

## HEALTH LAW

### Regulating Nanomedicine at the Food and Drug Administration

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#### Abstract

The US Food and Drug Administration (FDA) oversees safety and efficacy of a broad spectrum of medical products (ie, drugs, biologics, and devices) under the auspices of federal legislation and agency regulations and policy. Complex and emerging nanoscale products challenge this regulatory framework and illuminate its shortcomings for combination products that integrate multiple mechanisms of therapeutic action. This article surveys current FDA regulatory structures and nanotechnology-specific guidance, discusses relevant nanomedicine products, and identifies regulatory challenges.

#### Regulatory Demands of Nanotechnology

Nanotechnology is research and technology development on the nanoscale (traditionally 100 nanometers (nm) or less, or one billionth of a meter) at which particles have novel properties and functions because of their size.<sup>1</sup> At this size, materials exhibit quantum effects, impacting fluorescence, conductivity, magnetic permeability, melting point, and reactivity.<sup>1</sup> The ability to control atoms and molecules at the nanoscale has significantly advanced medical science and catalyzed the field of nanomedicine, defined by the National Institutes of Health as a “highly specific medical intervention at the molecular scale for curing disease or repairing damaged tissues, such as bone, muscle, or nerve.”<sup>2</sup> Nanomedicine also includes nanotechnology applications for “diagnosis, monitoring, and control of biological systems.”<sup>3</sup>

Cutting-edge nanomedicine applications often integrate chemical, mechanical, and biological properties to enable and enhance detection, diagnostic capabilities, and therapeutic modes of action. In the near future, it will be possible for a single nanomedicine product, once deployed in a patient’s body, to be programmed to target specific organs and tissues, create images, measure vital signs, diagnose in real time, and subsequently provide tailored therapeutics.

The US Food and Drug Administration (FDA), as a gatekeeper of health care products, plays a vital role in assessing nanomedicine products. However, its decades-old classifications to distinguish products for purposes of review and approval prove challenging for nanomedicine products due to their novel characteristics and cross-

category features. In addition, nanoscale particles and materials have different risk profiles given their decreased size, increased biological activity, and unique properties. These risk profiles, which are largely unknown, create novel [legal and ethical challenges](#) for clinical trials, patient use, and public health.

### Traditional Regulatory Approaches

The FDA is tasked with protecting public health and promoting innovations and striking a balance between the two when evaluating products generated by science and emerging technologies. The FDA regulates products under 2 primary statutes: the Food, Drug, and Cosmetic Act (FDCA), which addresses chemically synthesized drugs as well as devices; and the Public Health Service Act (PHSA), which addresses biologically derived therapeutic products.<sup>4</sup> The FDA must characterize products under definitions provided by Congress in both the FDCA and the PHSA. Fundamentally, these definitions and supplemental FDA policies distinguish among 3 product areas based on whether the product has a chemical mode of action (drug), a mechanical mode of action (device), or a biological source. The Table provides statutory definitions for each of the 3 product domains. Nanotechnology products span all 3 regulated domains, and many products' mechanisms of action span 2 or more of these domains.

**Table.** Food and Drug Administration Product Definition Overview

Product Domain	Definition
Drug	Generally, a drug is any chemically synthesized product intended for use in the "diagnosis, cure, mitigation, treatment, or prevention of disease"; products "intended to affect the structure or any function of the body"; and components. <sup>a</sup> New drugs are those "not generally recognized" by qualified experts "as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof" <sup>b</sup> and must undergo clinical trials as a requirement for approval.
Biologic	A biological product is a product that is "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein ... or analogous product ... applicable to the prevention, treatment, or cure of a disease or condition of human beings." <sup>c</sup>
Device	A medical device is a product that is not a drug, meaning that it does not act through chemical action and is not dependent upon metabolism to achieve its primary intended purpose. Medical devices are "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease ... or ... intended to affect the structure or any function of the body." <sup>d</sup>
<sup>a</sup> Quotation from United States Code. <sup>5</sup> <sup>b</sup> Quotation from United States Code. <sup>6</sup> <sup>c</sup> Quotation from United States Code. <sup>7</sup> <sup>d</sup> Quotation from United States Code. <sup>8</sup>	

The approval process for both new drugs and biological products is subject to 3 phases of clinical trials. Each phase includes laboratory and manufacturing controls; protections for human subjects; review and approval procedures; and requirements for labeling, adverse event disclosure, reporting and tracking, and [postmarket surveillance](#), including ongoing assessment to ensure safety and efficacy using a risk-benefit approach tailored to a product's intended use.<sup>4,9</sup> Products developed to address an unmet health need or to treat a serious or life-threatening disease may qualify for abbreviated review and approval under breakthrough therapy status and other accelerated mechanisms.<sup>10</sup> There are also abbreviated routes to market for drugs and biologics through the generic<sup>11</sup> and biosimilar<sup>12</sup> pathways based on comparisons to reference innovator products already approved by the FDA. These routes to market do not require full-scale clinical trials but only a showing of bioequivalence (for generics) and biosimilarity (for biosimilars).

Based on level of risk, devices enter the market in 1 of 2 ways: a premarket approval (PMA) process or a premarket notification (PMN) process. Like the new drug and biologic approval process, the PMA process for [high-risk devices](#) deemed potentially life saving and life supporting involves clinical trials tailored to a device's perceived risk classification and may involve specific safeguards to protect research subjects and demonstrate safety and efficacy.<sup>13</sup> The PMN process, otherwise known as a "clearance" process for lower-risk devices, requires an applicant to demonstrate that a device is substantially equivalent to a device already on the market with the same or similar technological characteristics and intended use.<sup>14</sup> Laboratory and manufacturing controls and requirements for labeling, tracking and adverse event reporting, and postmarket surveillance and ongoing assessment also apply to devices. The Government Accountability Office estimated that between 2003 and 2007, almost one-third of medical devices entered the market through the PMN clearance process, 67% were exempt from premarket review, and 1% were subject to the PMA process.<sup>14</sup> Currently, the FDA requires first-in-kind devices, which hold promise to play a diagnostic or imaging role via a drug or biologic, to undergo market entry through the PMA process.<sup>15</sup>

### **Combination Product Regulatory Approach**

The FDA's Office of Combination Products (OCP) assesses emerging technologies at the interface of the 3 product domains.<sup>16</sup> A combination product is one containing a drug and a device; a drug and a biologic; a device and a biologic; or all 3 types of products. A combination product is categorized and reviewed according to its primary mode of action, which is the mode of action by which the product achieves its primary therapeutic effect—whether chemical, biological, or mechanical.<sup>17</sup> Once the primary mode of action is determined, the FDA evaluates the product according to applicable statutory and regulatory requirements. For example, if the product's primary mode of action is chemical, the FDA will apply drug requirements. The FDA can also adjust or combine regulatory requirements to address novel issues arising with combination products.

The combination product process has been subject to criticism for its shortcomings in classifying products that integrate chemical, biological, and mechanical elements; for a general lack of transparency; and for inconsistency in applying and making decisions about the requirements.<sup>18</sup> Notably, the 21st Century Cures Act, enacted in December 2016, contains provisions for transparency and consistency in FDA procedures for classifying and evaluating combination products and for the conduct of collaborative product assessment.<sup>19</sup> While not changing the FDCA in substance, the act served to nudge the agency on these issues. The FDA routinely classifies nanotechnology-derived products as combination products, assigning a primary regulatory route (ie, drug, device, or biologic) and supplementing with ad hoc requirements as necessary to assure safety and efficacy.

### **Nanomedicine Landscape**

Nanoscale research reveals that, as particle size decreases, surface area increases along with the biological activity of particles.<sup>20</sup> The unique physical properties of nanoparticles hold promise for surmounting some of the most difficult barriers to therapeutic and diagnostic efficacy. Nanoscale properties involving optical absorbance, fluorescence, and electrical and magnetic conductivity enable targeted localization, visualization, and treatment of cancerous tumors, for example.<sup>1</sup> Nanoscale properties involving pharmacokinetics, biodistribution, and cell permeability assist in precision drug formulation and in getting the correct drug load to an exact location faster.<sup>1,21</sup> Nanoparticles' ability to interact directly with biological systems within the body increases the efficacy of myriad health applications.<sup>18</sup>

Review and approval of drugs, biologics, and devices in the nanorealm is ongoing, with many nanoproducts designated as combination products. For example, the FDA has approved nanoformulations of paclitaxel and doxorubicin as new cancer drugs, a nanoformulation of sirolimus (an immunosuppressant), and a nanoformulation of estradiol topical emulsion.<sup>22</sup> The first approved nanodrug, the liposomal formulation of doxorubicin, consists of a nanoscale closed vesicle for drug delivery.<sup>23</sup> These vesicles can also be composed of polymers, creating polymersomes that create a steric barrier and confer stealth properties to the drug carrier.<sup>23</sup> Device nanoproducts that have entered the market through the PMN clearance process include a tissue reinforcement and hernia repair device (constructed with a nanoscale covalent-bonded titanium coating, imparting increased flexibility), a bone graft substitute (using betatricalcium phosphate nanoparticles that aggregate into 3-dimensional scaffolds with increased surface area for enhanced resorption), and a tissue-sealing and hemostasis system for laparoscopic and open surgery (using enhanced fluorescence properties of nanoparticles).<sup>24</sup> A nanoformulation of the hepatitis A vaccine was also approved as a biologic.<sup>22</sup>

The FDA has published several nanotechnology-specific guidance documents instructing industry on agency policy.<sup>25,26</sup> Topics include whether an FDA-regulated product involves

an application of nanotechnology, drug and biological products that contain nanomaterials, and safety of nanomaterials in cosmetics and food products.<sup>26</sup> Acknowledging that nanotechnology “poses questions regarding the adequacy and application of our regulatory authorities,” the FDA’s Nanotechnology Task Force, assembled in August 2006 at the direction of the FDA commissioner, was asked to determine appropriate regulatory approaches and to identify and recommend mechanisms to address knowledge gaps.<sup>27</sup> In July 2007, the task force concluded that nanoscale products did not warrant novel regulatory frameworks and thus were subject to traditional legal frameworks, including the combination product mechanism.<sup>27</sup> Nanotechnology combination products were named by the task force as necessitating further exploration—specifically, whether employing the combination product approach to determine the regulatory pathway to market as a drug, medical device, or biological product was appropriate. The report states:

The very nature of nanoscale materials—their dynamic quality as the size of nanoscale features change, for example, and their potential for diverse applications—could permit development of highly integrated combinations of drugs, biological products, and/or devices, having multiple types of uses, such as combined diagnostic and therapeutic intended uses. As a consequence, the adequacy of the current paradigm for selecting regulatory pathways for ‘combination products’ should be assessed to ensure predictable determinations of the most appropriate pathway for such highly integrated combination products.<sup>27</sup>

Subsequently, the FDA published 2 guidance documents on nanotechnology in the context of medical products. One outlines considerations for industry when determining whether a product involves an application of nanotechnology, which indicates the need for sponsors to communicate nanotechnology status to the FDA as part of the product review process.<sup>28</sup> The other discusses a nanotechnology risk-based framework, specific requirements for conduct of nonclinical and clinical trials, manufacturing quality and controls, and special environmental considerations for drug and biologic products containing nanomaterials.<sup>29</sup>

### **Future Challenges**

The FDA continues to use a case-by-case approach for evaluating nanotechnology products, applying the combination product framework to determine the type of product and resulting regulatory requirements. There are persistent pleas from medical, scientific, and legal experts such as the National Academy of Medicine (formerly the Institute of Medicine) to fix inconsistent and inadequate drug, biologic, and device classifications as well as the combination product framework itself.<sup>14</sup> Concomitant with the debate about whether existing regulatory structures and processes are adequate, broader questions have emerged regarding inherent risks of nanotechnology and products containing nanoparticles. Areas of concern include nanoparticle toxicity and human health impacts of exposure, especially effects of various exposure routes and routes of administration,<sup>30</sup> unintended effects of nanoparticles’ ability to cross the blood-brain barrier, and long-term effects of nanoparticles.<sup>31</sup>

The FDA faces numerous challenges as nanomedicine progresses, and 3 core challenges stand out. The first is the adequacy of the regulatory framework itself; nanomedicine highlights the rigidity of product domains that dictate product approval requirements. At the nanoscale, decades-old definitions of chemical and mechanical action may not be suitable to characterize products with novel mechanisms of action and properties. For the purpose of evaluating such products, traditional definitional distinctions and accompanying legal requirements for review, approval, and postmarket surveillance and assessment may not be ideal. Current regulatory structures and processes may work for existing products, but the increasing complexity of nanotechnology and its convergence with other fields (eg, neurotechnologies and genetics) will likely strain their limits. Ongoing deliberations, stakeholder input, and agency policy must assess whether and to what extent current regulations are adaptable to newly emerging nanomedicine products or whether implementation of new frameworks is necessary to ensure safety and efficacy.

A second challenge has to do with the potential for [novel risks](#), which raise questions about traditional safety and efficacy requirements' appropriateness. Questions persist about whether nanoscale properties alter established risk-benefit measures and assessments of clinical trials and research protocols; whether and when abbreviated review of nanomedicine products is appropriate; and whether and when postmarket assessments should be tailored to address nano-specific toxicology and exposure concerns. As nanotechnology advances, particularly in the realm of human health, ample attention to scientific developments should also be paid to characterizing, assessing, and reporting adverse events. As part of the National Nanotechnology Initiative and other federal agency collaborations, large-scale research efforts are underway to characterize nanoscale materials and quantify their impact for purposes of developing toxicological assessment and testing tools.<sup>32</sup> Information obtained from this research should be integrated into FDA review and approval processes as appropriate.

A third challenge has to do with whether labeling of nanomedicine products for consumers is sufficient to inform them that products contain nanotechnology or nanomaterials. This is not to say that explicit labeling should be a requirement; however, the FDA must contemplate whether increased patient and consumer education and consumer engagement is warranted and whether FDA policy on labeling requirements for nanoproducts responds well to public sentiment and the public's health literacy needs. For these efforts to succeed—similar to consumer awareness campaigns and advocacy efforts in the realm of genetically modified food and biotechnology—positive perceptions and understanding of applications is essential.

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