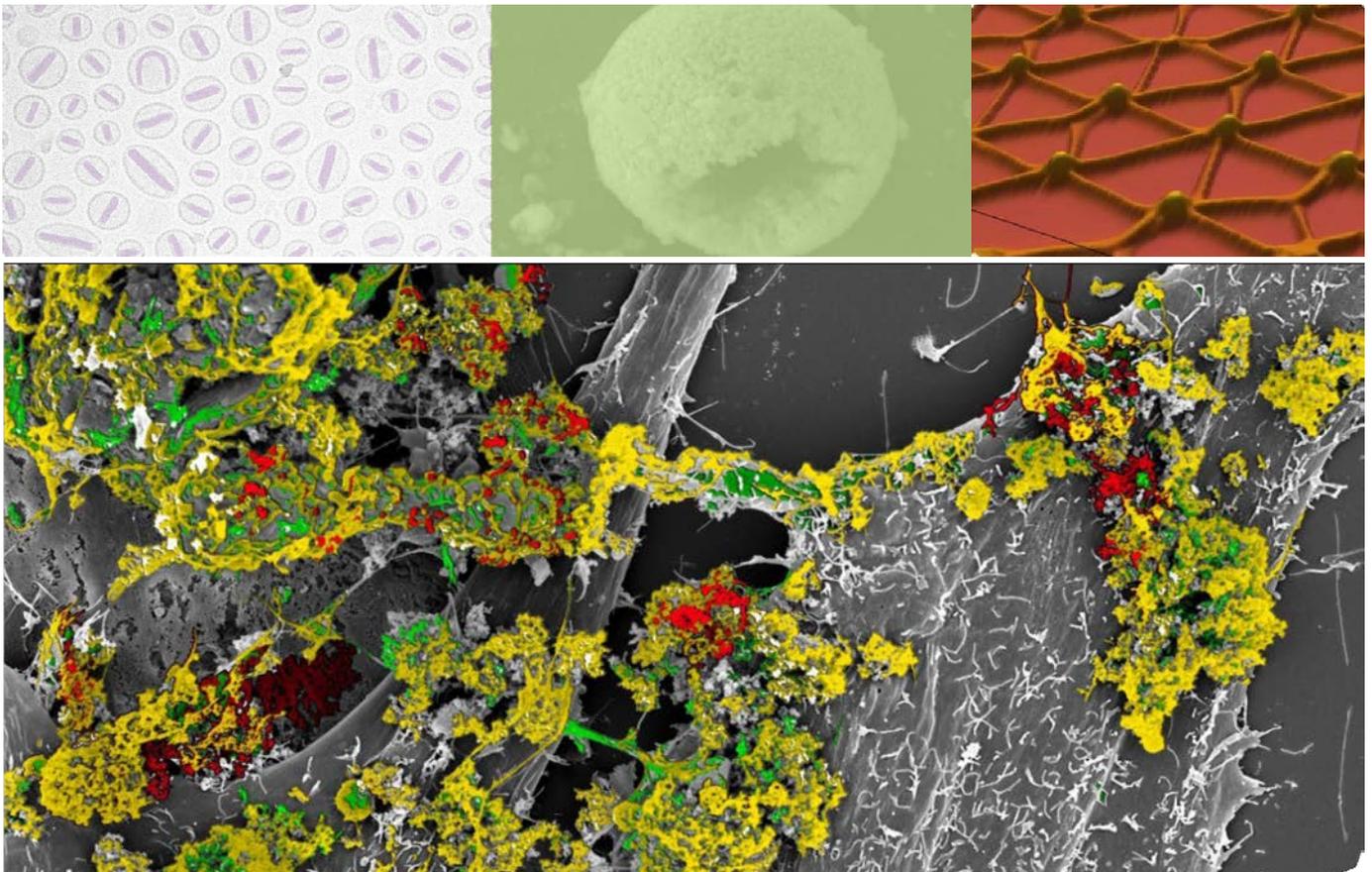


Nanotechnology—Over a Decade of Progress and Innovation

A REPORT BY THE U.S. FOOD AND DRUG ADMINISTRATION

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I. Executive Summary

According to the National Nanotechnology Initiative,¹ nanotechnology² includes the control of matter at the nanoscale, where unique phenomena and unusual properties enable novel applications. The creation of the [National Nanotechnology Initiative](#) (NNI) in the year 2000, jump-started research and development investments by U.S. government agencies in nanotechnology, resulting in significant advances in this field and enabling novel solutions to complex problems.

Anticipating an increase in the submissions to FDA of products that involve the application of nanotechnology, the then-Acting Commissioner of the Food and Drug Administration (FDA) launched the Nanotechnology Task Force (NTF) in 2006 to help assess FDA's regulatory authorities concerning the current state of the science for nanotechnology. The NTF released a comprehensive [public report in 2007](#) highlighting its findings and recommendations to the Commissioner. Since the release of this report, FDA has seen a gradual increase in the number of submissions for products containing nanomaterials submitted for regulatory review.

With a dedicated nanotechnology budget, FDA has continued to strengthen our research infrastructure by establishing two core facilities to support nanotechnology regulatory science research and to build scientific expertise and capacity. FDA has conducted internal research on advanced physico-chemical characterization, in vitro biocompatibility, and in vivo safety studies to ascertain the critical quality attributes of nanomaterial, and to prepare FDA scientists and reviewers for the emerging products.

Additionally, FDA has increased collaboration with external domestic and international stakeholders to:

- anticipate emerging challenges;
- build and share regulatory science knowledge;
- facilitate innovation; and
- coordinate policy to fulfill FDA's mission.

FDA has also increased its participation in the development and use of both national and international documentary nanotechnology standards. It has issued several guidance documents for industry to offer FDA's current thinking on the subject and provide advice, including advice relevant to determining the regulatory status of nanotechnology products and evaluating their safety. The strengthening of FDA's

¹<https://www.nano.gov/nanotech-101/what>

² FDA has not established regulatory definitions of "nanotechnology," "nanomaterial," "nanoscale," or other related terms. However, for the purpose of this update, when describing FDA's activities, we use the terms "nanotechnology," "nanomaterial," and "nanotechnology product" to refer to examples that would generally fall within the two points for considering whether an FDA-regulated product involves the application of nanotechnology articulated in the Agency's guidance for industry, *Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology*, which are further discussed in Section III.A. below.

research infrastructure has enabled the Agency to make a significant contribution to public knowledge in this area, as evidenced by the publication of hundreds of peer-reviewed articles.

This report highlights FDA's advancements in the field of nanotechnology since it released its last report in 2007,³ and its role in advancing the public health through its regulation of products within its jurisdiction that involve the application of nanotechnology. Moving forward, FDA will continue to:

- monitor scientific and technological advancements and convergence of emerging technologies with nanotechnology;
- support standards development through stakeholder involvement;
- collaborate with other agencies through NNI;
- conduct regulatory science research to understand the science to advance public health and make resulting information available to the public; and
- support innovative development of beneficial nanotechnology products.

³ <https://www.fda.gov/science-research/nanotechnology-programs-fda/nanotechnology-task-force-report-2007>

II. Introduction

The U.S. Food and Drug Administration (FDA) is responsible for protecting the public health by ensuring the safety, effectiveness, quality, and security of human and animal drugs, vaccines as well as other biological products, and medical devices. FDA is also responsible for the safety of most of our nation's food supply, as well as cosmetics, and products that emit radiation. Additionally, FDA regulates tobacco products.

Nanotechnology, which involves the engineering and control of matter at small dimensions, has potentially beneficial applications in a wide range of FDA-regulated product categories. As nanotechnology products continue to evolve, such as moving from simple systems to highly complex, multi-component, multi-functional materials, so do FDA's efforts to understand the science and advance public health by supporting innovation for developing beneficial nanotechnology products.

FDA anticipates that nanotechnology may play a critical role in the design, development, and manufacture of next-generation products – including drugs, medical devices, and foods. While many basic questions and assumptions have been addressed, and many best practices and standards concerning nanotechnology applications have been established and continue to be updated by the scientific community, it is critical that FDA develop an advanced understanding of new nanomaterials in the emerging products from a safety, efficacy, and physicochemical characterization perspective to fulfill our mission to protect and promote public health.

A. The Current State of Nanomaterials Science and Nanotechnology

Since our last report in 2007, rapid advancements in fields such as life sciences, engineering, and medicine have increased our knowledge and understanding of nanotechnology and its current and potential applications in FDA-regulated products. Nanotechnology has also converged with other fields, such as biotechnology, which has the potential to improve our understanding of biosystems at the molecular level, and make possible the discovery of innovative solutions to unmet health needs. Such advances are reflected in the diversity, complexity, and volume of products included in regulatory submissions for FDA review.

For example, since 1970, FDA's Center for Drug Evaluation and Research (CDER) has received more than 600 applications (investigational new drug (IND), new drug application (NDA), and abbreviated new drug application (ANDA)) for human drug products containing nanomaterials – half of which were submitted within the last 10 years.⁴ Figure 1 shows the submission trend of drug products containing nanomaterials submitted to CDER over the years.

⁴ D'Mello S et al. FDA/CDER analysis of drug products containing nanomaterials, *Nature Nanotechnology* 12(6) 523-529 (2017).

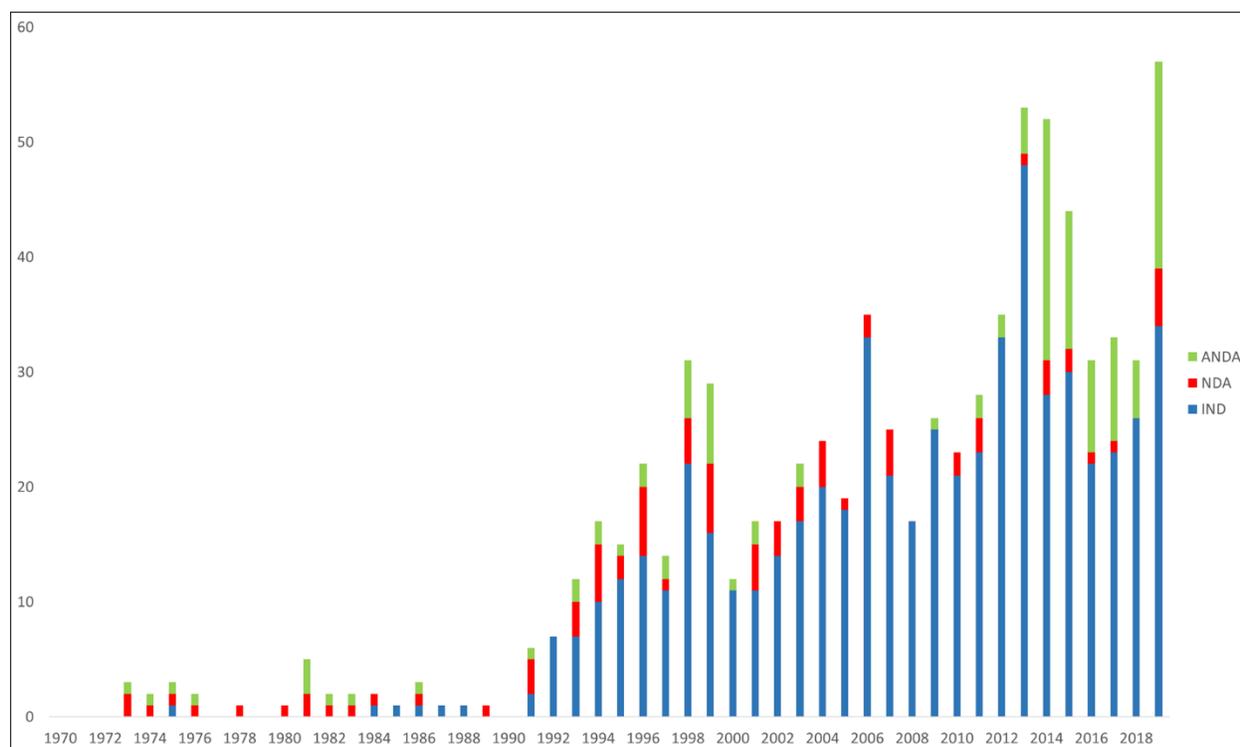


Figure 1: Human drug product submissions to FDA containing nanomaterials between 1970-2019.

FDA is also aware of research into the use of nanomaterials in animal drugs. FDA's Center for Veterinary Medicine (CVM) has approved a few new animal drug applications for animal drugs that use nanotechnology. Due to this technology's diverse advantages, FDA's Center for Devices and Radiological Health (CDRH) has also seen an increase in the number of premarket notifications (510(k)) and premarket approval applications (PMA) that specify the incorporation of discrete nanoparticles or use of nano-engineered surfaces with specific performance claims, ranging from antimicrobial activity to enhanced cell proliferation and tissue integration.

There have also been scientific advances that show promise for the development or analysis of nanotechnology-derived products in foods (including dietary supplements) and cosmetics; FDA encourages stakeholders to consult with the Agency when exploring use of new technologies in such submissions. For example, FDA's Center for Food Safety and Applied Nutrition (CFSAN) is conducting research to ensure that FDA scientists are ready to address new challenges that may arise when reviewing future applications of nanotechnology to CFSAN-regulated products.

The Office of Regulatory Affairs (ORA), continues to conduct collaborative research to develop analytical methods for detecting and characterizing nanomaterials in FDA-regulated products. Such methods will enable FDA to identify potential risks associated with products that contain nanomaterials through pre- and postmarket oversight. Once

validated, these methods can be useful to sponsors and reviewers for future approval of products.

Additionally, FDA's National Center for Toxicological Research (NCTR) is carrying out research to help FDA better understand novel scientific issues associated with nanomaterial use. This research informs the work of FDA reviewers who evaluate the safety of nanotechnology-based products and is incorporated into internal FDA training programs to share information about nanotechnology and nanotechnology applications in FDA-regulated products with Agency scientists.

B. FDA's Nanotechnology Task Force Report and Progress

In 2006, FDA initiated a process to improve its scientific knowledge of nanotechnology to ensure that FDA scientists were prepared to address regulatory challenges that nanotechnology products may present. FDA created a nanotechnology task force (NTF) charged with identifying regulatory approaches that encourage the continued development of innovative, safe, and effective FDA-regulated products that use this technology, and to identify and recommend ways to address knowledge or policy gaps to enable FDA to evaluate innovative products and protect the public health.

In 2007, the NTF issued a report that found that nanotechnology use presents regulatory challenges like those posed by products using other emerging technologies. It made several recommendations for FDA action on scientific and regulatory policy issues concerning nanotechnology to further our mission to protect and promote public health.⁵

In the years since this report was issued, our understanding of different nanomaterials and their interactions with biological systems, as well as specific approaches for assessing safety and quality of nanotechnology products, has greatly increased. FDA continues to use a science-based, flexible, product-focused regulatory approach that considers the effects of nanomaterials in the specific biological and mechanical context of each product and its intended use. In developing our approach to ensuring our readiness to evaluate this technology, FDA has also prioritized training staff, building research capacity and infrastructure, and forging partnerships to strengthen our regulatory science research capabilities.

FDA collaborates with and leverages the work of other federal agencies, academic institutions, and international regulatory counterparts on important issues, such as characterization of nanomaterials and standards development. FDA has also worked to help provide our stakeholders with additional clarity about the Agency's current thinking

⁵ Nanotechnology – A Report of the U.S. Food and Drug Administration Nanotechnology Task Force, July 25, 2007 (Available at: <https://www.fda.gov/science-research/nanotechnology-programs-fda/nanotechnology-task-force-report-2007>).

on regulatory issues through guidance documents, and has worked to develop procedures to ensure consistency in our product reviews.

FDA is issuing this update⁶ to discuss these and other efforts we have taken to advance nanotechnology science and policy since the 2007 NTF report, including those aligned with recommendations of that report. FDA has made great progress in its efforts to better understand nanotechnology applications in FDA-regulated products. This will help to ensure that FDA continues to be prepared to effectively and efficiently evaluate emerging and evolving technologies and ensure the safety, quality, and efficacy of the products we regulate.

III. Science-Based, Product-Focused Regulatory Policy for Nanotechnology

As part of our implementation of the 2007 report, FDA has clarified our regulatory approach to nanotechnology products and has issued guidance for industry.

FDA does not categorically judge nanotechnology products as intrinsically benign or harmful. Rather, by applying a science-based, product-focused regulatory policy, FDA regulates nanotechnology products under existing statutory authorities, in accordance with the specific legal standards applicable to each type of product under the Agency's jurisdiction. This approach enables FDA to consider any unique properties and behaviors that the use of nanotechnology may impart as part of its evaluations of a product's safety, effectiveness, public health impact, or regulatory status. In addition, recognizing that FDA's statutory authorities vary among different product categories, this flexibility enables FDA to tailor its approach to reflect the characteristics of specific products, considering the biological or, where applicable, mechanical context relevant to the product's intended use.

Other key attributes of FDA's policy approach include encouraging industry to consult with the Agency early in product development to identify and address any questions of safety or regulatory status; actively communicating with the public to share information and seek input; and collaborating with domestic and international counterparts to advance regulatory science and cooperation.⁷

A. Guidance for Industry

FDA has issued guidance for industry to offer advice, including advice to determine the regulatory status of nanotechnology products and evaluating their safety. While guidance documents provide recommendations that are not binding, they are a valuable tool for FDA to communicate our current thinking on a topic, and can help provide

⁶ This document is intended to inform stakeholders of FDA's nanotechnology science and policy development work; it is not intended to provide guidance or recommendations, or establish new policy.

⁷ FDA's Approach to Regulation of Nanotechnology Products, last updated March 23, 2018 (Available at: <https://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm301114.htm>).

additional clarity for our stakeholders. To date, FDA has issued five final guidance documents and one that is currently in draft form. Each of these was developed with stakeholder input that was received through a public docket and/or at public meetings.

- **Final Guidance for Industry: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology**⁸ – This guidance describes an overarching framework for FDA’s approach to the regulation of nanotechnology products and identifies two points to consider that are broadly applicable to all FDA-regulated products. When considering whether an FDA-regulated product involves the application of nanotechnology, FDA will ask:
 - 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); and
 - 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).

We intend to apply these considerations broadly to all FDA-regulated products. An affirmative finding to either of the points to consider might suggest the need for FDA’s and/or industry’s particular attention to the product to identify and address potential implications for its safety, effectiveness, public health impact, or regulatory status.

- **Final Guidance for Industry: Safety of Nanomaterials in Cosmetic Products**⁹ – This guidance describes FDA’s current thinking on the safety assessment of nanomaterials in cosmetic products. The guidance explains that, in general, the principles for assessing the safety of cosmetics also apply to cosmetics containing nanomaterials. However, data needs and testing methods should be evaluated considering the properties, behaviors, and/or effects that may be exhibited by nanomaterials used in cosmetic products.
- **Final Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact**

⁸ Final Guidance for Industry: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology, June 2014 (Available at: <https://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm>).

⁹ Final Guidance for Industry: Safety of Nanomaterials in Cosmetic Products, June 2014 (Available at: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-safety-nanomaterials-cosmetic-products>).

Substances, Including Food Ingredients that are Color Additives¹⁰ – This guidance informs manufacturers of the potential impact of a significant manufacturing process change, including one involving nanotechnology, on the safety and regulatory status of food substances. This guidance describes the factors that manufacturers should consider when determining whether a significant change in manufacturing process for a food substance already in the market affects: the identity of the food substance; the safety of the use of the food substance; and the regulatory status of the use of the food substance; and whether this change warrants a regulatory submission to FDA.

- **Final Guidance for Industry: Use of Nanomaterials in Food for Animals**¹¹ – This guidance addresses the legal framework for adding substances to food for animals and includes recommendations for submitting a Food Additive Petition (FAP) for a nanomaterial animal food ingredient. This guidance also recommends that manufacturers consult with FDA early in the development of their nanomaterial animal food ingredient and before submitting an FAP.
- **Final Guidance for Industry- Liposome Drug Products**¹² – This guidance discusses what types of information an applicant should submit in a new drug application (NDA) or abbreviated new drug application (ANDA) for a liposome drug product reviewed by CDER. The discussion involves chemistry, manufacturing, and controls; human pharmacokinetics, bioavailability, and/or bioequivalence; and labeling. This guidance is the first “class-specific” guidance on a particular type of nanomaterial. Liposomes comprise more than a third of the nanotechnology submissions CDER receives.
- **Draft Guidance for Industry – Drug Products, Including Biological Products, that Contain Nanomaterials**¹³ – This draft guidance, issued for public comment, discusses both general principles and specific considerations for developing drug products containing nanomaterials, including those products proposed in applications submitted pursuant to abbreviated approval pathways. The document discusses considerations for quality, nonclinical, and clinical studies as they relate to

¹⁰ Final Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that are Color Additives, June 2014 (Available at: <https://www.fda.gov/RegulatoryInformation/Guidances/ucm300661.htm>).

¹¹ Final Guidance for Industry: Use of Nanomaterials in Food for Animals, August 2015 (Available at: <https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM401508.pdf>).

¹² Final Guidance for Industry: Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation, April 2018 (<https://www.fda.gov/media/70837/download>)

¹³ Draft Guidance for Industry – Drug Products, Including Biological Products, that Contain Nanomaterials, December 2017 (Available at: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM588857.pdf>).

drug products containing nanomaterials throughout product development and production. The comment period ended on March 19, 2018, and FDA is reviewing public input received to determine what revisions may be necessary before issuing a final guidance document.

For additional information about FDA's guidance documents relevant to nanotechnology products please visit FDA's website.¹⁴

IV. Strengthening Regulatory Science Research in Nanotechnology

FDA's strategy for strengthening nanotechnology-related research relies on a robust framework that coordinates regulatory science activities across all FDA product centers. FDA's 2013 Nanotechnology Regulatory Science Research Plan lays out a framework and implementation plan to provide coordinated leadership on regulatory science activities on products that contain nanomaterials.¹⁵ The framework is designed to help FDA identify and address gaps in scientific knowledge, methods, or tools needed for regulatory decision-making. This work fosters the responsible development of FDA-regulated products that involve the application of nanotechnology by strengthening the research infrastructure to support nanotechnology regulatory science research; promoting cross-center coordination through a nanotechnology-specific intramural grants program; and building in-house scientific expertise and capacity to train our scientists to address data gaps and critical aspects of nanotechnology product reviews.

A. Strengthening Research Infrastructure for Nanotechnology

To support and facilitate regulatory science research involving nanotechnology and address regulatory challenges across all FDA product centers, FDA established two nanotechnology core facilities in 2011. One is located at [FDA headquarters](#) in Maryland, and the other at the [Jefferson Labs](#) in Arkansas. These core facilities were designed to:

- 1) provide FDA researchers with a centralized set of characterization tools and technical support to conduct nanotechnology-related research;
- 2) give FDA reviewers hands-on training in nanotechnology and materials characterization to bridge knowledge gaps in product review and regulatory science; and
- 3) conduct research on FDA-regulated products to address specific regulatory issues and establish the foundation for science-based decisions.

The nanotechnology core facility in Arkansas (NanoCore) is a joint effort by NCTR, FDA's Office of Regulatory Affairs Arkansas Laboratory (ORA/ARKL), and the U.S. Department of Health and Human Services National Toxicology Program (NTP). It

¹⁴ <https://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm602536.htm>

¹⁵ <https://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm273325.htm>

supports regulatory science research at NCTR and ORA and supports the work of other FDA centers, including CDER, CFSAN, and CDRH.

The NanoCore facility has advanced state-of-the-art equipment in spectroscopy, particle size, surface composition, stability analysis, and characterization, elemental analysis, microscopy, separation/fractionation, and chromatography to support the needs of NCTR and ORA/ARL investigators and research personnel who conduct analyses in nanotechnology (See [Appendix](#)).

The equipment housed in the NanoCore facility enables FDA to develop analytical methods to accurately monitor nanotechnology-based, FDA-regulated products to ensure safety, and, where appropriate, effectiveness. Key research that has been performed at the NanoCore/NCTR includes nanomaterial identification and characterization in FDA-regulated products; evaluation of sunscreens & their dermal penetration potential; pharmacokinetics, efficacy, and biodistribution studies to support in vivo and in vitro correlations; cellular- and geno-toxicity; and host resistance assays to determine the effects of bioaccumulation of nanoparticles.

For example, one significant study at NCTR, which is supported by the NTP, evaluated particulate and ionic forms of silver and silver particle size for differences in silver accumulation, distribution, morphology, and toxicity when administered daily by oral gavage to Sprague-Dawley rats for 13 weeks.¹⁶ Compared to rats exposed to silver acetate, rats exposed to silver nanoparticles showed: differences in the distributional pattern and morphology of silver deposits; significant dose-dependent and silver nanoparticle size-dependent tissue accumulations of silver; and significant sex differences in silver tissue accumulations.

The Advanced Characterization Facility at FDA's Maryland headquarters campus, includes many of the same state-of-the-art instruments seen in the Arkansas NanoCore Facility, and is available for use by on-site and visiting FDA scientists. The facility is operated and managed by members of the CDRH research team in the Office of Science and Engineering Laboratories. Work in the Advanced Characterization Facility focuses on developing and advancing the methods, tools, and approaches that will improve and enhance the evaluations of the physico-chemical characterization, safety, and efficacy of engineered nanomaterials in medical products. Research projects at the Advanced Characterization Facility are focused on four broad areas of investigation:

- 1) complex drug products and medical devices containing discrete nanoparticles, such as liposomes, emulsions, nanosilver and iron-oxide;
- 2) medical devices with immobilized surface nanostructures and topographies for orthopedic and dental implant applications;
- 3) genotoxicity assessment of nanomaterials using standard and alternative methods; and
- 4) developing provisional tolerable intake values for nanomaterials using toxicological risk assessment approaches.

¹⁶ Boudreau MD et al., *Differential Effects of Silver Nanoparticles and Silver Ions on Tissue Accumulation, Distribution, and Toxicity in the Sprague Dawley Rat Following Daily Oral Gavage Administration for 13 Weeks. Toxicological Science* 150(1) 2016.

B. CORES (Collaborative Opportunities for Research Excellence in Science) Intramural Grants Program

Regulatory science research in nanotechnology is inherently multidisciplinary, drawing from scientific disciplines such as chemistry, biology, and physics. Advances in multidisciplinary research have led to an increased number of products developed through applications of novel science and technology and products that include aspects regulated by multiple FDA product centers. As such, FDA believes that intramural collaboration is essential for addressing the increasingly complex regulatory landscape; understanding how these new technologies affect product safety, efficacy, and quality; and providing information to inform development of regulatory policy relevant to these innovations. To address these needs and foster cross-cutting research activities in nanotechnology, FDA developed the competitive CORES intramural grants program in 2010.

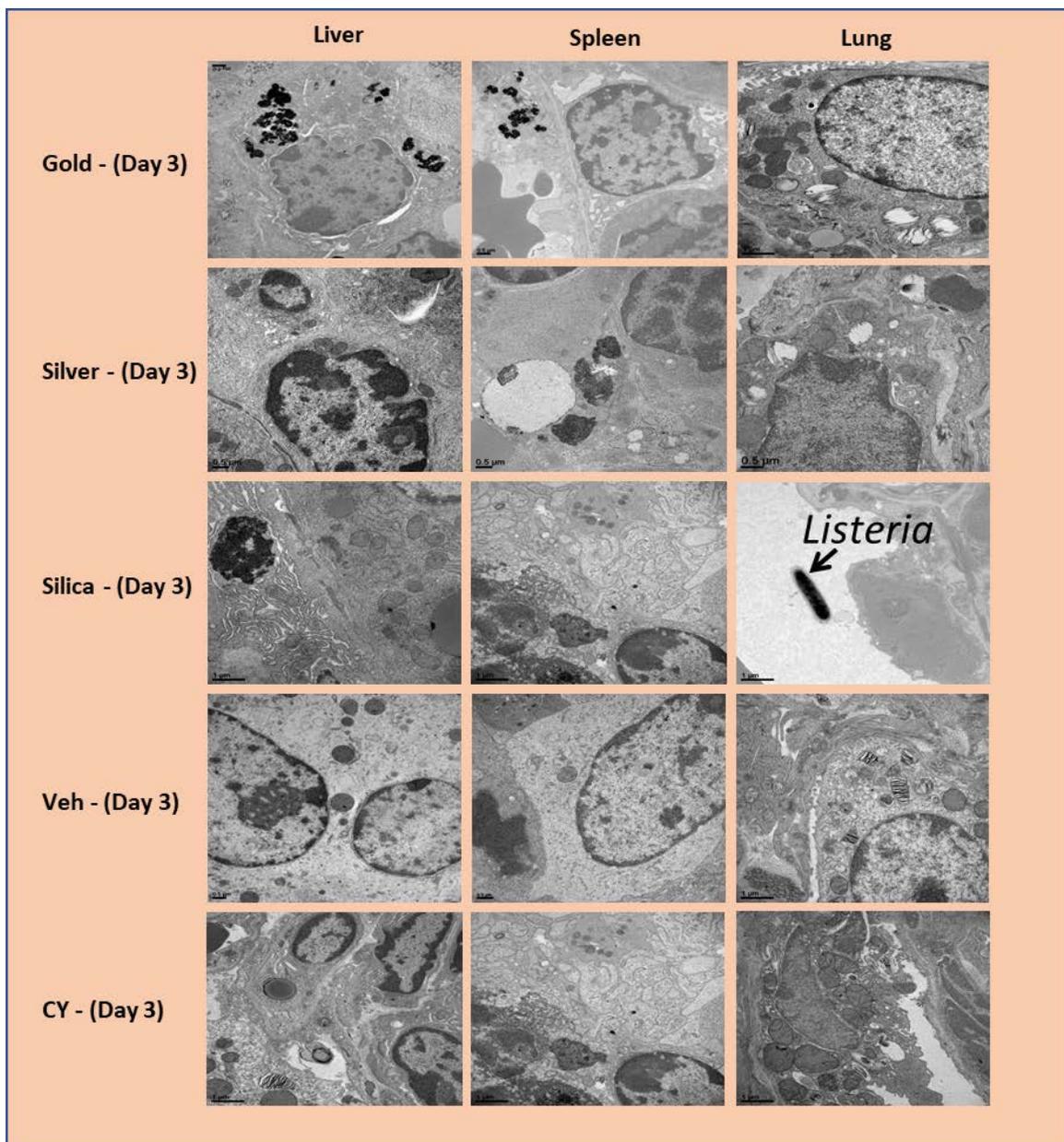


Figure 2. Representative transmission electron microscopy images of liver, spleen, and lung samples of mice 3 days after infection with *Listeria*. Different dosing groups of mice were pretreated with gold, silver, and silica nanoparticles, vehicle control and a positive control CY prior to *Listeria* infection. Arrow: CY-Spleen (day 3) shows presence of *Listeria monocytogenes* in the spleen.” This study informed guidance and review activities¹⁷.

¹⁷ Khan S et al. Investigating the susceptibility of mice to a bacterial challenge after intravenous exposure to durable nanoparticles. *Nanomedicine* 12(17) 2017.

The CORES grants program is designed to promote cross-center and external collaborative research opportunities to address high-priority FDA regulatory science nanotechnology research needs. These identified research needs reflect the priorities of National Nanotechnology Initiative (NNI) - Environmental, Health, and Safety Research Strategy, including nanomaterial characterization, assessing nanomaterial biocompatibility, and investigating toxicokinetics, in vitro toxicity, and in vivo toxicity testing for nanomaterials.¹⁸ Research outcomes from CORES grants have provided data (Figure 2) to support the issuance of guidance documents for industry and the development of vital regulatory science tools, such as assays, assessment methodologies, and test protocols that FDA uses to evaluate nanotechnology in FDA-regulated products.¹⁹ Moreover, the CORES program has increased collaboration across FDA and continues to strengthen the Agency's relationship with academia, industry, and other federal agencies.

C. Supporting Nanotechnology-related Staff Training and Professional Development

To keep pace with the extraordinary breakthroughs in product development resulting from nanotechnology, FDA requires highly skilled scientific and technical experts. To address these rapidly evolving regulatory science needs and help ensure FDA experts are prepared to address new regulatory challenges, the Agency developed and continues to sponsor nanotechnology-specific trainings.

Since nanotechnology has potential applications in all FDA-regulated product areas and the Agency is tasked with regulating this emerging technology under several different regulatory frameworks, FDA developed an *Introduction to Nanotechnology Science and Regulation* course. This course introduced FDA professionals to the basic science of nanotechnology and applications of nanotechnology in FDA-regulated products. Following this introductory course, FDA offered the *Applied Sciences Course in Nanotechnology* that addresses: 1) characterization and manufacturing; and 2) safety and toxicology.

These in-depth trainings highlighted the diversity of nanomaterials that have the potential to be used in FDA-regulated products; gave a wide-ranging overview of manufacturing and analytical techniques; explored current safety and toxicity testing assays; analyzed effects that dosimetrics and physicochemical properties have on toxicity; and discussed the impacts of routes of exposure.

Another critical training is the annual NTF-sponsored *Hands-on Nanotechnology Training*, which provides basic training at the two nanotechnology core facilities (Arkansas and Maryland) for scientists and reviewers tasked with evaluating product submissions that involve nanotechnology. This course evaluates different classes of

¹⁸ https://www.nano.gov/sites/default/files/pub_resource/2016-nni-strategic-plan.pdf

¹⁹ Riaz Ahmed KB et al. *Silver nanoparticles: Significance of physicochemical properties and in vitro studies in toxicological risk assessment. Toxicology In Vitro* 38, 2017.

nanomaterials and offers hands-on training with the common tools used for nanomaterial physicochemical characterization. It teaches scientists and reviewers the strengths and weaknesses of each method when considering a dataset submitted to FDA in support of a product application.

To keep up with preclinical product development in nanotechnology, the *Hands-on Nanotechnology Training* also includes advanced lectures on innovations in FDA-regulated product areas, such as new drugs, generic drugs, and medical devices. These advanced lectures integrate relevant case studies using real-world examples that provide information on factors that influence biocompatibility, methods to evaluate and measure biocompatibility through fractionation techniques, hyphenated methods, and surface analytical tools. Since its inception in 2012, more than 120 research scientists and reviewers from across FDA have been trained through this program.

Additionally, individual FDA product centers have sponsored training for their scientists and product reviewers to ensure that experts are aware of advances in the field of nanotechnology. For example, in 2013 CDER sponsored discipline-specific training for their professionals involved in the review of drug products containing nanomaterials. Additional trainings have also included review- or method-specific training. These trainings are often held in collaboration with the NTF, so that advances in technology, including analytical techniques, can be shared broadly with FDA reviewers in a timely manner (example: *Lab-based training for particle sizing technique* 2017).

In addition to developing internal trainings for FDA scientists and reviewers, FDA has supported training developed by external partners, such as the Nanotechnology Characterization Laboratory (NCL) at the National Cancer Institute (NCI). In 2004, FDA partnered with the National Institute of Standards and Technology (NIST) and NCI to establish NCL to perform multidisciplinary testing for cancer therapies, which is vital to the clinical translation of nanomedicine candidates. NCL offered a *Lessons Learned Workshop* at FDA describing their experience with different nanomaterial-containing products for cancer therapy in 2011. FDA has also given staff training through seminars by external/academic experts on emerging topics of interest in nanotechnology.

V. Collaborating with Federal Agencies, Academic Institutions, and International Partners

The 2007 NTF report called for promoting and participating in collaborative efforts to further the understanding of biological interactions of nanoscale materials and to explore opportunities to enable innovation using nanoscale materials to develop safe and effective products under FDA's regulatory jurisdiction. FDA works collaboratively with a wide variety of partners – including other federal agencies, academic institutions, and international regulatory partners – to build regulatory science knowledge, effectively leverage resources, facilitate innovation, and coordinate policy to fulfill FDA's mission to safeguard the public's health.

A. Domestic and International Coordination

FDA actively participated in the White House Emerging Technologies Interagency Policy Coordination Committee (ETIPC), a U.S. government group charged with developing and coordinating cross-cutting policies associated with emerging technologies. FDA formulated and issued its science-based policy approach to nanotechnology products in coordination with federal partners and consistent with federal policy. FDA also worked actively to promote regulatory cooperation in international forums, such as in bilateral and multilateral trade forums, international organizations, and regulator-to-regulator discussions, to enhance understanding of the U.S. science- and risk-based regulatory approach to ensure the safety of nanotechnology products and, to the extent feasible, facilitate regulatory alignment.

FDA is a member of the National Nanotechnology Initiative (NNI),²⁰ and interacts with other U.S. government agencies through participation in the Nanoscale Science, Engineering and Technology (NSET) Subcommittee and the Nanotechnology Environmental and Health Implications (NEHI) working group. These meetings convene scientists from NNI agencies to discuss ongoing nanotechnology research, research strategies, priorities, challenges and collaborations, nanotechnology signature initiatives, funding, and domestic and international engagement. FDA, along with other agencies, submits an annual report to NNI, including significant accomplishments, budget, and policy updates.

Examples of the activities FDA is engaged in through NNI include:

- Participating in the U.S.–E.U. Communities of Research (CoR),²¹ established to bring researchers together to exchange information and foster potential collaborations. FDA experts currently serve as co-chairs of the Characterization CoR and the Nanomedicine CoR. These engagements resulted in collaborative consensus standards development and helped facilitate regulatory science discussions on a variety of nanotechnology topics.
- Working with the National Institute of Standards and Technology (NIST) and European Commission/Joint Research Center (JRC) to co-develop standards for regulatory purposes. FDA laboratories also participate in international inter-laboratory studies on reference material standards developed at the JRC.
- Participating in the U.S.–India Emerging Materials and Manufacturing Sciences working group discussions led by the Office of Science and Technology Policy (OSTP) in the Executive Office of the President (EOP) in 2016. Subsequent collaborative work led by FDA resulted in the Indo-U.S. Science and Technology Forum-sponsored Symposium on Nanotechnology Regulatory Science, held in Hyderabad, India, in February 2018. The symposium was attended by many scientists from the U.S. and Indian government agencies. It provided a venue to

²⁰ See: <http://www.nano.gov/>

²¹ See: <https://us-eu.org/communities-of-research>

discuss research, guidance, and policy issues and to identify topics of mutual interest for future interactions.

FDA also issues annual reports as part of the President’s budget supplement for Nanotechnology, which is coordinated through the National Nanotechnology Coordination Office.²² These annual reports list FDA’s nanotechnology budget and major research and regulatory science achievements. FDA’s cumulative investment in nanotechnology research since 2009 exceeds \$133 million, as captured in Figure 3. It has helped FDA address emerging challenges in nanotechnology science and policy and inform important science-based regulatory decisions.²³

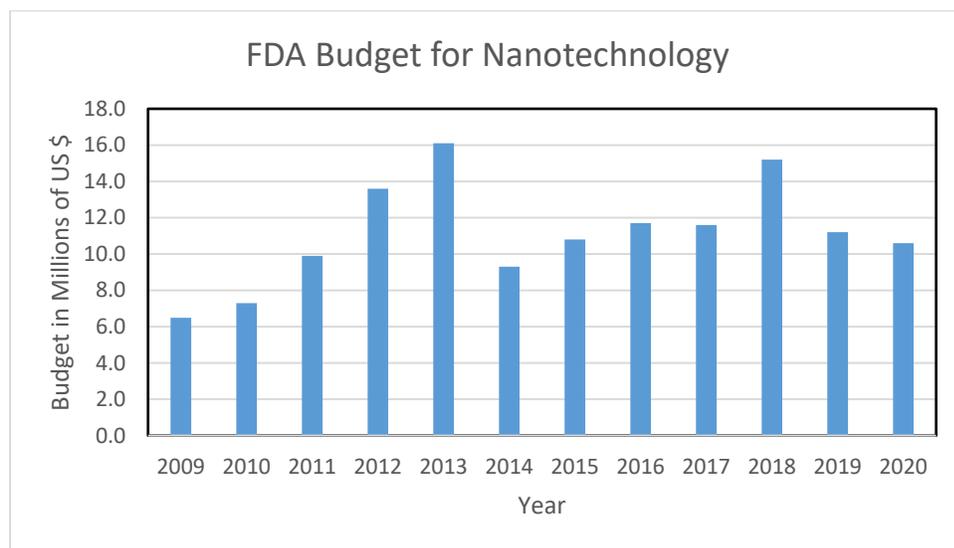


Figure 3: Nanotechnology budget at FDA

Examples of how FDA collaborates with other federal agencies and academia on nanotechnology research include:

- In 2004, FDA, NCI, and NIST, entered into a Memorandum of Understanding (MoU) to establish the Nanotechnology Characterization Laboratory (NCL) at NCI. The goal was to develop standardized assays for nanomaterial assessment and to support preclinical characterization of nanomaterial intended for medical applications.²⁴ Through this partnership, NCL generated more than 40 assays that have been standardized and reviewed by FDA scientists. This MoU was renewed in 2015 and in 2020 so that FDA continues to receive data generated by the NCL to support regulatory decision-making.
- FDA established a collaboration with the Consumer Protection Safety Commission (CPSC) to conduct nanotechnology research on topics of mutual

²² See: <http://www.nano.gov/about-nni/nngo>

²³ See: http://nanodashboard.nano.gov/data/NNI_Investments_by_Agency_PCA_2001_2018.xlsx

²⁴ See: <https://ncl.cancer.gov/resources/assay-cascade-protocols>

interest that include a project on food-contact material, the leaching potential of nanomaterial through laboratory research, and the development of models to understand potential exposure.

- CDER and CDRH have both collaborated with the Defense Advanced Research Projects Agency (DARPA) and the Defense Threat Reduction Agency (DTRA) in their nanotechnology programs. The collaboration includes providing regulatory expertise to DARPA or DTRA program managers, drafting calls for proposals, serving on review panels, and participating in technical committees.
- In 2015, the United States Pharmacopeia (USP) began organizing efforts involving drug products that contained nanomaterials, which had two major results: 1) an International Pharmaceutical Federation/USP workshop that was held in 2016 and 2) the formation of the Nanotechnology Joint Subcommittee. The sub-committee is held jointly within the USP Expert Committees on Dosage Forms and the Expert Committee on Physical Analysis and includes CDER and CVM representatives. The subcommittee defines nanomaterials currently found in applications in pharmaceutical products in the U.S. and identifies analytical technology being used to characterize and control manufactured products that contain nanomaterials.
- NCTR organizes an annual *Nanotechnology for Healthcare Conference* in collaboration with Arkansas universities, the Arkansas Research Alliance, and Winthrop Rockefeller Institute.²⁵ This conference brings together FDA scientists, faculty, and students from Arkansas universities, and other national and international experts to discuss developments in the diagnosis and treatment of human disease using nanotechnology.

FDA interacts with regulatory bodies worldwide to stay current with product development occurring outside the U.S., since these products may be submitted to FDA for review and approval. In this context, informing regulators from other countries about FDA's experience in nanotechnology regulatory science, capacity-building, and developing consensus can assist in advancing the responsible development of nanotechnology-based products. Recently, the focus of FDA's international interactions with regulators has been to communicate on our standards activities, which are critical to ensuring quality for FDA-regulated products. In nanotechnology, FDA's primary outreach is through Nanotechnology Working Groups at the International Pharmaceutical Regulators Programme (IPRP) and the Global Summit in Regulatory Science (GSRs).

The IPRP Nanotechnology Working group is tasked with mapping activities (e.g. formal identification of processes and products across regions) for generic products and general critical quality attributes of drug products containing nanomaterials. The group's work was instrumental in facilitating the efforts of FDA scientists to lead a Nanotechnology Regulatory Research Training in 2018 to Health Canada and to Canadian Food Inspection Agency reviewers and scientists.

²⁵ See: <http://rockefellerinstitute.org/blog/index.php/institute-programs/nano>

The GSRS offers a platform where regulators, policy-makers, and scientists from various countries can exchange views on harmonizing strategy and determining how innovative methodologies can be developed for, applied to, and implemented into regulatory assessments via global collaboration.²⁶ In 2016, a GSRS on Nanotechnology Standards and Applications was held in Bethesda, Maryland. The 2016 GSRS brought together regulatory, standards, and research experts from 19 countries to discuss innovative research and regulatory models, and to identify the reference material and documentary standards (e.g. guides, test methods) needed to advance science and regulatory review.²⁷

Outcomes of the 2016 GSRS led to the development of standards priorities in nanomaterial containing drugs, devices, food, and personal care products. Since the summit, this coalition has been partnering with consensus standard development organizations to either develop new standards or update their current documentary standards to reflect current advances in nanotechnology.

As well as meeting with sponsors during a specific product submission, FDA engages industry on nanotechnology-related issues by participating in, presenting at, and organizing public conferences, workshops, and symposia. FDA often discusses draft and final guidance for industry at these public meetings to share FDA's current thinking. FDA also actively engages with industry stakeholders through standards development organizations (SDOs), such as the International Organization for Standardization Technical Committee 229 Nanotechnologies (ISO TC/229), American Society for Testing and Materials Committee E56 on Nanotechnology (ASTM E56), the Organization for Economic Cooperation and Development (OECD Working Party on Manufacturing Nanomaterial), where FDA and industry collaborate on developing consensus standards. In addition to these interactions, several FDA representatives participated in the International Life Sciences Institute's effort to summarize the state of the art of nanotechnology applications in food, which concluded with findings published in several scientific articles.²⁸

Overall, domestic and international coordination enables FDA to leverage resources and other entities' work, helping to prevent redundant research, track advancements in the nanotechnology field, and collaborate on shared priorities to advance scientific understanding of nanotechnology applications in FDA-regulated products. FDA's engagement in domestic and international forums facilitates an open dialogue with regulated industry and FDA's regulatory counterparts. This promotes a shared

²⁶ See:

<https://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofScientificandMedicalPrograms/NCTR/WhatWeDo/ucm289679.htm>

²⁷ See: <https://www.astm.org/COMMIT/GSRS16%20Final%20Report.pdf>

²⁸ <https://onlinelibrary.wiley.com/doi/10.1002/wnan.1333> and <https://onlinelibrary.wiley.com/doi/full/10.1111/1541-4337.12077>

understanding of the state of the science to ensure that the Agency and the nation are prepared to address this rapidly evolving field.

B. Providing Leadership in International Standards Development

Standards are an invaluable resource for both industry and FDA staff. For decades, FDA has supported the development and use of national and international documentary standards in support of the Agency's mission to protect and promote the public health. The use of standards can increase predictability, streamline premarket review, and facilitate market entry and use of safe and effective products.

As FDA's understanding of how nanotechnology applications are or may be used in FDA-regulated products has grown, we have also increased our participation in standards development organizations, such as ISO TC/229 and ASTM E56. To effectively coordinate this work across all FDA centers, the NTF established the Nanotechnology Standards Subcommittee in 2016 with the goals of:

- 1) consolidating and coordinating FDA comments for nanotechnology standards being considered for review;
- 2) prioritizing nanotechnology standards based on Agency needs; and
- 3) assisting in the development of standards.

The Subcommittee includes members from all FDA centers with interest in nanotechnology and facilitates a coordinated and consistent review process for documentary standards under development. To date, the Subcommittee has reviewed and provided comments on more than 55 consensus work items that were being developed by industry and government stakeholders as documentary standards. Moreover, to further FDA's regulatory priorities and needs, some FDA centers have begun to identify a prioritized list of standards needs through interaction with other regulatory agencies. Some of these standards, where FDA has expertise, interest, and need, are being developed with stakeholder involvement through SDOs and NTP support.

To date, nine FDA-generated work items are going through the consensus process through SDOs in collaboration with stakeholders and experts. Two work items that FDA was heavily engaged in during development were, 1) *Standard Practice for Performing Cryo-Transmission Electron Microscopy of Liposomes*, and 2) Standard Test Method for Quantitative Measurement of the Chemoattractant Capacity of a Nanoparticulate Material in vitro, which became standards and are available through ASTM International.²⁹ These standards on high-priority areas, such as characterization methods to ascertain reproducibility and safety, ultimately provide common ground for industry and FDA to help facilitate the development of products containing nanomaterials.

²⁹ See: <https://www.astm.org/Standards/E3143.htm>

FDA also actively assesses the impact of published consensus nanotechnology standards on the premarket review process and recognizes these standards, as appropriate. The list of such recognized standards by CDRH is published in the *Federal Register* and is searchable on FDA's website³⁰ (select “nanotechnology” under “Specialty Task Group Area” to search for recognized nanotechnology standards).

VI. Future Perspectives

FDA will continue to monitor scientific and technological advancements in products that involve the application of nanotechnology. The next generation of nanotechnology-enabled products may involve a convergence of technologies, such as nanotechnology and modern molecular techniques and 3D printing of devices containing nanofeatures and nanomaterials, which would potentially result in increasing complexity and diversity of products and their uses.

Nanotechnology is already incorporated into various products and is likely to be used even more in the future. We recognize that, for FDA to achieve its mission of protecting and promoting public health, we must be prepared and understand the science behind such emerging products. FDA will rely on a combination of horizon-scanning activities to stay abreast of new developments and product applications, including by:

- participating in scientific and trade forums;
- participating in standards development;
- continuing discussions with national and international counterparts;
- monitoring scientific and trade literature;
- engaging with academia and developers; and
- performing prospective regulatory science on emerging technologies.

In addition, FDA's Emerging Sciences Working Group, a cross-Agency, science-based forum established in 2016, continues to identify science and technology trends of relevance to FDA's regulatory responsibilities, including those for nanotechnology products. FDA's science-based, product-focused regulatory framework is sufficiently flexible and robust to help ensure product safety (and effectiveness, as applicable) while supporting innovation for the development of beneficial nanotechnology products.

³⁰ See: <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm>

VII. Appendix: FDA Nanotechnology Core Facility and Advanced Characterization Facility Equipment List

Nanotechnology Core Facility, Jefferson Laboratories, Arkansas

An NCTR, ORA, and NIEHS/NTP collaboration to support regulatory science research

Nanocore equipment:

Electron Microscopy

- JEOL 2100 Transmission Electron Microscope (TEM) with EDS detector (STEM)
- JEOL 1400 TEM with EDS detector
- Two Zeiss MERLIN Scanning Electron Microscopes (SEM)
 - Unit #1 Equipped with two EDAX EDS detectors (30-mm² chip) and one EDAX WDS detector for elemental analysis/mapping
 - Unit #2 Equipped with optional Gatan 3View2XP (in-situ ultra-microtome) to achieve 3D reconstructions of large volumes of soft matter
- JEOL JSM 6610LV SEM with EDS detector
- Delong America Low Voltage Electron Microscope (LVEM25)

Atomic and Optical Microscopy

- Asylum Research MFP-3D Atomic Force Microscope (AFM)
- Veeco diCaliber Scanning Probe Microscope
- Nikon Eclipse Ti-U Inverted Microscope with Epifluorescence Illuminator
- Horiba-Jobin-Yvon Confocal LabRaman-HR Microscope with Raman and FTIR detection
- CytoViva Darkfield Hyperspectral Imaging System
- CytoViva Brightfield Hyperspectral Imaging System

Spectroscopy

- Perkin-Elmer Lambda 45 UV-Vis Spectrophotometer
- Perkin-Elmer LS 55 Fluorescence Spectrometer
- Perkin-Elmer Spectrum 400 Infrared Spectrometer
- PicoQuant FluoTime 200 High Performance Fluorescence Lifetime Spectrometer
- Beacon 2000 Variable Temperature Fluorescence Polarization System
- NS3 Raman, Fluorescence and Absorption for Singl-Walled Carbon Nanotube Analysis

Particle Size Analysis and Characterization

- Malvern Zetasizer Nano ZS
- Malvern Mastersizer 3000
- Two Nanosight LM-10HS Nanoparticle Tracking Analyzer with red or green/blue laser modules
- Sympatec NanoPhox Photon Cross Correlation Detector
- Brookhaven ZetaPALS Zeta Potential and Particle Size Analyzer
- Izon QNano
- Beckman Coulter Surface Area and Pore Size Analyzer SA3100
- Quantachrome Instruments Autosorb iQ₂ Automated Gas Sorption Analyzer

Elemental Analysis

- Thermo Scientific X Series 2 Inductively Coupled Plasma-Mass Spectrometer (ICP-MS) equipped with a New Wave Instruments UP-213 UV laser ablation sampling system
- Two Agilent 7700-X ICP-MS; stand-alone or coupled to a high-performance liquid chromatography or capillary electrophoresis system
- Agilent QQQ ICP-MS
- Perkin Elmer ICP-MS
- CEM MARS-Xpress Microwave Accelerated Reaction System (n=3)
- CEM Discover SP-D Microwave Digestion System
- Rigaku X-ray Fluorescence (XRF) Primus II Analyzer
- Innov-X 5000 Portable XRF Analyzer
- Bruker D2 Phaser X-ray Diffraction System

Instrumentation for Separation/Fractionation

- Agilent 7100 Capillary Electrophoresis System
- Two Agilent 1260 Infinity Binary Pump High Performance Liquid Chromatography (HPLC) Systems with fraction collector, diode array UV-visible detector, and fluorescence detector, Refractive Index detector, Evaporative Light Scattering and Charged Aerosol detectors.
- Waters Ultrahigh Performance Liquid Chromatography QQQ Mass Spectrometer (UPLC-MS)
- Two Wyatt Technology Eclipse 3+ Asymmetric Flow-Field-Flow Fractionation (AFFF) System with Dawn Heleos-II multi-angle light scattering detector (and Optilab T-rEX refractive index detector)
- GE Fast Protein Liquid Chromatography system (FPLC)
- Postnova Centrifugal Flow Field Flow Fractionation system with MALLS and UV-Vis detectors
- CPS Disc Centrifuge system

Additional Equipment

- CH Instruments 630D Electrochemical Analyzer
- Cambridge VISCOpro 2000 Viscometer
- DNA SpeedVac Concentrator/Evaporator
- Qiagen Tissue Lyser (n=2)
- Thermo Scientific Sorvall WX Ultracentrifuge
- BioTek Synergy 2 Micro-plate Reader
- CEM Discover SP/Explorer Hybrid Synthesis System
- TSI ElectroSpray Aerosol Generator/Aerosol Sampler

Advanced Characterization Facility, FDA Headquarters, Maryland

**A collaboration between CDRH, CDER, CBER, and CFSAN to support
regulatory science research**

Advanced Characterization Facility Equipment

- Transmission Electron Microscopy (TEM)
- Scanning Electron Microscopy (SEM)
- Atomic Force Microscopy (AFM)
- Inductive Coupled Plasma Mass Spectrometry (ICP-MS)
- Laser Ablation system
- Ion Chromatography
- TEM Grid Glow Discharger
- Turbo Pumped Sputter Coater
- TEM Grid Plunger Freezer
- Ultramicrotome
- Microwave tissue embedding processor
- Microwave digestion system
- Dynamic Light Scattering and Zeta Analyzer
- Nanosight Particle Analyzer
- qNano Tunable Resistive Pulse Sensing Particle Analyzer



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ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Office of the Commissioner
Office of the Chief Scientist

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