

Comment on FDA Draft Guidance for Industry: *Drug Products, Including Biological Products, that Contain Nanomaterials*, 82 FR 60019
(proposed Dec. 18, 2017)

Authors¹: Towqir Aziz, Andrew Darnell, Jimin Hu, Anna Lukasiewicz, Jamal Moss

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I. Introduction

A. Who We Are

The Duke Science Regulation Lab (“SciReg Lab”) is composed of graduate students in a variety of disciplines at Duke University, including science, law, ethics, and policy. The Science Regulation Lab was originally inspired by the traditional role of *amicus curiae*: to provide a court with the unbiased information necessary to reach a binding decision. As an extension of that concept, we now provide government agencies with the scientific information necessary to undertake effective rulemaking.

Modern society requires our government to handle increasingly complex scientific issues when deciding cases or making policy. We, the Duke Science Regulation Lab, believe that the general public benefits from judgments that are based on sound scientific knowledge. To assist decision makers in

¹ The authors are all graduate students in the Duke Science Regulation Lab, an interdisciplinary course offered through the Duke Law and Graduate Schools. Michael B. Waitzkin is the faculty member who runs the Science Regulation Lab, with the assistance of J. H. Pate Skene, Associate Research Professor of Neurobiology at Duke University. Michael B. Waitzkin also oversaw the preparation of this Comment.

understanding a scientific matter at hand, the students of the Science Regulation Lab combine their expertise to offer a non-partisan, accurate, and accessible explanatory brief or comment to serve as a resource for the decision makers.

The academic focuses of the members of the Duke Science Regulation Lab are varied. **Jamal Moss** is a Masters student studying Bioethics and Science Policy. **Andrew Darnell** is a 2019 JD candidate, and 2015 graduate of the Bioethics and Science Policy MA program. **Jimin Hu** is a first-year PhD student in Cell and Molecular Biology, researching on protein glycosylation. **Towqir Aziz** is also a Masters student studying Bioethics and Science Policy. **Anna Lukasiewicz** is a 2019 JD/LLM Candidate.

B. Introduction to the Draft Guidance

In December of 2017, the Food and Drug Administration (hereafter referred to as “FDA” or the “Agency”) announced a draft guidance for industry entitled “Drug Products, Including Biological Products, that Contain Nanomaterials” [1] in a Notice of Availability in the Federal Register.

The FDA drafted this guidance to inform industry of the Agency’s latest thinking with regards to the development of human drug products and biological products containing nanomaterials in the finished dosage form. The draft guidance provides recommendations for those who are applying for— or sponsoring—investigational, premarket, and post-market submissions for both drug products and biological products that contain nanomaterials.

Overall, the draft guidance states that it will not presuppose what the inclusion of nanomaterials might mean in terms of any particular drug’s ultimate regulatory outcome. Instead, the FDA will consider the specific impact-- in terms of safety, effectiveness, public health impact, or the regulatory status of drug products-- of particular nanomaterials in each individual instance. In other words, the

FDA will review each nanomaterial-containing drug on case-by case process, as it already does in its existing drug and biologic review processes [1].

For the purpose of discussion with this guidance, “drug products” are defined as “any human drug product or products in finished dosage form, including those that are also biological products, unless otherwise specified”, which also involves “the drug or biologic constituent part of a combination product” [1].

In determining whether a material is a "nanomaterial", the FDA will consider:

1. *“Whether a material or end product is engineered to have at least one external dimension, or an internal or surface structure, in the nanoscale range (approximately 1 nm to 100 nm); or*
2. *Whether a material or end product is engineered to exhibit properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer (1,000 nm).”*

[1]

The Agency includes materials and/or end products outside of the nanoscale range-- approximately 1 nm to 100 nm-- because materials can still exhibit unique nanoscale-related properties or phenomena, that may critically affect the FDA’s evaluations.

This description of “nanomaterial” is consistent with FDA’s previous industry guidances regarding nanotechnology: one specifically for cosmetics [2] and another for animal food [3].

This guidance also differentiates between naturally occurring nanomaterials, products incidentally containing nanomaterials, and manufactured nanomaterials. For naturally occurring nanomaterials, it states that—

“This draft guidance does not apply to biological products composed of proteins, cells, viruses, nucleic acids, or other biological materials that naturally occur at particle sizes ranging up to 1 micrometer (1000nm), such as gene therapy or vaccine products, unless a material that has been deliberately manipulated to have dimensions between 1-100 nm or to exhibit dimension-dependent properties or phenomena up to 1 micrometer, is also present in the product (e.g., as a carrier or an inactive ingredient).” [1]

The guidance further specifies incidental nanomaterials:

“This draft guidance also does not apply to drug products that incidentally contain or may contain particles in the nanoscale range due to conventional manufacture or storage...” [1]

After establishing the proposed parameters for nanomaterials, the guidance proposes a risk-based framework to consider products with nanomaterials. Specific risk factors were listed, including characterization of material structure and its function, physical and chemical stability, and bioavailability, distribution, and accumulation of drug products containing nanomaterials. For certain risk factors, the guidance specifies areas for quality testing. It also touches on both nonclinical and clinical studies of drugs with nanomaterials, and environmental impact considerations.

Our comment will focus on the following aspects of the guidance with information from experts, related regulations, and primary literature:

- a. Characterization of nanomaterials;
- b. Risk factor testing and regulation;
- c. Data reporting regulation;
- d. Environmental impact of nanomaterials.

C. Background of the Draft Guidance

In the past few years, the FDA issued several draft guidances related to nanotechnology. Two analogous documents to this guidance for drugs were issued for industry related to cosmetics [2] and food [3]. Like the current draft guidance, these earlier guidance documents generally are not meant to establish legally enforceable responsibilities. Instead, they offer non-binding recommendations to help facilitate industrial innovation in a safe and thoughtful manner.

In the spirit of promoting innovation by avoiding overly stringent regulation, the FDA guidance has not established any regulatory definitions of “nanotechnology,” “nanomaterial,” “nanoscale,” or other related terms. This logic is consistent with federal guidance on regulatory oversight regarding nanotechnology [4], as seen in President Obama’s Executive Order 13563, from 2011, which said—

“A focus on novel properties and phenomena observed in nanomaterials may ultimately be more useful than a categorical definition based on size alone,” [4]

—as well as with the broader federal guidance on regulatory oversight of emerging technologies [5].

In 2014, the guidance for nanomaterials in cosmetics was issued as part of the FDA’s continuing response to its Nanotechnology Task Force, established in 2007. Since it serves as an industry guide for cosmetics products, the guidance endeavors to describe “safety issues that manufacturers should consider to ensure that cosmetic products made with nanomaterials are safe and not adulterated.” [2]. The guidance characterizes nanomaterials somewhat further, as too diverse in “composition, morphology, and other characteristics and [therefore] cannot be considered a uniform group of substances.” [2]. The first recommended step for industry is therefore to analyze the composition, structure, and configuration of all nanoscale materials involved in manufacturing, as well as the final product.

Since the FDA concentrates on adulterated or mislabeled cosmetics and does not have the authority to require premarket approval for cosmetic products or ingredients, the guidance encourages manufacturers and distributors to consider the potentially unique and unanticipated effects of nanomaterials when determining whether traditional reliance on available toxicological data is sufficient to ensure the product’s safety. To be precise, this is recommended when the material’s size “can affect the distribution of that material in the body and that material’s interaction with biological systems.” [2]. However, in practice, it would be almost impossible to determine that the size of nanoscale particles has no potential impact on how the body processes it, especially before characterizing and testing the material.

In 2015, the FDA followed with a guidance for nanomaterials in food substances for animals [3]. This guidance encompasses animal food ingredients that either contain or involve the use of nanomaterials. Similar to previous guidances, this document avoids precisely characterizing nanomaterials. Here, however, the FDA is clear that it will not be considering guidance for the use of substances that “naturally exist at small scales,” unless they have been subsequently altered through technological means. [3] Along the same lines, the discussion section describes nanotechnology as involving “manipulation of materials” on the nanoscale and focuses the subsequent analysis on “the application of nanotechnology,” rather than the involvement of nanomaterials [3]. In defining the scope, the FDA also exempts from this guidance products containing “incidental” levels of nanoscale material and received GRAS or petition-based approval.

Although the FDA circumvents establishing a regulatory definition, the characterizations used for discussion of the guidance documents are consistent, as indicated in the previous section. Similarly, the FDA guidance has been applied consistently to manufactured nanomaterial—even if the

nanomaterial is present only as a carrier or an inactive ingredient. The FDA provided justification for this differentiation of manufactured versus naturally occurring nanomaterials, saying—

“(The) FDA is particularly interested in the deliberate and purposeful manipulation and control of dimensions to produce specific properties, because the emergence of these new properties or phenomena may raise questions about the safety, effectiveness, performance, quality or public health impact that may warrant further evaluation.” [1]

The FDA guidelines have also consistently precluded application of the guidelines to products that incidentally contain or may contain particles in the nanoscale range due to conventional manufacture or storage. This has not changed in the latest draft guideline. However, as part of the FDA’s existing drug review process, evaluations of conventionally-manufactured drug products may include a consideration of effects regarding the safety or effectiveness of the product, if any, that may be due to the incidental presence of particles in the nanoscale range.

Some agencies have handled nanomaterials in analogous ways. The Department of Health and Human Services produced Approaches to Safe Nanotechnology in 2009, emphasizing the exposure hazard of working with nanomaterials. In this document, the National Institute for Occupational Safety and Health emphasizes the reasonable basis for scrutinizing nanoparticles for their potential health effects, urges a precautionary approach to the use of nanomaterials, and makes recommendations for the minimization of workplace exposure. Like the FDA, they rely primarily on particle size and treat naturally occurring and synthetic nanomaterials differently, although they place more emphasis on human activity:

“Engineered nanoparticles are materials purposefully produced with at least one dimension between 1 and 100 nanometers. Nanoparticles often exhibit unique physical and chemical properties

that impart specific characteristics. . . Nanotechnology involves the manipulation of matter at nanometer scales to produce new materials, structures, and devices.” [6]

However, other institutions and agencies take a different approach to characterizing nanomaterials, which will be discussed below.

II. Our Recommendations

A. Characterization of Nanomaterials

Despite general alignment, there are, however, inconsistencies between the FDA’s characterization of nanomaterials compared to other institutions and agencies within the United States. One such example is the characterization used by the Federal Government’s nanotechnology research and development program, the National Nanotechnology Initiative (NNI). NNI literature first echoes the FDA that:

“Size is by far the driving characteristic in all of the definitions developed for nanotechnology and nanomaterials to date.” [7]

It continues with more detailed definition related to dimensions of nanomaterials, which the FDA guidance does not mention:

“Most definitions of nanomaterials contain a size-specific range (e.g., within the nanoscale range, which is commonly referred to as approximately 1-100 nm) along at least one dimension, but some definitions apply the size range to two or more dimensions--using either external or internal structures as units to be measured. Some definitions also include criteria related to physical or chemical characteristics (e.g. size distribution, shape, charge, or the ratio of surface area to volume) or to the display of unique or novel properties or "nanoscale phenomena." [7]

The Environmental Protection Agency (EPA) embraces a more specific description of nanomaterials, which included dimensionality, surface area to volume ratio, number of surface atoms and their arrangements. [8]

Globally, nanomaterials are defined in a manner different from the FDA's two-part characterization. The European Commission provides a more technical definition of nanomaterials, similar to the EPA's description of nanomaterials:

*“A **natural, incidental or manufactured material** containing particles, in an unbound state or as an **aggregate** or as an agglomerate and where, for **50 % or more** of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm - 100 nm.*

*In specific cases and where warranted by **concerns for the environment, health, safety or competitiveness** the number size distribution threshold of 50 % may be replaced by a threshold between **1 and 50 %**.*

*By derogation from the above, **fullerenes, graphene flakes and single wall carbon nanotubes** with one or more external dimensions below 1 nm should be considered as nanomaterials.” [9]*

This definition includes a broader range of categories for nanomaterials, and employed a more detailed description of nanomaterials involving state and constituent property. It also considers impact on environment as in the definition, and lists specific nanomaterials to be considered as exceptions to the size limit.

The discrepancies of characterizations between domestic agencies and inside the international community suggests opportunities for the FDA to more accurately define the relevant characteristics of nanomaterials. Therefore, we propose four areas of clarification for the characterization of nanomaterials:

- a. The size description should be complemented with dimension requirement, as seen in NNI's and EU's definitions.
- b. The percentage of nano-sized particles within the materials should be specified as done by the EU.
- c. The distinction between naturally occurring versus manufactured materials needs to be clarified. The agency should establish what percentage of the nanomaterial needs to be modified to constitute "engineered" products. The agency also needs to specify what manipulations to naturally occurring materials change the property of the materials to "manufactured".
- d. Nanomaterials under 1nm should be regulated under some circumstances, as the EU suggests.

We suggest that these clarifications will help the FDA standardize the characterization of nanomaterials.

B. Risk Factor Testing and Regulation

Much of this guidance discusses the mechanisms by which nanomaterials interact with biologic systems in humans. [1] Assessment of the risk posed by nanomaterials included in drugs and biologics is likely impossible without identifying the underlying interactions between the nanomaterial and biologic system in which it acts. Nanomaterials can be highly toxic because their small size allows them to more easily penetrate bodily systems, including the brain, and interact deleteriously therein, being associated with conditions such as myocardial infarctions and atherosclerosis, as well as generating harmful immune responses (immunogenicity, discussed below). [10] To this extent, we

agree with much of the discussion contained within the clinical development section. However, we would recommend clarifying several underlying points.

Primarily, it is important to note that much of nanomaterials' interaction with biologic systems is determined from physical characteristics of the material, such as size and shape, but also from surface characteristics of the materials, such as charge, and surface functional groups. [11] Further, several key characteristics of nanomaterials, including how fast the material uptake occurs by cells, is determined based on how that material agglomerates in solution, rather than by the characteristics of the material measured as a single, standalone particle. [12]

Surface characteristics play a substantive role in nanomaterials' *in vivo* behavior. [13] Most notable and frequently recurring in literature is surface charge, which affects agglomeration rate, as well as colloidal stabilization rate (how quickly proteins coalesce around the nanomaterial). This in turn affects bio-distribution, intracellular trafficking, clearance, and uptake rates. [14] Because these cellular mechanisms importantly affect the risk and toxicity associated with the nanomaterial, as discussed below, careful attention should be paid to surface characteristics and charge to ensure safety and efficacy in nanomaterials being employed.

Further guidance is also required with regard to immunogenicity reporting requirements. There exists substantial support in the literature regarding immunogenicity and potentially adverse outcomes in the context of nanomaterials. [15] We do not believe that the two previously issued general immunogenicity guidelines are sufficient guidance in this area, given how complex and varied the mechanisms by which nanomaterials trigger immunogenic responses are. [15] Nanomaterials can cause extreme toxicity in biologic systems based on immunogenic responses determined by a number of the physical characteristics of the materials including surface charge, and composition of the

nanomaterials. [16] As such, immunogenic review guidance should be issued specifically for nanomaterials.

In subsection four of the guidance, standards to analyze the stability of nanomaterial in drug products are described. Current FDA guidance requires stability data and testing conditions to support drug product applications. [17] The same guidance will be applicable to drug products with nanomaterial. This includes analyzing specific risk factors such as physical and chemical stability of the nanomaterial during handling and storage in different climate conditions. For this reason, the current guidance suggests examining specific properties that are susceptible to modification when the nanomaterial is exposed to different environments including nanomaterial properties related to size, shape, charge, association and disassociation factors, and degradation rate. This information is coupled with data analyzing the nanomaterial's interaction with its immediate environment such as the formulation or container closure system. We agree this is an appropriate method, and factors, by which to analyze individual nanomaterials, their individual immunogenicity standards, and potential risk and toxicity in biologic systems.

C. Data Reporting Regulation

To this end, the FDA is well positioned within this guidance to institute a more systematic method of reporting the most critical attributes of the nanomaterial. One of the problems with the several public repositories of information surrounding nanoparticles is their lack of standardization, which suggests a clear public need, and utility, in the FDA playing this gatekeeper role [18]. As currently written, data relevant to the toxicity and risks associated with nanomaterials, can be reported through a number of different pathways (e.g. 505(b)(2), 505(j), and 351(k), see p.17–23), based on how they are intended to be administered and anticipated risk level. We believe that all data reported

through these pathways should be homogenous in template and in certain characteristics of the nanomaterials reported, as they relate to toxicity in biologic systems.

Therefore, we suggest that the FDA standardize the data reporting process with specific parameters as reference, which can be transformed into a public registry of nanomaterials used in drug products. By emphasizing constant variables to be reported among new nanomaterials and their effect in biologic systems, the FDA can build up a database where researchers can use along with predictive algorithms to better anticipate the *in vivo* behavior of future materials, and associated toxicity rates. The aggregation of data, particularly being able to aggregate data from nanomaterials obtaining clearance through various different regulatory pathways, will also ease the FDA in the inspection process, provide basis for industry in production, and offer public good for other parties interested in gaining insights on nanomaterial regulation.

A method to provide specific dimensions of nanomaterial properties with attainable efforts is needed for this purpose. One available approach is the idea of minimal information about nanomaterials (MIAN), developed by researchers of RTI International, a nonprofit research institute in Durham, NC [19].

The idea behind MIAN comes from the current status of nanomaterial research, which still lacks accurate standards. MIAN requires a list of physical-chemical characteristics for a nanoparticle so that the particle is sufficiently described, which adheres to FDA's regulation purpose of a well-controlled number of factors to consider. As more data are accumulated, the FDA can obtain more accurate knowledge about the numerical ranges considered safe for risk factors, which is not included in the current guidance. Specific numbers also facilitate the industry to follow the guidance precisely when manufacturing new nanomaterials.

One problem with nanomaterials is that measurement can be highly affected by the state of the nanomaterial. Therefore, the authors of the MIAN methodology also proposed factors included in the instance of characterization (IOC) [19]. IOCs detail the time and conditions in which nanoparticles are analyzed, and are listed with three categories: "as synthesized (native state of nanomaterial when synthesized)", "as received (native state of the nanomaterial when purchased or received)", and "as processed (non-native state of the nanomaterial once modified, and how modified)". We suggest that the FDA consider those categories and clearly incorporate them into specific standards, which document possible changes of nanoparticles properties based on the environment of the inspected nanomaterial.

Since factors surrounding nanomaterials are complex, adopting a systematic way of thinking like the “functional assay” by Hendren et al. would be useful [20]. “Functional assays” are used to quantify parameters which specify processes/functions resulted from a given system. Since this study was based on environmental impact of nanomaterials, the quantitative metrics emphasized would need to be adapted to drug regulation, but the structure would enhance the clarity of FDA's approach to regulating nanomaterials.

The assay is built up on three founding factors: intrinsic properties, extrinsic properties, and system properties. Intrinsic properties are inherent to the nanomaterial; if altered, the nanomaterial has a new identity. Extrinsic properties fluctuate with the system the nanomaterial is positioned in. Defining the system of the nanoparticle is crucial to separate the two types of properties, so it becomes the third factor as the basis for functional assays [20]. Within the framework, commonly-seen systems can be categorized. In the case of drug particles, the regions in the body where the particles are effective can be used as reference systems, and specific metrics of the system can be determined, like

the pH, blood pressure, density of fluid etc. Since functional assays are quantitative, the intrinsic and extrinsic factors of nanomaterials will be considered in concrete numerical values, within the identified reference system.

With the MIAN as a major idea for data collection, combining IOC in the framework of functional assays, the FDA can establish a more specific, more regulated method for data reporting, which is practical and convenient for both the industry and the FDA regulators. Furthermore, the gathered data can be entered into a repository, which serves as a reference for the FDA, industry, researchers, and the general public as well.

D. Environmental Impact of Nanomaterials

Drugs with nanomaterials are emerging in preclinical studies and will soon be common in the prescription drug market. Since 1950, 50 new drugs containing nanomaterials have emerged due to the physical advantages of using the technology. [21] Drugs that are considered hazardous, such as chemotherapy, can now be modified by incorporating nanomaterials to improve therapeutic index and improve efficacy while decreasing toxicity. [21] Finished drug products can use nanomaterial to protect the drug from degradation, help the drug target specific cells and improve its biological effect. However, as these therapeutics become more widely accepted as effective treatments for disease, guidance is needed to characterize nanomaterial behavior in diverse settings, including the environment.

The proposed guidance has no explicit language regarding the disposal of drugs with nanomaterial and environmental implications. Currently, FDA guidance for certain drugs recommends disposing leftover prescriptions drugs by flushing them, throwing them in the trash, or utilizing take back programs organized by the Drug Enforcement Agency. [22] Although there are drug products that

pose negligible eco-toxicological risk, [22] the same cannot be concluded for drugs containing nanomaterials. As drugs with nanomaterials become more accessible, the FDA should consider how pharmaceutical companies will analyze their ecotoxicity with particular attention to drug disposal pathways. Due to these circumstances, we recommend the FDA assess all drugs with nanomaterials until their "end of life cycle" or waste disposal, according to the life cycle approach, which includes analyzing environmental implications. For drugs containing nanomaterials, to permit FDA to make this assessment, the new drug application should include a full explanation of the nanomaterials' environmental toxicity and the procedures needed to address such issues. There is considerable precedent for this approach in the requirement to prepare a Risk Assessment and Mitigation Survey ("REMS") for other drugs presenting significant risk profiles.

The life cycle approach proposes a holistic evaluation of drug products and has the potential to address issues that arise from all steps of the drug process including manufacturing, packaging, consumption and disposal through biological and environmental mechanisms. [23] The FDA currently uses the life cycle approach as a framework to assess drug products, as described in the proposed guidance; however, that does not always include the end of life cycle. The end of the life cycle is described as the disposal pathway that leads to incineration, acidification or other forms of waste management. Nanomaterials can enter the environment via sewage treatment and waste incineration plants, and leachate draining in landfills. [24]

Until recently, there has been limited research on the impact of nanomaterial on environmental soil, water and sediments. [25] Although there had been a considerable amount of research conducted on nanotoxicology, much of that research was completed in highly controlled laboratory studies with single species in simple media. [25] Many studies concluded that nano-ecotoxicology can have adverse

effects on humans, animals, plants, microorganisms and different ecosystems. [24] As a result, more research is needed to fill in knowledge gaps about engineered nanomaterial and the environmental phenomena that occur due to its interaction with components of the environment such as water, soil and atmosphere.

The FDA should consider the health risks associated with the environmental release of pharmaceuticals with nanomaterial and their stability in environments that are not traditionally required for the initial evaluation of the drug. In the proposed guidance, section seven titled "Environmental Impact Considerations" articulates a system that operates on a case-by-case basis to evaluate the environmental impact of drugs with nanomaterial via an Environmental Assessment (EA). In addition to considering the form, the route, and the mass of nanomaterial entering the environment, the EA also analyzes the fate and transport of nanomaterial entering the environment, the fate and transport of nanomaterial in environmental media (i.e., natural soil, sediment, surface or groundwaters), organismal responses to nanomaterial exposure (ecotoxicology) and the effects of nanomaterial inputs on ecological communities and biogeochemical processes. [25] Companies that submit a claim for categorical exclusion when requesting agency action on a drug or biologic application, and get approved, do not have to submit an EA.

Due to the limited knowledge on nanomaterial environmental impact, we recommend the FDA guidance follow a precautionary principle and only permit waivers where the science regarding downstream effect of nanomaterial is well-established and unequivocal. In all other cases, FDA should require an environmental assessment for drugs containing nanomaterials. The agency should also consider requiring the sponsors of the drugs already on the market to prepare an environmental assessment unless the nanomaterials they contain meet the "well-established" and unequivocal

standard. Such a policy can provide useful data for learning about the end of life cycle of nanomaterials once they enter the environment. FDA should continue to require such EAs for new drug applications until sufficient evidence is accumulated to establish that the particular nanomaterials contained within the drug product poses no more than a *de minimis* risk to the environment. In addition, the FDA should require that drugs with nanomaterials be added to a "do not flush" list and require that those drugs be included in the national prescription drug take back campaign.

III. Conclusion

Since nanotechnology is a fast-growing area of innovation, we think the regulations should be comprehensive yet flexible to face the opportunities and challenges posed by nanotechnology. We hope that this comment can assist the FDA in its decision-making process and contribute to the regulation of nanomaterials in drug products.

IV. Acknowledgement

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Thank you for considering this submission.

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