PROGRESS AND PLANS OF NATIONAL NANOTECHNOLOGY INITIATIVE (NNI) AGENCIES

March 2019

Department of Health and Human Services (HHS)[1]

Food and Drug Administration (FDA)

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, Office of the Chief Scientist, 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.

As needed and appropriate, FDA continues to foster and develop collaborative relationships with other Federal agencies through participation in the National Nanotechnology Initiative 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 efforts, with the goal of strengthening global regulatory research efforts aimed at the development of novel characterization/measurement tools and consensus standards. These collaborations allow 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) has developed a "Guidance for Industry: Liposome Drug Products."

- The document was published in final form in fiscal year 2018.[2]
- Liposomes are the most common form of nanomaterial seen in drug products.

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.
- CDER has revised the PSG for doxorubicin HCl liposome injection.[3]

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

FDA continues to participate in the development of the Nanotechnology for Sensors and Sensors for Nanotechnology Signature Initiative (NSI). The FDA Center for Devices and Radiological Health (CDRH) participated in developing this NSI topic with the goal to support better communication with the *in vitro* diagnostics (IVD) community about the importance of interacting with FDA early in the development process. With this goal in mind, CDRH provided links and information about sensor development for IVDs.[4]

Furthermore, CDRH is conducting research to addresses fundamental data gaps and challenges associated with the physico-chemical characterization and safety assessment of nano-objects (nanoparticles) and immobilized surface nanostructures incorporated into medical devices. Research efforts have been focused on evaluating and refining biological test methods for nanoparticle interactions, including genotoxicity and cytotoxicity, and in assessing the toxicologic risk of nanoparticles associated with medical devices.

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.[5] Additionally, CBER is exploring the use of nanoparticles to track cell therapies *in vivo*.

NCTR is conducting collaborative regulatory science research on the advanced characterization, safety, and biodistribution of nanomaterials in FDA-regulated products. The critical scientific data and information

[2] https://www.fda.gov/media/70837/download

[3] https://www.accessdata.fda.gov/drugsatfda_docs/psg/Doxorubicin%20Hydrochloride_draft_Injection%20injec%20lipo_RLD%2050718_RC09-18.pdf

[4] http://www.nano.gov/sites/default/files/sapsford_nsi_webinar_nov_2015_slides_with_captions_final.pdf

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

generated through 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 determine problems that can impact product safety. Additionally, these regulated methods will provide guidance to sponsors/reviewers for 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 in the areas of quality considerations for complex drug products, bioequivalence of drug products containing nanomaterials, and advanced and emerging characterization methods.

CDRH has continued to conduct nanotechnology research to better understand the complex interactions that occur between the body's physiological processes and various types of nanoengineered surfaces. 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.

CDRH nanotechnology research also has resulted in meaningful FDA-related contributions to ASTM and International Organization for Standardization (ISO) standards. In 2018, CDRH added four ASTM E56 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 eight.

Goal 4. Support Responsible Development of Nanotechnology

In December of 2017, FDA announced the availability of its draft guidance on “Drug Products, Including Biological Products, that Contain Nanomaterials” for public comment.[6] The guidance was open for public comments, and revision of the draft guidance is ongoing per normal FDA procedures and timelines. FDA collaborates with domestic and international regulatory and research agencies to share information on the state of science, guidance documents, and regulatory research experience. Some of the avenues 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 on Nanotechnology Regulatory Science through the Indo-US Science and Technology Forum sponsorship, in India, to share FDA’s guidance documents, research, and regulatory perspective on medical products containing nanomaterials. This workshop is one of the action item that resulted from the US-India Science and Technology Joint Committee Meeting organized with the White House Office of Science and Technology Policy. A successful outcome of this activity with the Indian

[6] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM588857.pdf

Central Drug Standards Control Organization and Department of Biotechnology is the release of a revised draft guidance document by the Indian government on “Guidelines for Evaluation of Nanopharmaceuticals in India” in February 2019.