FDA Drug Products, Including Biological Products, that Contain Nanomaterials (Draft Guidance for Industry)

Provides guidance for industry on the development of human drug products in which a nanomaterial is present in the final dosage form.

Updated last **March 12, 2018**
for the December 2017 draft guidance.

WHAT IT DOES

In December 2017, the Food and Drug Administration (FDA) released its draft guidance for industry titled Drug Products, Including Biological Products, that Contain Nanomaterials. This draft guidance (noticed via 82 FR 60019) provides guidance to industry on the development of human drug products in which a nanomaterial is present in the final dosage form. The guidance discusses a risk-based framework of general principles and specific considerations for quality assessment, nonclinical, and clinical studies as they relate to the development of drug products containing nanomaterials. Specifically, this framework encompasses how manufacturers should characterize their nanomaterials, using the following considerations:

- Adequacy of the characterization of material structure, structure complexity (e.g. the number of molecules attached to the nanomaterial), and function.
- Understanding of in vivo release mechanisms, how the nanomaterial's physicochemical properties elicit biological reactions, and the reliability of in vitro methods for predicting in vivo release. Physical and chemical stability of the material can contribute to a nanomaterial's rate of dissolution and bioavailability. And the FDA considers the predictability of these factors, as well as biodegradation, accumulation, and biodistribution, based on animal studies.
- Maturity of the nanotechnology—manufacturing and analytical methods may evolve throughout commercial development, so these changes must be accounted for when interpreting nanomaterial data. Throughout development, manufacturers should identify process controls that relate to the critical quality attributes of the drug product.
- The route of administration and the physical state of the nanomaterial upon administration.

Taking these risk factors into consideration, the FDA recommends that industry take the following steps to maintain quality during the development of drug products containing nanomaterials:

- Description of the Nanomaterial(s) in the Drug Product – The description of the nanomaterial should sufficiently describe the physical characteristics of the product (size, charge, shape, morphology, composition, and complexation), as well as the functionality of the product. The descriptions will depend on the stage of product development and should be revised as more information becomes available in later development stages.
- Nanomaterial Quality Attributes and Structural Characterization – The physical and chemical attributes of the nanomaterial that are essential to product quality (critical quality attributes, or CQAs) should be determined, specifically as they relate to its function and potential impact on product performance. CQAs are likely to be specific to each product and nanomaterial; thus, the manufacturer should determine which attributes are relevant and justify their characterization. When nanomaterials are added as inactive ingredients, or excipients, the properties of the excipient should be determined based on its intended function. Issues of stability specific to nanoparticles should also be considered. The suitability of physicochemical methods used to complete the characterization should be assessed, demonstrated, and justified. Characterization methods should also account for sample size, preparation and potential interactions of the analytical equipment with the nanomaterial.
- Dissolution/In Vitro Drug Release Methods for Quality Testing – These methods are used to determine how the manufacturing and formulation of the drug product will impact the release and dissolution of the drug product, which contribute to the clinical performance of the product. It may be necessary for manufacturers to develop their own methods for their product, but the FDA is open to consultations with industry.

- Manufacturing and In-Process Controls – Due to the dynamic and expanding uses of nanomaterials in drug products, there is not a comprehensive body of knowledge regarding the effect of nanomaterial attributes and their effect on manufacturing practices. It is important that industry thoroughly assesses its products and manufacturing process to enable the building of this knowledgebase, as well as be aware of risk factors that may arise because of chemistry, manufacturing, and controls (CMC) changes.

The guidance also provides considerations for nonclinical studies, which include:

- Absorption, Distribution, Metabolism, and Excretion – The inclusion of a nanomaterial in a drug product may impact the human body in unpredictable ways. The stability and biocompatibility of the nanomaterial in human plasma and blood, as well as the metabolism and clearance of the nanomaterial should be determined. The possibility of the nanomaterial eliciting an immune response should also be considered.
- Specific Routes of Administration – There are potential risks that are specific to the way in which the nanomaterial-containing product is administered (topically, subcutaneously, orally, etc.). Route-specific risks should be considered as applicable to the product.
- Testing of Representative Nanomaterial – The nanomaterial being tested should be made reproducible and representative of the product to which humans will be exposed.
- Bridging Toxicology from a Drug Product without Nanomaterials to a Drug Product Containing Nanomaterials – When a previously-approved drug is modified to include a nanomaterial, industry should consider the potential impacts the nanomaterial may have on the drug's biodistribution and toxicity.

When seeking approval of a new drug product containing nanomaterials, industry may pursue:

- A 505(b)(2) submission if they wish to create a new dosage form of an existing drug by incorporating a nanomaterial, for example, and bridge the performance of this new drug to that of a reference drug. The guidance recommends industry apply a risk-based approach, considering whether the nanomaterial is an active ingredient and what effect the nanomaterial will have on pharmacokinetics-pharmacodynamics (PK-PD);
- A 505(j) submission for approval of a generic product to demonstrate that the new drug product containing nanomaterials is identical to the previously approved brand-name drug product containing nanomaterials;
- Or a 351(k) submission to demonstrate that the new drug product is biosimilar to a reference biological product containing nanomaterials.

Finally, environmental impacts of drug products containing nanomaterials should be considered. Applicants must submit an assessment of environment impact or claim an exclusion to this assessment, which the FDA will review on a case-by-case basis.

RELEVANT SCIENCE

While a universal definition does not exist, scientists generally consider materials that are 100 nanometers (nm) or less—each nanometer being one-billionth of a meter—as nanomaterials. At this size range, a material's surface area to volume ratio increases and electrons can become spatially confined, both of which can result in new physical or chemical properties. Companies may incorporate a nanomaterial into a drug product for a variety of reasons: to serve as an active ingredient or to promote product delivery without the nanomaterial directly providing any therapeutic benefit.

Nanotechnology is a rapidly evolving field that is revolutionizing therapeutic capabilities. Some drug products utilizing nanotechnology are already available, such as chemotherapy drugs Doxil and Abraxane, and many other medical applications of nanomaterials are being developed. For example, researchers at University of Colorado Boulder are investigating the use of light-activated quantum dots to treat antibiotic-resistant infections. To provide another example, nanomedicine company, CytImmune, is using gold nanoparticles to deliver chemotherapy drugs directly to cancer cells. The platform, called Aurimune, successfully completed a phase I clinical trial in 2009. The company is gearing up for a phase II clinical trial with Aurimune and is in preclinical trials with a second-generation therapy, which incorporates Taxol, a small molecule chemotherapy.

The Aurimune platform is designed to target tumor necrosis factor (TNF), a cancer-killing agent, to the site of a tumor without it being toxic to the patient. The therapy capitalizes on the fact that tumor blood vessels are inherently leaky, while healthy blood vessels are not. This difference in blood vessel integrity results in higher accumulation of the nanomedicine in tumor tissue over regular tissue, a concept called the enhanced permeability and retention (EPR) effect. Traveling through healthy blood vessels, the gold nanoparticles are too large to escape, reducing toxic side effects. However, the nanoparticle can leak through leaky vessels associated with its target, tumors. Because the precise size of the nanoparticle determines how effectively the nanoparticles reach their target and distribute in the body, consistency in manufacturing is important.

To prevent the nanoparticle from being attacked by the immune system, the company utilizes a Trojan horse strategy in which the gold nanoparticle is surrounded by a shell of thiol-derivatized polyethylene glycol (PEG-thiol). The PEG-thiol absorbs water, creating a barrier around the nanoparticle and preventing immune detection. Although the PEG improves delivery, its presence adds to the complexity of the nanomaterial-containing platform, and more attachments would boost the structure's complexity.

Regardless of its intended purpose as an active or inactive ingredient, the incorporation of a nanomaterial into a drug product may alter the properties of the product in a variety of ways, including how the drug is distributed or expelled from the body. There is a diversity of nanomaterial-containing products being developed, and these products often have properties that differ from their large-scale counterparts. Because of their extremely small size, nanomaterials may have enhanced rates of dissolution and higher bioavailability than products that do not contain nanomaterials. Additionally, nanomaterials interact with proteins in an individual's blood plasma, which can lead to new physicochemical properties in the body.

WHY IT MATTERS

The ability of the FDA to establish clear guidelines for the development of increasingly complex drugs will be critical for ensuring that regulation is able to keep up with technological advancements. The FDA does not categorically define products containing nanomaterials as inherently *benign* or *harmful*, but rather considers the characteristics of each product when determining its safety for use. Therefore, the FDA requires thorough and comprehensive analyses of new drug products containing nanomaterials.

Nanotechnology is a growing field, and it is likely to continue expanding. Since fiscal year 2001, the United States National Nanotechnology Initiative (NNI) has invested more than $25 billion to support nanotechnology research and development (R&D). The number of submissions to the FDA for drug products containing nanomaterials has grown from less than five in 1990 to more than twenty in 2015, and this number is projected to grow.

Currently, a fundamental limitation in the development of nanomedicine is the lack of knowledge regarding interactions between nanomaterials and biological systems. Continuous and rigorous studies of new drug products containing nanomaterials will help fill these gaps. For example, this guidance documents helps manufacturers to identify how their nanomaterials should be studied, and how to apply these studies throughout developmental stages. Filling in the gaps will help the FDA and industry evaluate nanomaterials-containing drug products, reduce the complexity of New Drug Applications, and contribute to a knowledgebase for both stakeholders to use.

RELEVANT EXPERTS

Mark R. Wiesner, PhD, James P. Duke Professor and Chair of the Department of Civil and Environmental Engineering at Duke University. His research interests include nanomaterials and their fate in the environment.

Christine Ogilvie Hendren, Ph.D., Executive Director of the Center for the Environmental Implications of NanoTechnology (CEINT) Duke University, Research Scientist Duke University.

BACKGROUND

While the FDA has not established regulatory definitions for "nanomaterial" or related terms, the FDA considers two factors when determining if a product is categorized as utilizing nanotechnology: whether the material has an external dimension of 1-100 nm and whether the material is engineered to behave in a way that is attributable to its dimensions, even if these dimensions are outside of the 1-100 nm range, up to one micrometer (1,000 nm).

Nanomaterials have many applications in pharmaceuticals, consumer goods, electronics, and even environmental remediation. Despite these useful applications, the potential effects of nanomaterials on human health and the environment are not well understood. The FDA's Center for Drug Evaluation and Research (CDER) regulates over-the-counter and prescription drugs, including those containing nanomaterials. Over the past several years has worked to understand the properties of nanomaterials used in drug products. In June 2014, the FDA issued a guidance document to industry (noticed via 79 FR 36534) with information to determine whether an FDA-regulated product involves the application of nanotechnology. The recommendations of the December 2017 draft guidance discussed herein are in line with the FDA's nanotechnology considerations guidance of June 2014.

The FDA is requesting public comments on the draft guidance, due by March 19, 2018, as well as comment on the terminology used in the draft guidance, such as the term "nanomaterial."

ENDORSEMENTS & OPPOSITION

The Nanotechnology Industries Association (NIA), an international association serving members in the nanotechnology field, seeks to "support regulators and policymakers." They feel this mission is accomplished through transparency, collaboration and sharing of industry perspectives on issues relating to nanotechnology, which fosters effective regulation that should allow nanotech advancements to reach consumers in a safe and efficient manner.

No opposition has been published about this subject by nanomaterials scientists or industry leaders.

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RECOMMENDED CITATION

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