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Government Regulation of Nanorobots in Medicine: How the FDA and PTO Handle These New Technologies

Jessica L.A. Marks and Shana K. Cyr*

Not surprisingly, the nanorobotics industry is growing. As of 2014, there were over 200 companies pursuing commercial efforts in nanomedicine, with at least 23 in the advanced stages of development. The nanorobots market is expected to grow more than six percent each year until at least 2020, with the primary driver being their use in medicine. The authors of this article discuss government regulation of nanorobots.

The 1966 film *Fantastic Voyage* imagined a world where a submarine of doctors could be shrunk to "the size of a microbe" and ferried around the human body to attack a blood clot in a comatose patient's brain.[1] Over half a century later, there has been no movement on the idea of shrinking medical devices to the nanoscale, but there has been progress in building nanoscale technologies from the atom up. Although a nanorobot for *attacking* blood clots may not be on the horizon, a mechanical platelet or "clottocyte" has been proposed for *making* blood clots in patients with bleeding disorders,[2] and a nanorobot for *detecting* blood clots has also been designed.[3]

Scientists have contemplated nanorobots for a variety of medical uses beyond detecting blood clots. A nanoknife has been developed to conduct surgical procedures on individual neurons.[4] A nanorobot drill for drilling into cancer cells is being tested on microorganisms and fish.[5] And a transport nanorobot made of DNA has successfully carried and delivered a payload to targeted cells ex vivo, demonstrating that such robots could be used to provide targeted therapies inside the body.[6] Biocomputing structures that are programmed to detect and respond to different molecules have been shown to function within rat and mice models.[7] These biocomputers, currently programmable to use "Boolean logic gates (YES, NOT, AND,

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and OR) and bind to a target as a result of the computation," may serve as the "brains" for future nanorobot devices.[8]

More than personalized medicine, nanorobots offer the chance to customize treatment down to the cellular level, or even smaller. These targeted treatments have the possibility of increasing treatment effectiveness while decreasing side effects. One possible use was described by Muthukumaran et al. in 2015:

> A few generations from now someone diagnosed with cancer might be offered a new alternative to chemotherapy. A doctor practicing nanomedicine of chemotherapy would offer the patient an injection of a special type of nanorobot that would seek out cancer cells and destroy them, dispelling the disease at the source, leaving healthy cells untouched unlike the traditional treatment of radiation that kills not only cancer cells but also healthy human cells, causing hair loss, fatigue, nausea, depression, and a host of other symptoms.[9]

Not surprisingly, the nanorobotics industry is growing. As of 2014, there were over 200 companies pursuing commercial efforts in nanomedicine, with at least 23 in the advanced stages of development.[10] The nanorobots market is expected to grow more than six percent each year until at least 2020, with the primary driver being their use in medicine.[11]

The government is making efforts to address the advances in the industry and to foster further growth. The National Nanotechnology Initiative ("NNI") was started in 2000 as a research and development initiative to coordinate over 20 government departments and agencies working on various nanotechnology projects.[12] The NNI itself, however, does not conduct or fund research (other than offering some challenges with prizes), nor does it regulate the field.

For private industry looking to move products from the lab bench to the general public, the same funding and regulatory structures exist for nanorobots in medicine as for any other medical product. Perhaps the two most important federal agencies that a nanorobot developer encounters in the United States are (1) the U.S. Food and Drug Administration ("FDA"), which approves medical products; and (2) the U.S. Patent and Trademark Office ("PTO"), which oversees patent protection for inventions. Despite efforts by these agencies to address the novel aspects of nanorobots

in medicine, as explained below, companies face significant challenges in pursuing these products on a larger scale.

Nanorobots and the FDA

Recognizing that nanotechnology presents unique issues, the FDA created the Nanotechnology Task Force in 2006.[13] The Task Force issued a report in 2007 specifically noting the "need for timely development of a transparent, consistent, and predictable regulatory pathway" for nanorobots and related technologies.[14] But efforts to create such a pathway do not seem to have borne fruit where medical technologies are concerned.[15]

FDA's 2017 Guidance and Other Efforts

It was only in December 2017 that related draft guidance was issued by the FDA's Center for Drug Evaluation and Research ("CDER") and Center for Biologics Evaluation and Research ("CBER") that might relate to regulation of nanorobots (hereinafter, "Draft Guidance").[16] The Draft Guidance is directed to drug and biological products that contain nanomaterials; whether or to what extent it applies to nanorobots is unclear. The Draft Guidance discusses how nano*materials* may be treated in investigational new drug applications ("INDs"),[17] new drug applications ("NDAs"),[18] abbreviated new drug applications ("ANDAs"),[19] and biologics license applications ("BLAs").[20] But there is no mention of how nano*robots* might be handled in premarket notification ("PMN")[21] or premarket approval ("PMA")[22] submissions. Notably, the Draft Guidance was issued by CDER, which evaluates drug products, and CBER, which evaluates biological products, but the Center for Devices and Radiological Health ("CDRH") was not involved. CDRH regulates radiation-emitting products, which may be used in some nanorobot cancer therapies. But more importantly, CDRH regulates medical devices, which arguably covers most nanorobots.

Moreover, the Draft Guidance recognizes that the FDA does not have established definitions for the terms "nanotechnology," "nanomaterial," or "nanoscale," much less "nanorobots," and the Draft Guidance specifically states that the document is not attempting to create any definitions.[23]

The FDA's current stance on nanomaterials appears to largely involve researching issues[24] and incorporating review of nanomaterials into standing procedures.[25] The FDA's medical product premarket procedures depend on whether the product is mechanical, chemical, or biological.[26] Medical devices, which have a mechanical mode of action, are regulated by CDRH.[27] Drugs, which have a chemical mode of action, are regulated by CDER.[28] And biologics, which have a biological mode of action, are regulated by CBER.[29] If a medical product has more than one mode of action, then it is considered a combination product, and one center is assigned primary jurisdiction for the product's review based on the product's *primary* mode of action.[30]

The problem with this stance, however, is that nanotechnologies do not fit neatly into the FDA's standing procedures. The three categories are largely meaningless at the nanoscale. A nanorobot may be mechanically "drilling" into a cancer cell to induce apoptosis of the cell, but at that level, the interaction may be chemical in nature, with the atoms of the nanorobot interacting with those of the cancer cell to tear apart the chemical structures that comprise the cell wall. And whether the "drill" is made of biological material or chemicals is largely irrelevant at the nanoscale. The drill is basically atoms interacting with atoms, which could be classified as any one of the three categories depending on how the interaction is characterized.

Although the FDA arguably needs to create a new center or a new group within an existing center to handle the special case that nanorobots present, it is unlikely to do so before the first applications for approval of nanorobotic medical products are filed. The first cases are and will for the foreseeable future be reviewed under the current FDA structure.

Working with the FDA's Current Procedures

So, with all the uncertainty of which center will review nanorobots, what is a product sponsor to do? One way to attempt to gain clarity is to request classification of the product by the FDA. The Office of Combination Products ("OCP") was created to deal with the growing number of combination products submitted for FDA approval, and it is tasked with assigning classifications to products and selecting a lead center for review.[31] A product sponsor may ask

that the OCP formally assign its combination product to a center through the Request for Designation ("RFD") process.[32] The RFD requires a relatively comprehensive submission of data typically collected well into the development process. But the OCP also offers an alternative Pre-Request for Designation ("Pre-RFD").[33] The Pre-RFD requires less information, but is ultimately nonbinding.

Sponsors may increase the chances that their nanorobot product will be assigned a desired category by describing the product in a manner that influences the OCP's conclusion. For example, the sponsor may consistently characterize the product's therapeutic effect as attributed to the mechanical, chemical, or biological aspects of the product; analogize the product to other products that the OCP previously assigned to the desired category; or emphasize safety and effectiveness issues that call for the expertise of the preferred center. Under the 21st Century Cures Act, the FDA must provide a substantive rationale when it disagrees with a sponsor's determination of its product's primary mode of action.[34]

Ultimately, once a nanorobot is classified and assigned to a lead center, its review will likely be similar to the review of any other medical product at that center.

Classification as Mechanical, Biological, or Chemical Products

For many nanorobots, the primary mode of action may be considered mechanical. That is, for a nanorobot whose primary function is mere delivery of a drug to a site[35] or drilling into a cancer cell,[36] it would appear to be an "instrument . . . or similar or related article . . . which is . . . intended to affect the structure or any function of the body of man . . . , and which does not achieve its primary intended purposes through chemical action . . . and which is not dependent upon being metabolized."[37] As such, most nanorobots may be regulated by CDRH.

As noted above, however, CDRH has not issued any guidance documents on what is required or expected for the review of nanorobots. The focus of CDRH's nanotechnology program is on understanding the physico-chemical interactions of nanomaterials and on appropriately characterizing nanomaterials.[38] Information on how CDRH will treat (or potentially *is* treating) such products is not available.

Therefore, one must assume that a nanorobot with a primarily mechanistic mode of action will be assigned to CDRH for classification under its standard premarket review process as a Class I, Class II, or Class III device. Class I devices are those that are very low risk, requiring only registration and listing with the FDA, or low risk, requiring review through the 510(k) process under general controls. Class II devices are moderate risk, and require review through the 510(k) process with both general and special controls. Whenever the 510(k) process is used, the safety and efficacy of the device must be proven by a comparison to a substantially equivalent previously approved product. Class III devices require use of the premarket approval process where safety and efficacy are proven with clinical data.

Although "FDA does not categorically judge . . . nanotechnology as intrinsically benign or harmful,"[39] it seems more than likely that nanorobots will be considered Class III devices at least initially. This is because regardless of how similar their functions may be to previously approved devices (e.g., a nanorobot drill may create a hole in the target like a dentist's drill), the way they accomplish their functions is so different that the comparison is stretched beyond reason (e.g., the nanorobot drill may operate internally, requiring its degradation and/or removal from the body, and may rely on chemical forces to create the hole).

Some nanorobots may be considered combination products, especially if they are delivering a drug to a particular site. Nanorobots may also have dual functions for both the delivery of the treatment and the treatment itself, as "a particle's shape and the location of changes in its surface may affect the interactions of nanoscale materials with chemicals in the body."[40] In such instances, it seems likely that the primary center for review would still be the CDRH because the primary mode of action would be mechanical.

It is possible that some nanorobots may be deemed biological products, for example, if they are synthesized using biological materials and their effects arguably meet the definition of a drug.[41] Alternatively, nanorobots may be part of combination products, e.g., a delivery system for a biological product. Either way, CBER may be designated as the reviewing center.

Some nanorobots may be deemed drugs based on their action in the body, especially, for instance, if they are degraded while in the body and the degradation affects the body (e.g., in a process similar to the metabolization of small molecule drugs). Or

nanorobots could be a component of a combination product, e.g., for the delivery of a drug product. These hypotheticals open up the possibility of CDER as the reviewing center.

If a nanorobot is designated a biological product or a drug, the Draft Guidance may be central to its review. The Draft Guidance requires that the nanotechnology aspect of any product be clearly described in any BLA, NDA, or ANDA.[42] A simple listing of the materials used is not sufficient; the structure and the functionality must also be described.[43] The Draft Guidance states that any nanomaterial in a drug product should include descriptions of its chemical composition, average particle size, particle size distribution, general shape and morphology, and physical and chemical stability.[44] The Draft Guidance also indicates the additional considerations that should be addressed when analyzing a nanoparticle, such as whether the characterization methods for assessing the nanoparticles can adequately detect their characteristics and whether quality control testing can adequately determine the effects of manufacturing differences.[45]

Ultimately, the Draft Guidance primarily provides a list of considerations for the evaluation of nanoscale products by CBER and CDER;[46] there is little in the way of hard-and-fast rules or requirements. Thus, applicants will need to consult closely with the FDA regarding the data required to obtain approval for their nanorobots.

Nanorobots and the PTO

As touched upon above, the nanotechnology industry is rife with new discoveries. Inventors (and their investors) are keen to protect their inventions with patents. In 2016, the PTO granted over 8,400 nanotechnology patents[47] and published over 11,000 U.S. patent applications.[48] A study in 2011 found that many of the top entities seeking patents for medical applications of nanotechnologies were universities.[49] But many private companies are increasing their investment in nanotechnologies, with over 90 companies selling nanotechnology products in the medical field as of 2013.[50]

The requirements for obtaining a patent on nanotechnologies are the same as for any other invention. In general, an inventor presents an application for an invention to the PTO. The application must contain a clear written description of the invention[51] and include claims that clearly define the scope of the invention.[52]

The PTO then reviews the application and compares the inventor's claims to known technologies. The PTO considers whether the invention is a "new and useful process, machine, manufacture, or composition of matter, or [a] new and useful improvement thereof."[53] If the initial claims are not found patentable, then the inventor can provide arguments and amend the claims during the prosecution of the application. If the PTO determines that the claims meet all of the requirements, then it issues a patent.

Although the patent requirements for nanorobots are no different than they are for any other technology, nanorobot inventions pose additional hurdles. First, as a relatively new field, the terminology is not set. For example, the same nanorobot structure may be called a nanoparticle, a nanocrystal, a nanoparticulate, a quantum dot, a nanodot, or a colloidal crystal. To ensure the application meets the PTO's written description requirement, applicants should explain how they are using the terms in their applications. Applicants should consider listing the synonyms for the terms they are using and even definitions for the terms.[54] Drafting the application to ensure sufficient description of the terms also helps the PTO conduct its searches of known technologies, aiding in efficient prosecution of the application. Some argue that helping the PTO identify relevant known information leads to higher-quality patents that are more likely to withstand later challenges before the PTO or the courts.

Also, because nanorobots are relatively new, the literature the PTO searches is not as developed as in other, more established fields.[55] The PTO may be unable to find references that teach or suggest inventors' claims, leading to the issuance of overly broad patents.[56] An overly broad patent is not an immediate issue; most inventors would see such patents as success stories. But if the inventor attempts to assert an overly broad patent against a competitor, the competitor may challenge whether the patent should have been granted in the first place. The patent may be deemed unpatentable and cancelled in a post-grant PTO proceeding[57] or held invalid in a court case. To defend against such challenges, inventors should pursue several patents with claims of varying scope to cover their inventions. If the broadest claims are granted by the PTO, inventors should file continuation applications to obtain patents on additional claims. Inventors should pursue narrow claims that are specific to the particular nanorobots they are likely to commercialize, and they should consider claims directed to various aspects of

the invention, including claims to the nanorobot, to various parts of the nanorobot, to the process of making the nanorobot, and the methods of treating patients using the nanorobots.

Another problem that stems from the underdeveloped literature base in the field of nanorobots is that earlier references found by the PTO may include overreaching or hypothetical descriptions of what an inventor is now trying to claim in a patent application. Often, these early works do not really teach how to make the nanorobot—they merely provide conjecture. Therefore, applications should include background sections describing the state of the art and the challenges the inventor had to overcome to develop the claimed nanorobots, all while taking care not to inadvertently impair patent rights by enabling the prior art with the description.[58] If the application is rejected during prosecution based on an overbroad reference, the inventor will have an easier time arguing that the reference does not enable someone of ordinary skill in the art to make the claimed nanorobot. Often, the arguments against overly broad disclosures in prior art references must be accompanied by amendments to the claims. The claim amendments would add elements to the claims for the inventor's nanorobots that are not disclosed in the prior art reference.

Related to this is the possibility that the PTO granted overly broad claims to someone else. Then, during prosecution of the inventor's application, the PTO may refuse to grant new claims based on prior disclosure and the prior claims. In this situation, similar arguments regarding the lack of enablement of the prior patent may work, but the inventor should also argue that the disclosure or claim to the broad genus of nanorobots in the prior patent does not make the selection of the particular species the inventor is claiming obvious.[59] Ultimately, inventors may need or choose to challenge overly broad patent claims that are blocking the issuance of their own patents in a post-grant proceeding at the PTO.[60]

Finally, inventors of nanorobot technologies may face rejections from the PTO based on a known product or structure that is not nano-sized. Changing the size of a structure does not necessarily confer patentability. Therefore, the patent application should describe the challenges to creating a robot on the nanoscale, the unique considerations in the materials used, and the benefits of using such a small device.

In sum, the PTO process of obtaining patent protection for nanorobots seems more developed for this new technology than the

process for gaining FDA approval. But there are still many nuances that should be considered when drafting and prosecuting patent applications in the field of nanorobots.

Notes

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17. 21 C.F.R. § 312.

18. *Id.* §§ 314.50-314.54.

19. *Id.* §§ 314.92-314.99.

20. *Id.* § 601.

21. *Id.* §§ 807.81-807.100.

22. *Id.* § 814.

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24. The official statements of several centers in the FDA largely amount to plans to conduct further research and provide no timeline for the issuance of guidance for industry.

25. FDA, "FDA's Approach to Regulation of Nanotechnology Products," https://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm301114.htm (last updated Dec. 15, 2017) ("Where premarket review authority exists, attention to nanomaterials is being incorporated into standing procedures.").

26. *See, e.g., John Miller, Beyond Biotechnology: FDA Regulation of Nanomedicine,* 4 COLUM. SCI. & TECH. L. REV. 1, 24 (2002-2003).

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> an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is—

> (1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
>
> (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
>
> (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

21 U.S.C. § 321(h).

28. FDA Center for Drug Evaluation and Research (CDER), "Strategic Plan 2013-2017," at 3, https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM376545.pdf (last visited Feb. 6, 2018). The FDA's definition of a "drug" is

> (A) articles recognized in the official United States Pharmacopeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and
>
> (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and
>
> (C) articles (other than food) intended to affect the structure of any function of the body of man or other animals; and
>
> (D) articles intended for use as a component of any article specified in clause (A), (B), or (C).…

21 U.S.C. § 321(g)(1).

29. FDA, "CBER Vision & Mission," https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm122878.htm (last updated Feb. 5, 2018). The FDA's definition of a "biological product" is

> a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, … or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

42 U.S.C. § 262(i).

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34. 21st Century Cures Act of 2016, Pub. L. No. 114-255, § 3038(a)(4), 130 Stat. 1033, 1105-10 (amending 21 U.S.C. § 353(g)).

35. *See, e.g.,* Douglas, *supra* note 6.

36. *See, e.g.,* Brodie, *supra* note 5.

37. 21 U.S.C. § 321(h)(3).

38. FDA, "Center for Devices and Radiological Health Nanotechnology Programs," https://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm309678.htm (last updated Oct. 10, 2014).

39. FDA, "FDA's Approach to Regulation of Nanotechnology Products," https://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm301114.htm (last updated Dec. 12, 2017).

40. FDA Nanotechnology Task Force, "Nanotechnology Task Force Report 2007," at 11 (July 25, 2007), *available at* https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/Nanotechnology/ucm110856.pdf.

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42. Draft Guidance, *supra* note 16, at 6-7.

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45. *Id.* at 9-11.

46. *See, e.g., id.* at 15-17 (providing a list of risk considerations), 17-18 (providing general considerations for 505(b)(2) submissions).

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