaneous injection; VEGF, vascular endothelial growth factor.

Combination Products (OCP). Obviously, the OCP will be the first office within the FDA to review many nanoproducts. The OCP makes its assignments on a case-by-case basis depending on the PMOA. But this process is again, frequently imprecise as it is not always possible to clearly elucidate a combination product's PMOA, often because at the time of an investigational application it is not clear which mode of action provides the most important therapeutic action, or the product has two different equally critical modes of action. It is very possible that nanoproducts will blur the distinction between mechanical and chemical action at the nanoscale or that they may be both therapeutic and diagnostic in operation. In fact, this spanning of regulatory boundaries between the various categories has often resulted in inconsistency [33].

41.5 Recommendations, conclusions, and future prospects

Advances in medical or health-related nanotech and the FDA system for governing it are inevitably intertwined. However, the "baby steps" the agency has undertaken over the past decade have led to regulatory uncertainty. There are some excellent recent reports highlighting this issue [34–39].

It appears that the Environmental Protection Agency (EPA) is leading the way in nanomaterial regulation [27, 39]. However, numerous challenges confront federal agencies such as the FDA regarding reform of regulatory guidance for nanotoxicological evaluation. Among these are the limited availability of information correlating the physicochemical properties of nanomaterials with risks, and a lack of validated preclinical screens

and animal models for the assessment of nanomaterials [40]. 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, postmarket 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 [41], 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 [42], it is essential that long-term testing of nanoscale materials be in place to allow 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 in the past the FDA has downplayed nanoproduct safety issues [43] and the need for modification of the current regulatory regime, it is beginning to recognize that there are knowledge gaps and a lack of scientific expertise in these areas [13, 14, 21, 27, 28]. The FDA is also encountering problems in applying its current regulations to all nanoproducts, as well as in placing these products into its present classification scheme. However, if the FDA plans properly now to mitigate foreseeable problems in the future, it will go a long way toward overcoming scientific, ethical, commercialization, and legal obstacles. 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. Box 41.2 lists recommendations for the FDA to consider as it tackles the regulatory framework for nanomedicine.

Because the FDA regulates only the claims made by the manufacturer ("product sponsor"), if no nanoclaims regarding the manufacture or performance of the product are specified, the agency may be left in the dark during the product review and approval process. Related to this and as discussed previously is the critical issue of nomenclature and the definition of nanotech (Section 41.2).

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 [2, 3, 44] along with clear regulatory/safety guidelines from the FDA [5, 11–13, 18, 21, 27, 28, 34–38] is critical to any commercialization effort. In spite of the above-mentioned bottlenecks, a large number of FDA-approved nanomedicines (Table 41.1) have been launched, and many more are poised to receive regulatory approval [16, 17]. 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. It would be best if the FDA were to acknowledge that some nanomaterial-containing formulations (or "nanoformulations") are indeed new chemical entities (NCEs). When warranted, nanoversions of active ingredients should be treated by the FDA as NCEs. This will ensure that drugs, biologics, etc. that have been previously approved by the FDA but later modified as nanoversions will undergo a new and rigorous round of safety testing in order to obtain premarket approval.

It is difficult to foresee how nanoproducts will be regulated. Size changes within the nanoscale range and the potential unpredictability arising 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 put them into one of the available traditional classifications (i.e., drug, device, biologic, 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 [13, 27, 28, 32, 33].

Currently, there are few reliable means to identify marketed "nano-containing" products, and consumers are unable to judge for themselves which ones may be toxic. Given this, the FDA should seriously contemplate nano-ingredient

Box 41.2 Recommendations for the FDA regarding nanomedicine regulation.

- Safety and Risk
  - On a case-by-case basis and in conjunction with industry, identify unique safety issues associated with nanomedical products.
  - Actively seek product safety data from industry where FDA statutory authority exists for pre-market review.
  - Incentivise and encourage voluntary industry submissions of safety data on nanomaterials or products that incorporate nanotechnology prior to market launch, especially in cases (e.g., cosmetics) where the FDA lacks statutory authority for pre-market review.
  - Correlate physiochemical properties with *in vivo* biological behavior and therapeutic outcome.
  - Develop a research strategy that involves adsorption, distribution, metabolism, and excretion (ADME) studies.
  - Develop toxicology tests and conduct physicochemical characterization (PCC) studies for nanomaterials.
  - Understand mass transport across membranes and body compartments.
  - Determine accurate biodistribution profiles following systemic administration via a specific route.
  - Develop standards that correlate the biodistribution of various nanomaterials with safety/efficacy by using parameters such as size, surface charge, stability, surface characteristics, solubility, crystallinity, and density.
  - With industry input, create a databank relating to the interactions between nanomaterials and biological systems.
- Data
  - Adapt existing methodologies, as well as develop new paradigms for evaluating data pertaining to safety and efficacy of nanomedical products.
  - Develop guidance that provides specifics as to what kind of data is needed.
  - Share data in an internationally harmonized environment.
- Standardization
  - Create reference classes for nanomaterials that are synthesized and characterized.
  - Develop consensus testing protocols to provide benchmarks for the creation of classes of nanoscale materials.
  - Create uniform standards for and/or working definitions of nanomaterials.
  - Refine the current definitions of nanomaterial, nanotechnology, nanoscale and nanomedicine for the purpose of regulation.
  - Explore international harmonization efforts and formal treaties.
  - Involve standard-setting organizations such as the International Organization for Standardization (ISO) and ASTM International.
  - Consult and collaborate with other federal agencies in a more effective manner.
- Tools
  - Assist in developing unique tools and techniques to characterize nanoscale materials.
  - Develop imaging modalities for visualizing biodistribution.
  - Develop mathematical and computer models for risk/benefit analysis.
  - Monitor quality, safety, product liability, and effectiveness.
- Classification Scheme
  - Reevaluate the current FDA classification scheme.
  - Develop a classification based on (a) function or (b) risk of potential harm.

labeling on a case-by-case basis, 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.

For now, nanoproducts submitted for FDA review will continue to be subjected to an uncertain regulatory pathway. This could negatively impact venture funding, stifle research and development in nanomedicine, and erode public acceptance of nanoproducts. The end-result of this could be a delay in 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 unwise. Regulation of nanotech must balance innovation and R&D with the principle of ensuring maximum public health protection

and safety. Regulatory oversight must evolve in concert with newer generations of nanomedical products.

It is hoped that the "baby steps" that the FDA has taken in the past decade regarding nanogovernance will translate into more meaningful, flexible and science-based guidance in the near future. In the end, the long-term prognosis of nanomedicine will hinge on effective, valid nanogovernance requiring the full commitment of various regulatory agencies such as the FDA, as well as the regulated community such as the manufacturing sector.

41.6 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 chapter. 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 in this chapter is to be construed as the rendering of legal advice. Address for Correspondence: Bawa Biotech LLC, 21005 Starflower Way, Ashburn, Virginia 20147, USA; Office Tel: 703.723.0034; Cell: 703.582.1745; Fax: 571.223.1844; www.bawabiotech.com; bawa@bawabiotech.com

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