PROGRESS AND PLANS OF NATIONAL NANOTECHNOLOGY INITIATIVE (NNI) AGENCIES

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Department of Health and Human Services (HHS)

Food and Drug Administration (FDA)[1]

Summary

The Food and Drug Administration continues to invest in nanotechnology research to help address questions related to the safety, effectiveness, quality, and/or regulatory status of products that contain engineered nanomaterials (ENMs) or otherwise involve the use of nanotechnology; develop models for safety and efficacy assessment; and study the behavior of nanomaterials in biological systems and their effects on both human or non-human animal health. These investments continue to support FDA's mission to protect and promote public health and help support the responsible development of nanotechnology.

The FDA Office of the Commissioner, in partnership with the FDA Nanotechnology Task Force (NTF), continues to facilitate communication and cooperation across the agency on nanotechnology research, both within FDA and with national and international stakeholders. The NTF provides the overall coordination of FDA's nanotechnology research efforts in the following programmatic investment areas: (1) scientific staff development and professional training, (2) laboratory and product-testing capacity, and (3) collaborative and interdisciplinary nanotechnology research. In 2019, FDA actively participated in the informal interagency interest group on nanoplastics, where scientists from over 20 Federal agencies shared interest, research, and resources available to advance the understanding of this emerging global issue.

As needed and appropriate, FDA continues to foster and develop collaborative relationships with other Federal agencies through participation in the NNI and the Nanoscale Science, Engineering, and Technology Subcommittee of the National Science and Technology Council, as well as with regulatory agencies, healthcare professionals, industry, consumers, and other stakeholders. Most recently, the NTF has increased its international outreach, with the goal of strengthening global regulatory research efforts aimed at the development of novel characterization/measurement tools and consensus standards. In September 2019, FDA co-organized the Global Summit on Regulatory Science (GSRS19) on Nanotechnology and Nanoplastics, in collaboration with the Joint Research Centre of the European Commission, in Stresa, Italy. Regulators and stakeholders from over 30 countries participated in the summit to identify research gaps and priorities in regulatory science for nanotechnology and nanoplastics, and to facilitate collaboration and harmonization across the globe. These meetings allow for information to be exchanged efficiently and serve to identify research needs related to the use of ENMs in FDA-regulated products.

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Plans and Priorities by Program Component Area (PCA)

PCA 5. Environment, Health, and Safety

FDA's Center for Drug Evaluation and Research (CDER) drafts product-specific guidances (PSGs) for drug products containing nanomaterials.

- These guidances describe the agency's current thinking and expectations on how to develop generic drug products therapeutically equivalent to specific reference listed drugs.
- Drug products containing nanomaterials fall under CDER's definition of "complex products."
- In 2019, a new guidance entitled *Draft Guidance for Fish Oil; Medium Chain Triglycerides; Olive Oil; Soybean Oil IV Emulsion,* was published.[2]

The FDA Center for Biologics Evaluation and Research (CBER) continues to develop highly sensitive diagnostic assays for detection of viral antigens, antibodies, and nucleic acids in an enzyme-linked immunosorbent assay (ELISA), microarray, and microfluidics point-of-care format.

FDA's National Center for Toxicological Research (NCTR) and Office of Regulatory Affairs (ORA) continue to invest in advanced tools, safety assessment, staff training, standards methods, and methodology development to better understand emerging issues with nanomaterials in FDA-regulated products.

Key Technical Accomplishments by NNI Goal

Goal 1. Advance a World-Class Nanotechnology Research and Development Program

The FDA Center for Devices and Radiological Health (CDRH) continues to conduct research to addresses fundamental data gaps and challenges associated with safety assessment of medical devices containing nanomaterials. Research efforts have been focused on evaluating and refining biological test methods to address assay interferences during genotoxicity and cytotoxicity tests, as well as investigating the interaction of pulsed lasers with plasmonic nanoparticles used in emerging optical diagnostic and therapeutic products such as targeted cancer phototherapy, photoacoustic molecular imaging of cancer, and combined theranostics.

In addition, CBER has utilized nanosensors to develop novel and sensitive diagnostic assays for human immunodeficiency virus (HIV), influenza, West Nile virus (WNV), dengue virus, and Zika virus.[3] Additionally, CBER is exploring the use of nanoparticles to track cell therapies *in vivo*.

NCTR continues to conduct collaborative regulatory science research on the advanced characterization, safety, and biodistribution of nanomaterials in FDA-regulated products. The critical scientific data and information generated from this research helps FDA to ensure the safety of FDA-regulated products containing nanomaterials. This information is also utilized in staff training and development, as well as standards development.

ORA continues to conduct collaborative research to develop analytical methods for the characterization of nanomaterials in FDA-regulated products. Such methods will enable FDA to identify potential risks associated with products that contain nanomaterials through pre- and post-market oversight and

[2] https://www.accessdata.fda.gov/drugsatfda_docs/psg/Fish%20oil;%20Medium%20chain%20triglycerides;%20Olive%20oil;%20Soybean%20oil%20NDA%20207648%20Feb%202019.pdf

[3] https://www.ncbi.nlm.nih.gov/pubmed/29528198

determine problems that can impact product safety. Additionally, these regulated methods will provide guidance to sponsors/reviewers for the future approval of products.

Goal 2. Foster the Transfer of New Technologies into Products for Commercial and Public Benefit

CDER has worked over the past several years to understand the properties of nanomaterials as they are used in drug products to inform and ensure the development of a regulatory framework that appropriately assesses the impact of their unique physical properties on quality, safety, and efficacy for both new and generic drug products. Current research programs are focused in the areas of quality considerations for complex drug products, bioequivalence of drug products containing nanomaterials, and advanced and emerging characterization methods. CDER has collaborated with the FDA Advanced Characterization Facility (ACF) at CDRH and the Nanotechnology Core Facility located in Jefferson, Arkansas, to perform physicochemical characterization and *in vitro* release test of complex drugs to advance the development of product-specific guidances.

Because the use of traditional animal studies to test toxicity of all novel nanomaterials is cost-prohibitive, CDRH has worked towards developing and optimizing a microfluidic-based multi-organ model to better mimic the natural tissue environment in the body and enable better predictions of clinical outcomes of medical products containing nanomaterials. Compared to traditional biocompatibility assessment using two-dimensional cell culture systems, this approach will allow FDA staff to better understand the complex interactions that occur between the body's physiological processes and various types of engineered nanomaterials. Knowledge gained from this research has allowed FDA to better assess the safety and efficacy of medical products incorporating this novel technology, for premarket review, postmarket assessment, and guidance development.

Goal 4. Support Responsible Development of Nanotechnology

FDA collaborates with domestic and international regulatory and research agencies to share information on the state of science, guidance documents, and regulatory research experiences. Some of the venues for this dialogue include the Global Coalition for Regulatory Science Research (GCRSR) Nanotechnology Working Group, the International Pharmaceuticals Regulators Program (IPRP) Nanomedicines Working Group, and the US-EU Communities of Research facilitated through the U.S. National Nanotechnology Coordination Office and the European Commission.

FDA also co-organized a 2018 workshop in India on Nanotechnology Regulatory Science, with sponsorship from the Indo-US Science and Technology Forum, to share FDA's guidance documents, research, and regulatory perspective on medical products containing nanomaterials. This workshop is one of the action items that resulted from a US-India Science and Technology Joint Committee Meeting organized with the White House Office of Science and Technology Policy. A successful outcome from this activity with the Indian Central Drug Standards Control Organization and Department of Biotechnology was the release of a revised draft guidance document by the Indian government on "Guidelines for Evaluation of Nanopharmaceuticals in India" in February 2019.[4]

Standards Development

The FDA NTF established a subcommittee on nanotechnology standards. The goals of the subcommittee are to prioritize nanotechnology standards based upon agency needs; assist in the development of standards;

[4] http://dbtindia.gov.in/sites/default/files/uploadfiles/Guidelines_For_Evaluation_of_Nanopharmaceuticals_in_India_24.10.19.pdf

and consolidate FDA comments for nanotechnology standards for review. The subcommittee actively participates in ASTM E56 (Nanotechnology), and ISO TC 229 (Nanotechnologies). In addition, members of the subcommittee serve as FDA liaisons to relevant working groups in United States Pharmacopeia (USP) and the Organisation for Economic Co-operation and Development (OECD).

The use of documentary standards can increase predictability, streamline premarket review, and facilitate market entry and use of safe and effective products. CDRH actively assesses the impact of published consensus nanotechnology standards on the premarket review process and recognizes these standards. In 2019, CDRH added five ASTM E56 standards and four ISO TC 229 standards to its list of recognized consensus standards for nanotechnology, bringing the total number of standards adopted for the use of nanotechnology in medical devices to fourteen. NCTR is actively contributing to consensus standards in nanotechnology, in collaboration with the National Toxicology Program and other academic and industry stakeholders. In 2019, a total of seven work items were proposed through the ASTM E56-08 subcommittee on Nano-enabled Medical Products. One *in vitro* test method is finalized through the consensus process and is slated to be published as a standard in early 2020.