The National Academies

March 14, 2019

U.S. FOOD & DRUG ADMINISTRATION

Recent Progress on Nanotechnology at FDA

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Director, Nanocore, NCTR
U.S. Food and Drug Administration

Disclaimer: The views expressed are of the presenter and should not be considered as the official position or policy of U.S. FDA

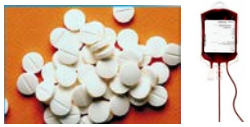
Food and Drug Administration Mission

The FDA is responsible for

- Protecting the public health
  - by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.

- Advancing the public health by helping to speed innovations
  - that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.


Food


Drugs & Biologics


Devices

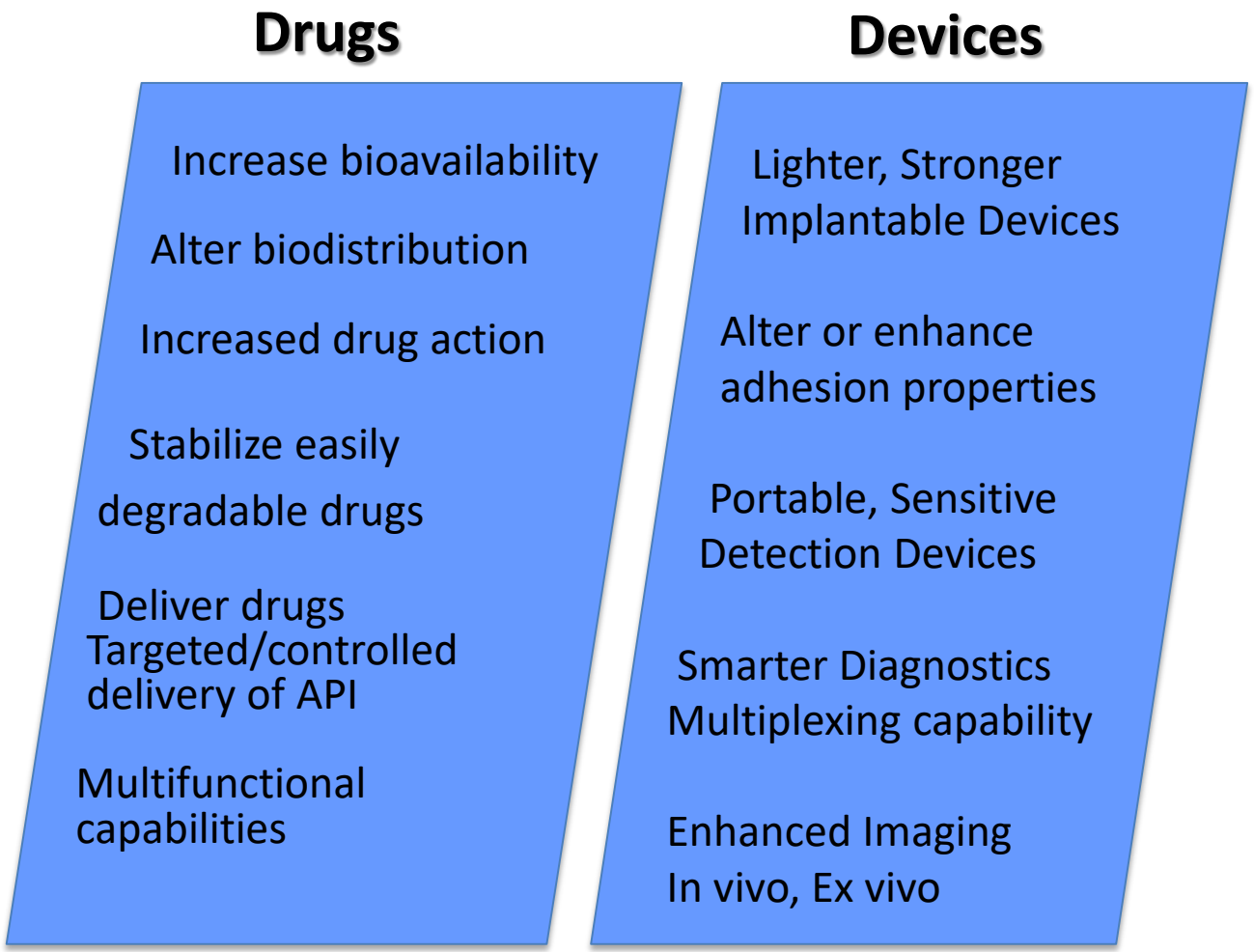

Cosmetics


Veterinary


OTC Products

<u>25%</u> of US domestic spending is on products regulated by FDA

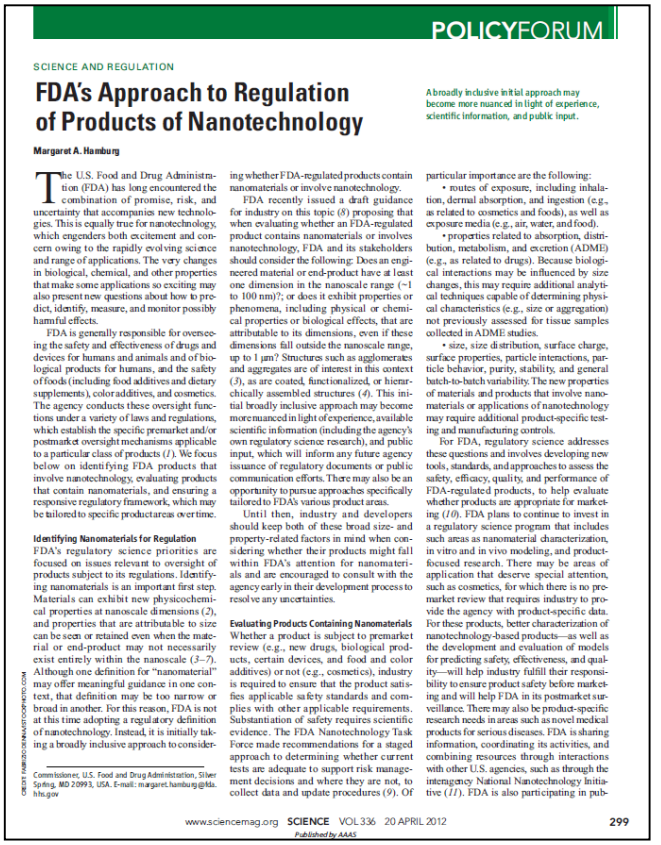
Benefits of Nanotechnology



Risk Benefit Evaluation and post-market surveillance

FDA's Approach to Regulation of Products of Nanotechnology

- Continue post-market monitoring
- Industry remains responsible for ensuring that products meet all applicable requirements, including safety standards
- Encourage early industry consultation
- Collaborate, as appropriate, with domestic and international regulatory counterparts and other stakeholders
- Offer technical advice and guidance, as needed, to help industry meet its statutory obligations.



POLICYFORUM

SCIENCE AND REGULATION

FDA's Approach to Regulation of Products of Nanotechnology

A broadly inclusive initial approach may become more nuanced in light of experience, scientific information, and public input.

Margaret A. Hamburg

The U.S. Food and Drug Administration (FDA) has long encountered the combination of promise, risk, and uncertainty that accompanies new technologies. This is equally true for nanotechnology, which engenders both excitement and concern owing to the rapidly evolving science and range of applications. The very changes in biological, chemical, and other properties that make some applications so exciting may also present new questions about how to predict, identify, measure, and monitor possibly harmful effects.

FDA is generally responsible for overseeing the safety and effectiveness of drugs and devices for humans and animals and of biological products for humans, and the safety of foods (including food additives and dietary supplements), color additives, and cosmetics. The agency conducts these oversight functions under a variety of laws and regulations, which establish the specific premarket and/or postmarket oversight mechanisms applicable to a particular class of products (*1*). We focus below on identifying FDA products that involve nanotechnology, evaluating products that contain nanomaterials, and ensuring a responsive regulatory framework, which may be tailored to specific product areas over time.

Identifying Nanomaterials for Regulation

FDA's regulatory science priorities are focused on issues relevant to oversight of products subject to its regulations. Identifying nanomaterials is an important first step. Materials can exhibit new physicochemical properties at nanoscale dimensions (*2*), and properties that are attributable to size can be seen or retained even when the material or end-product may not necessarily exist entirely within the nanoscale (*3*–*7*). Although one definition for "nanomaterial" may offer meaningful guidance in one context, that definition may be too narrow or broad in another. For this reason, FDA is not at this time adopting a regulatory definition of nanotechnology. Instead, it is initially taking a broadly inclusive approach to considering whether FDA-regulated products contain nanomaterials or involve nanotechnology.

FDA recently issued a draft guidance for industry on this topic (*8*) proposing that when evaluating whether an FDA-regulated product contains nanomaterials or involves nanotechnology, FDA and its stakeholders should consider the following: Does an engineered material or end-product have at least one dimension in the nanoscale range (~1 to 100 nm)?; or does it exhibit properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimensions, even if these dimensions fall outside the nanoscale range, up to 1 μm? Structures such as agglomerates and aggregates are of interest in this context (*3*), as are coated, functionalized, or hierarchically assembled structures (*4*). This initial broadly inclusive approach may become more nuanced in light of experience, available scientific information (including the agency's own regulatory science research), and public input, which will inform any future agency issuance of regulatory documents or public communication efforts. There may also be an opportunity to pursue approaches specifically tailored to FDA's various product areas.

Until then, industry and developers should keep both of these broad size- and property-related factors in mind when considering whether their products might fall within FDA's attention for nanomaterials and are encouraged to consult with the agency early in their development process to resolve any uncertainties.

Evaluating Products Containing Nanomaterials

Whether a product is subject to premarket review (e.g., new drugs, biological products, certain devices, and food and color additives) or not (e.g., cosmetics), industry is required to ensure that the product satisfies applicable safety standards and complies with other applicable requirements. Substantiation of safety requires scientific evidence. The FDA Nanotechnology Task Force made recommendations for a staged approach to determining whether current tests are adequate to support risk management decisions and where they are not, to collect data and update procedures (*9*). Of particular importance are the following:

- routes of exposure, including inhalation, dermal absorption, and ingestion (e.g., as related to cosmetics and foods), as well as exposure media (e.g., air, water, and food).
- properties related to absorption, distribution, metabolism, and excretion (ADME) (e.g., as related to drugs). Because biological interactions may be influenced by size changes, this may require additional analytical techniques capable of determining physical characteristics (e.g., size or aggregation) not previously assessed for tissue samples collected in ADME studies.
- size, size distribution, surface charge, surface properties, particle interactions, particle behavior, purity, stability, and general batch-to-batch variability. The new properties of materials and products that involve nanomaterials or applications of nanotechnology may require additional product-specific testing and manufacturing controls.

For FDA, regulatory science addresses these questions and involves developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products, to help evaluate whether products are appropriate for marketing (*10*). FDA plans to continue to invest in a regulatory science program that includes such areas as nanomaterial characterization, in vitro and in vivo modeling, and product-focused research. There may be areas of application that deserve special attention, such as cosmetics, for which there is no premarket review that requires industry to provide the agency with product-specific data. For these products, better characterization of nanotechnology-based products—as well as the development and evaluation of models for predicting safety, effectiveness, and quality—will help industry fulfill their responsibility to ensure product safety before marketing and will help FDA in its postmarket surveillance. There may also be product-specific research needs in areas such as novel medical products for serious diseases. FDA is sharing information, coordinating its activities, and combining resources through interactions with other U.S. agencies, such as through the interagency National Nanotechnology Initiative (*11*). FDA is also participating in pub-

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www.sciencemag.org SCIENCE VOL 336 20 APRIL 2012 299

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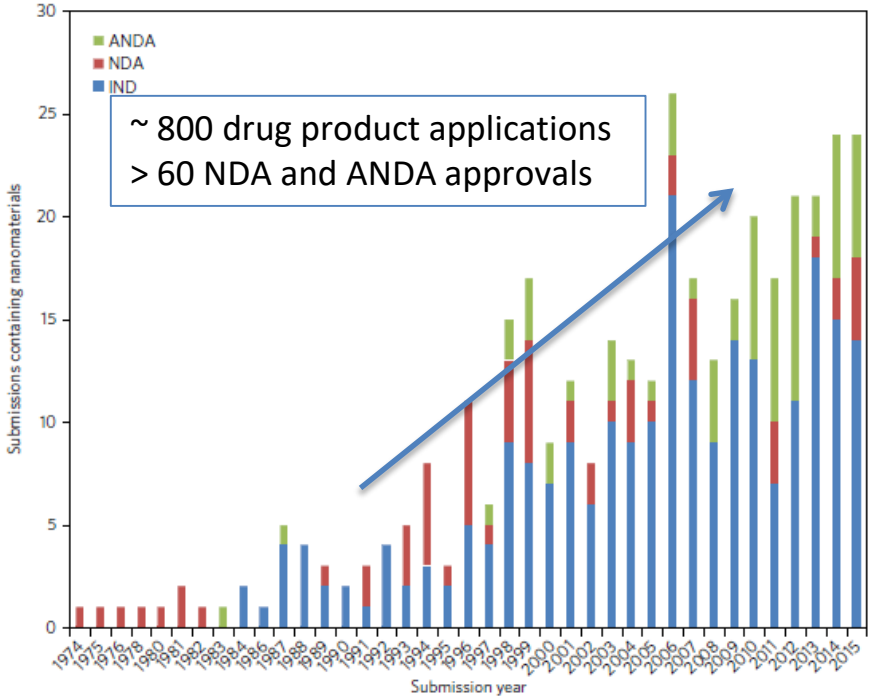
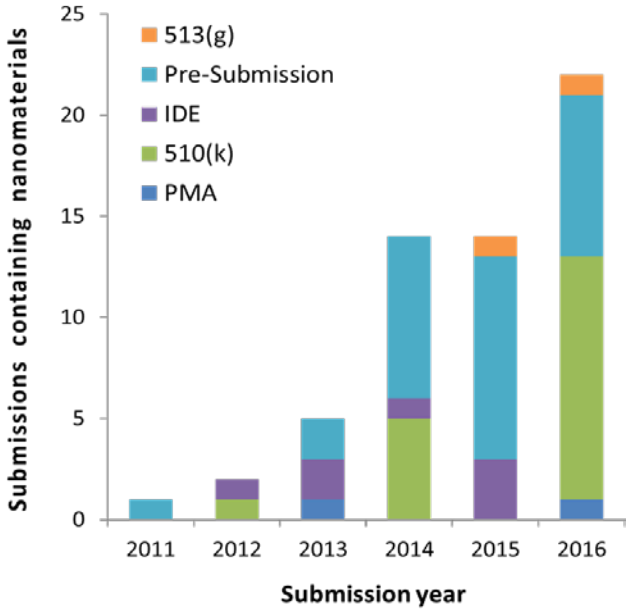
Hamburg, **2012**. *Science* 336: 299-300.

Submissions to the US FDA of Drug Products and Devices Containing Nanomaterials





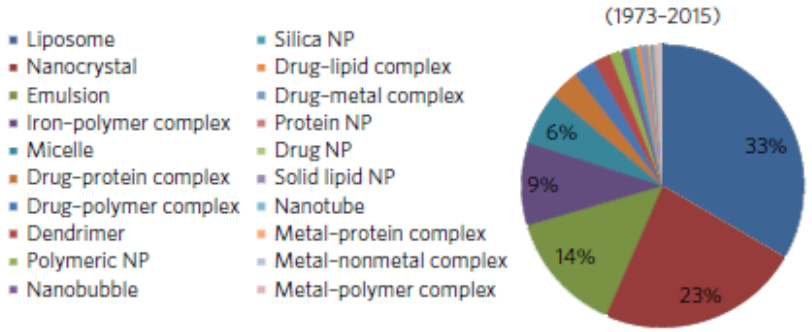
Wu and Zheng, 2017

- Evolution from simpler drug delivery systems to highly complex, multicomponent, multifunctional structures and devices
- FDA's efforts to understand science, advance public health by supporting innovation by promoting beneficial nanotechnology product development

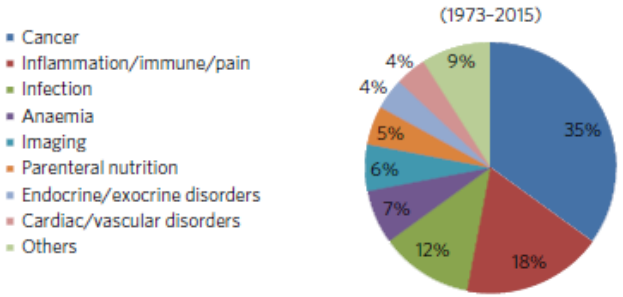
D'Mello S. et al. Nature Nanotechnology DOI: 10.1038/NNANO.2017.67

FDA Survey of Nanomaterial Submissions

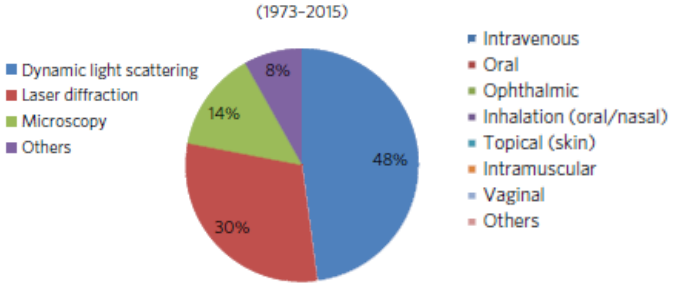
Types of Nanomaterial used in Drug Products



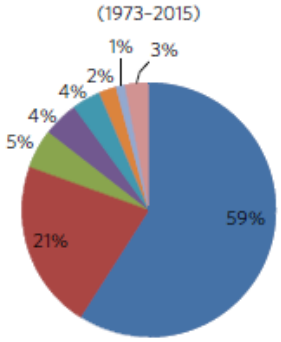
Indications

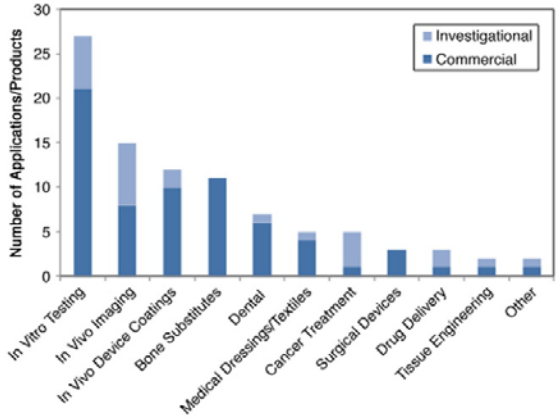


Particle size measurement



Route of Administration



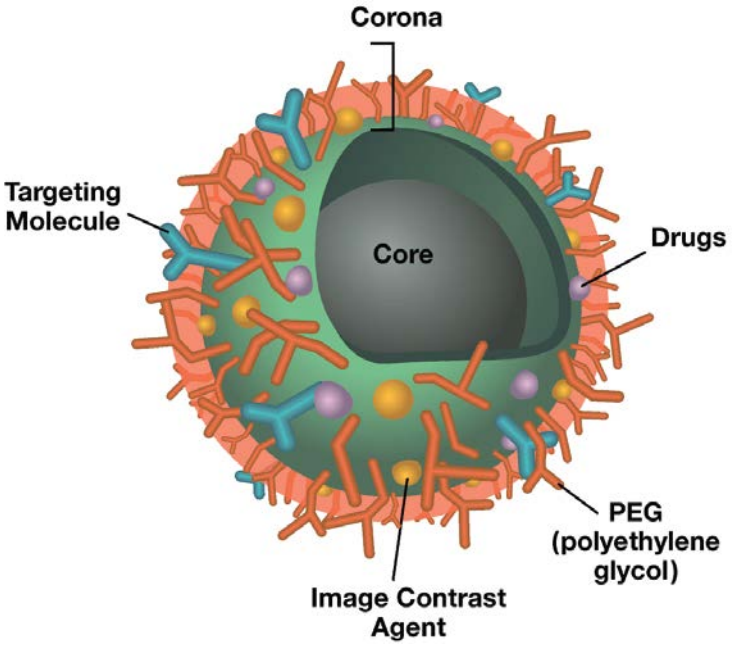


- 1/3rd of the drug product submissions were liposome-based formulations
- 1/3rd of the submissions were for cancer indication
- Intravenous mode of administration is predominant for nanoparticle-based drugs
- Half of the submissions use Dynamic Light Scattering to monitor size

D'Mello, S. R. et. al. Nature Nanotechnology, 2017 DOI: 10.1038/NNANO.2017.67

Multifunctional Nanoparticles

Challenges in Regulatory Science



- Keeping up with Science
- Reproducible science

- Critical Quality Attributes

- Size, Size distribution
- Shape
- Surface
- Therapeutic
- Coatings
- Targeting ligands
- Homogeneity/Inhomogeneity
- Imaging agents

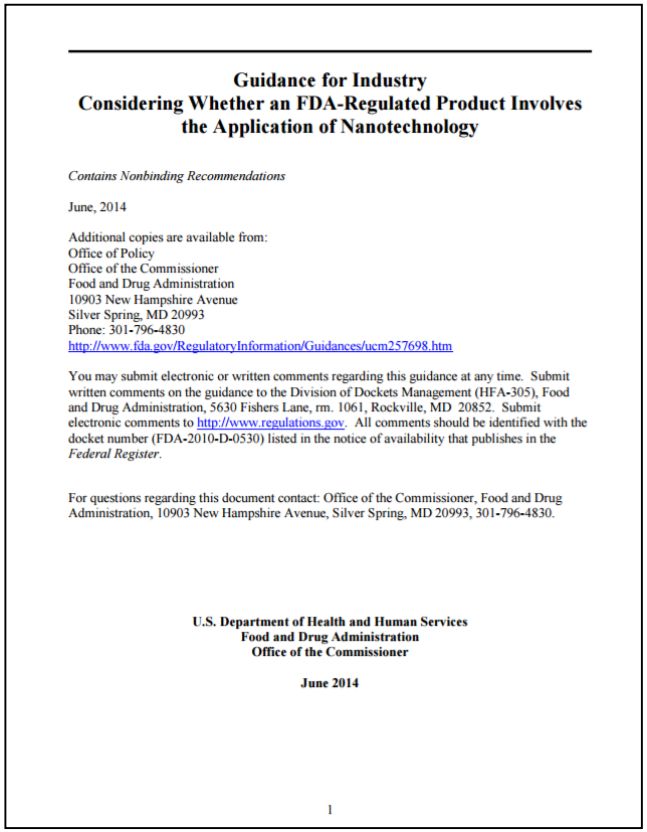
Resolution and sensitivity of instruments is increasing

See things you couldn't see before

Characterize material with greater clarity

Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology

- **Points to Consider**
  - 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);
  - 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)



Guidance for Industry
Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology

Contains Nonbinding Recommendations

June, 2014

Additional copies are available from:
Office of Policy
Office of the Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: 301-796-4830
http://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm

You may submit electronic or written comments regarding this guidance at any time. Submit written comments on the guidance to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. All comments should be identified with the docket number (FDA-2010-D-0530) listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document contact: Office of the Commissioner, Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, 301-796-4830.

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

June 2014

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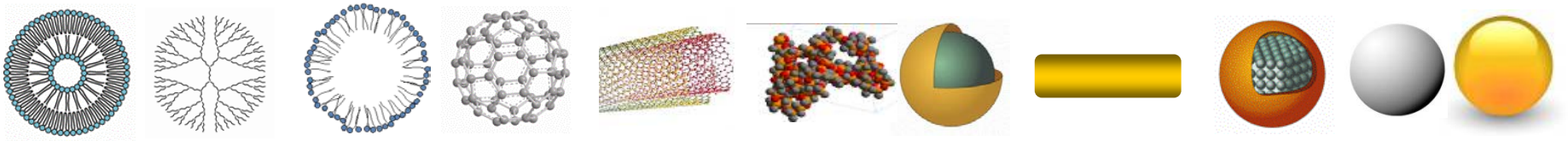


Liposomes Dendrimers Nanoemulsions Fullerenes Carbon Nanotubes Polymers Core-Shell Nanorods Quantum Dots Colloidal

http://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm

The Nanotechnology Task Force

- Intra-agency coordination and inter agency communication through NSET & NEHI
- Regulatory Science Research
  - CORES
  - > 40 grants were given
  - FY 19: 2 year and 1 year grants
- Staff Training and Professional Development
  - Basic Hands-on Nanotechnology Training
  - > 120 reviewers and staff were trained
  - Center-specific training
  - Seminars
  - ORISE and Guest scientists
- Standards sub-committee
  - Strategically important to facilitate products review

Consensus Standards Recognized by FDA/CDRH

	Publication Date	Specialit Task Group Area	Recognition Number	SDO	Standard Designation	Title of Standard
1	8/21/2017	Nanotechnology	18-5	ASTM	E2859-11	Standard Guide for Size Measurement of Nanoparticles Using Atomic Force Microscopy
2	8/21/2017	Nanotechnology	18-6	ASTM	E2865-12	Standard Guide for Measurement of Electrophoretic Mobility and Zeta Potential of Nanosized Biological Materials
3	8/21/2017	Nanotechnology	18-7	ASTM	E2834-12	Standard Guide for Measurement of Particle Size Distribution of Nanomaterials in Suspension by Nanoparticle Tracking Analysis (NTA)
4	8/21/2017	Nanotechnology	18-8	ASTM	E2578-07	Standard Practice for Calculation of Mean Sizes/Diameters and Standard Deviations of Particle Size Distributions
5	4/4/2016	Nanotechnology	18-1	ASTM	E2490-09	Standard Guide for Measurement of Particle Size Distribution of Nanomaterials in Suspension by Photon Correlation Spectroscopy (PCS)
6	8/14/2015	Nanotechnology	18-4	ISO	TS 80004-6	Nanotechnologies - Vocabulary - Part 6: Nano-object characterization
7	1/27/2015	Nanotechnology	18-3	ISO	TS 14101	Surface characterization of gold nanoparticles for nanomaterial specific toxicity screening: FT-IR method
8	7/9/2014	Nanotechnology	18-2	ASTM	E2535-07	Standard Guide for Handling Unbound Engineered Nanoscale Particles in Occupational Settings

Publication of Recognized Standards in Federal Register (FR) recognizing all or part of appropriate standards

- Currently 1200 recognized standards from CDRH
- 8 standards recognized by CDRH under Nanotechnology

CDRH Database

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

FDA Issued Final Guidance and Draft Guidance Related to Nanotechnology

- *Final* Guidance for Industry: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology
- *Final* Guidance for Industry: Safety of Nanomaterials in Cosmetics
- *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
- Draft Guidance for Industry: Drug Products Including Biological Products that Containing Nanomaterials
- Other relevant guidances: Liposomes, Devices, Polymers

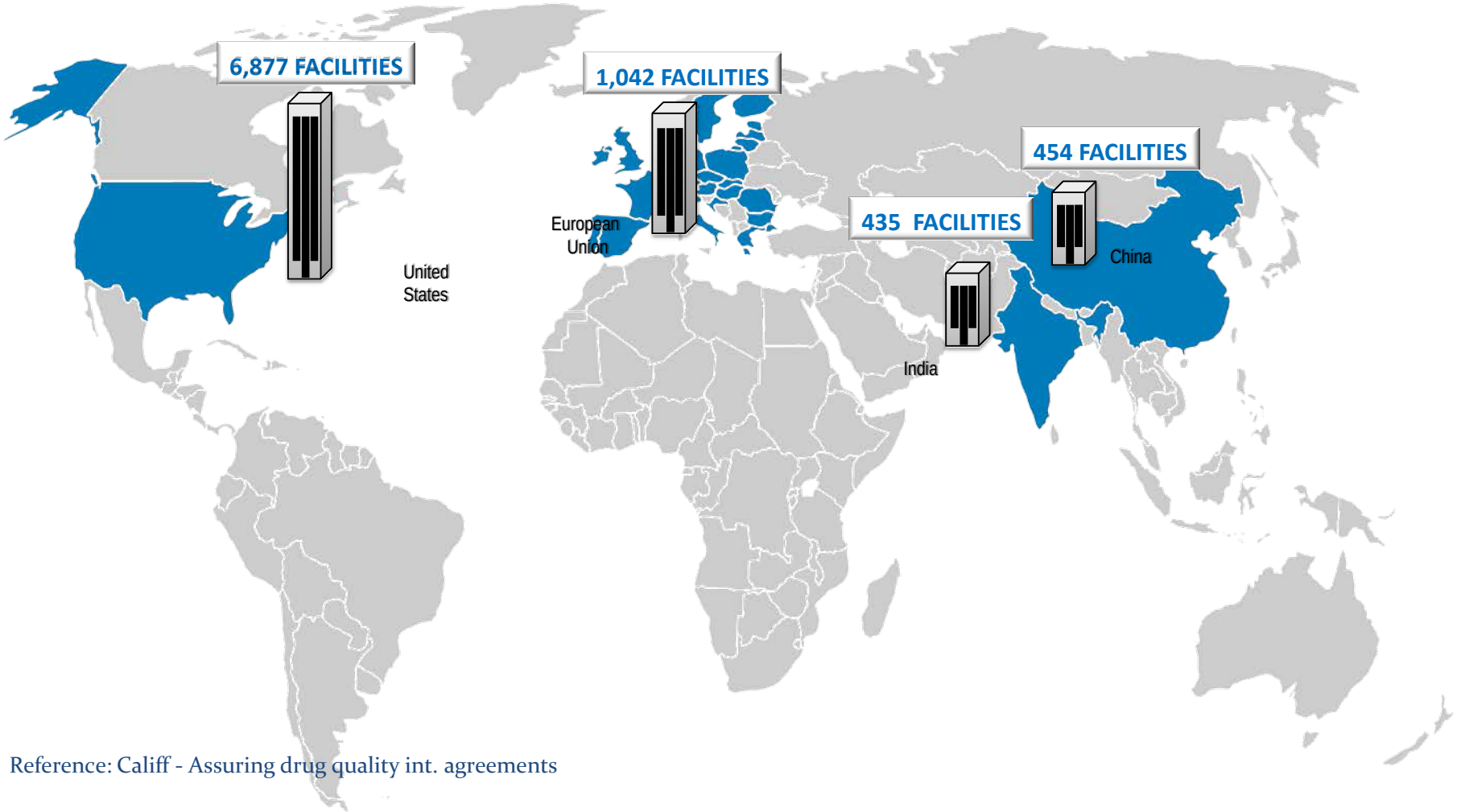
http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm301114.htm#guidance

Inter-agency Coordination

- National Nanotechnology Coordination Office (NNCO)
  - NSET, NEHI
  - US-EU Communities of Research
  - US-India Materials and Manufacturing Sciences WG
    - Nanotechnology Regulatory Science – Feb 2018
- NCI-NIST-FDA MOU
  - NCL Client Reports: >70 available on NTF Sharepoint site
- Collaboration with CPSC on Food Contact Material
- CDER and CDRH Collaboration with DARPA & DTRA

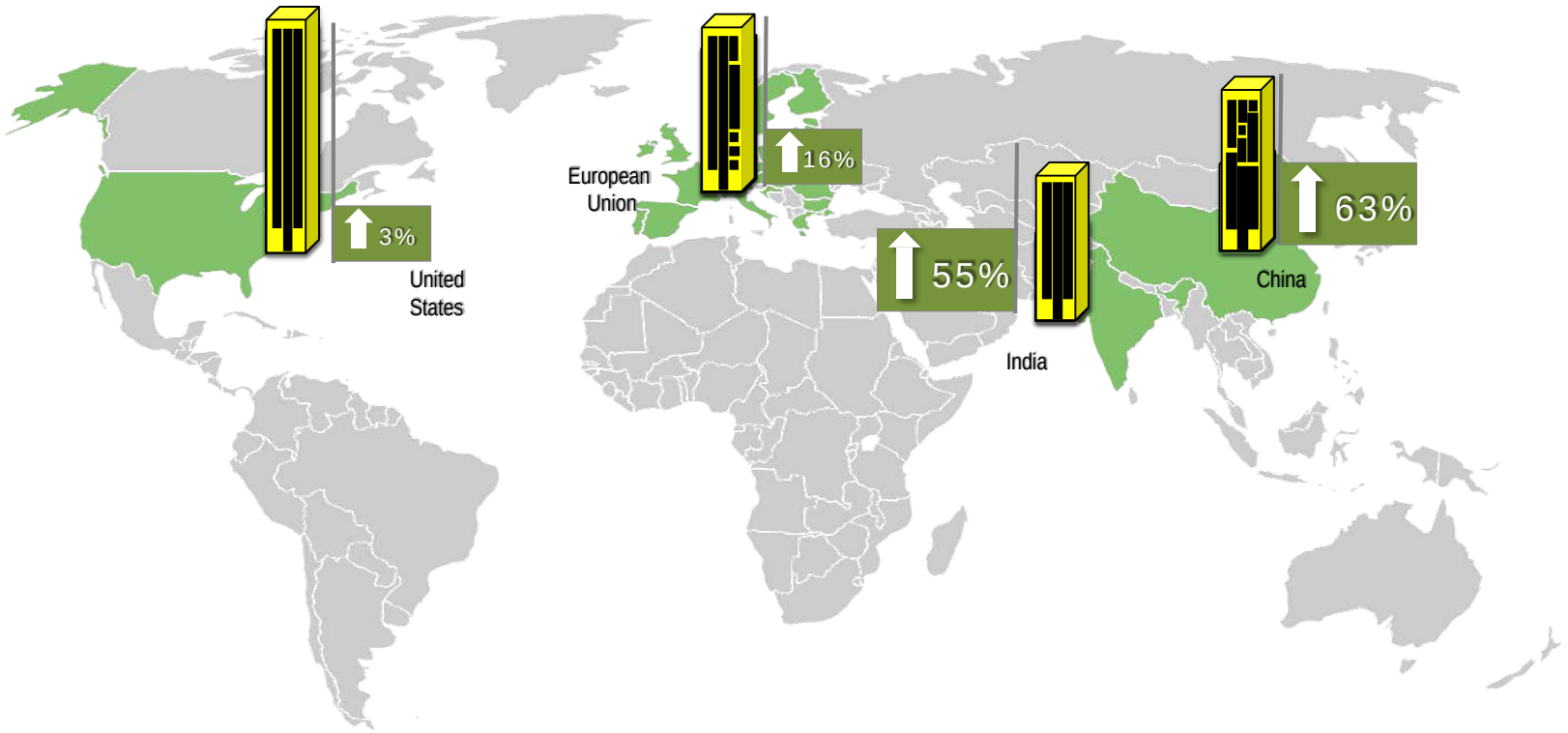
Global Collaborations and Interactions

FDA Registered Drug Facilities 2011



Reference: Califf - Assuring drug quality int. agreements

FDA Registered Drug Facilities 2015



India

- 2nd largest exporter of drug and biologic products to U.S. (after Canada)
- Largest number of registered generic drug manufacturing facilities outside of the U.S.

Reference: Califf - Assuring drug quality int. agreements; For a current listing of registered facilities see: https://www.fda.gov/Drugs/InformationOnDrugs/ucm135778.htm

Health Canada and Canadian Food Inspection Agency (CFIA) Regulatory Science Training

- Held upon request from HC in Ottawa – May 2018
- More than 50 participants
- Condensed version of FDA Nanotechnology training

Indo-US Nanotechnology Workshops

- IUSSTF – Nanotechnology Regulatory Science Workshop - February 2018 in India
- Continued effort in capacity building: OIP/FDA India
- Indo-US Workshop: September 2018
- DCGI, CDSCO and GOI research staff
- Guidelines for Evaluation of Nanopharmaceuticals in India
  - February 2019

Current Collaborations

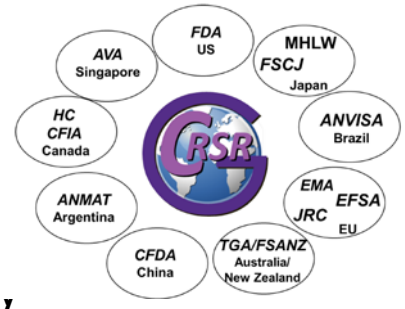
Global Coalition for Regulatory Science Research (GCRSR)

International coalition of global regulatory bodies

Nanotechnology Working Group

GSRS16: Nanotechnology Standards and Applications

GSRS19: Scheduled from September 24-26, 2019, JRC; Ital,



International Pharmaceuticals Regulators Program (IPRP)

Nanomedicines Working Group

i-p-r-f.org
International Pharmaceutical Regulators Forum

Standards Development

ISO TC229, ISO TC24, ASTM E56, OECD

US-EU Communities of Research

Characterization CoR

Nanomedicines CoR

NCL-NCI – collaboration with EU-NCL

Lessons learned

Standard assays and methods development

US-EU Communities of Research

The US-EU dialogue, bridging nanoEHS research, has three goals

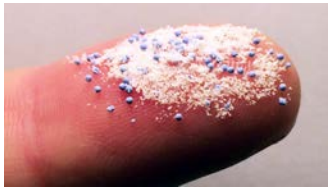
- Engage in an active discussion about environmental, health, and safety questions for nano-enabled products;
- Encourage joint programs of work that would leverage resources; and
- Support the Communities of Research.

- Databases and Computation Modeling for NanoEHS
- Characterization
- Human Toxicity
- Risk Management & Control
- Exposure through Product Life
- Risk Assessment
- Ecotoxicity
- Nanomedicine

https://us-eu.org/

What are Micro and Nanoplastics

- Micro and nanoplastics can be engineered particles or generated from bulk plastics through degradation
- No standard definition exists



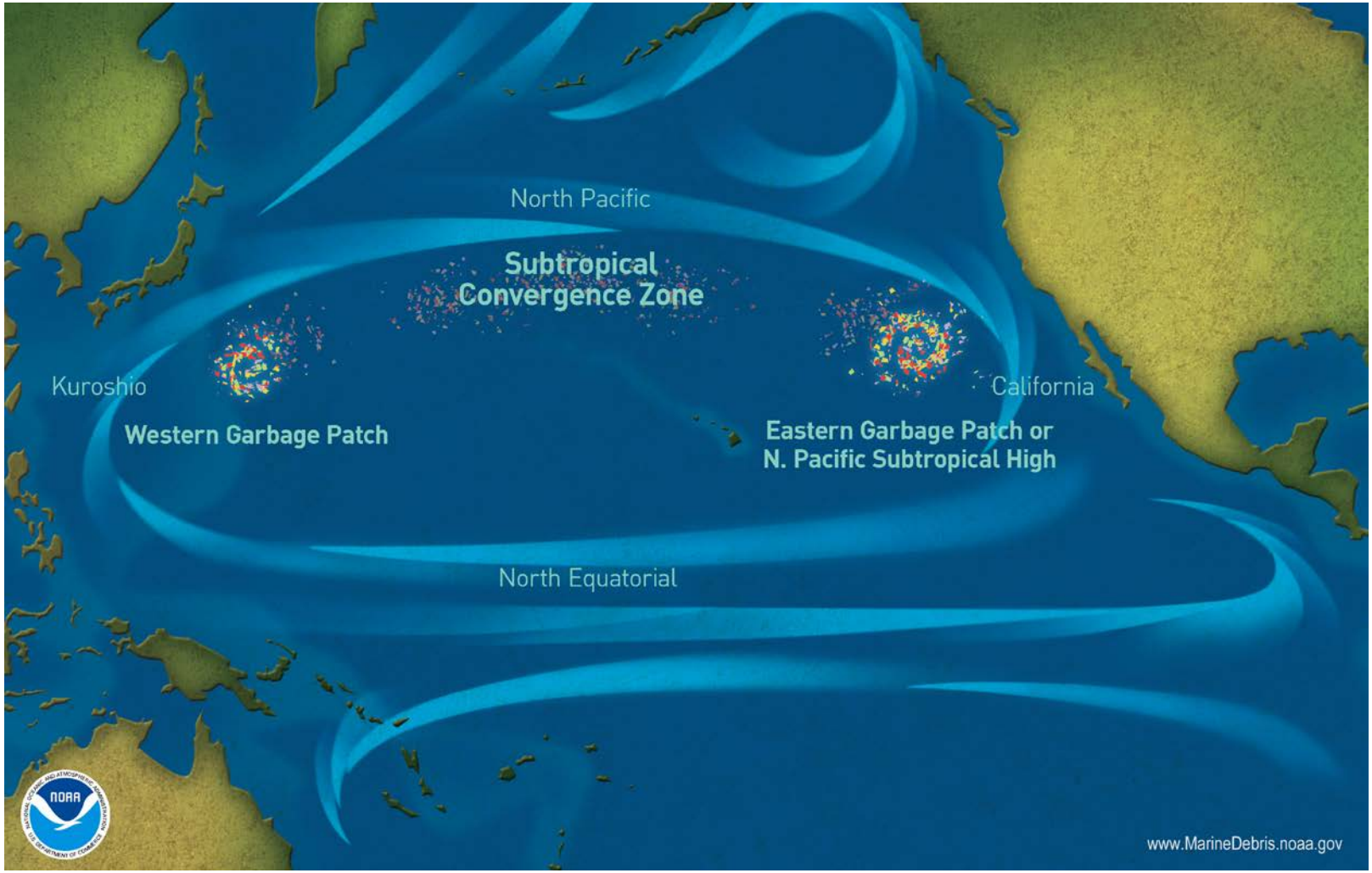
Micro plastics
0.1 µm – 5 mm

Nanoplastics
1 nm-100 nm

Fragments, Fibers, Spheroids, Granules, Pellets, Flakes, Beads

- Primary particles: Particle made commercially in micron or nano size range
- Secondary particles: Particles from degradation of bulk/primary particles

The Great Pacific Garbage Patch

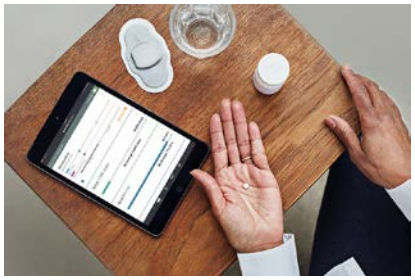


Interest in US and Abroad

- GSRS16 discussions
- NNI/NEHI Working Group
  - CPSC interested in the compositional analysis to the source of material
  - CDC/ATSDR: Nanoplastics in environment
  - EPA: Water
  - NIST: Ecotoxicology and Standards
  - NIOSH: Occupational exposure
- NOAA: Marine Debris Program
- CFIA: Methods development for nanoplastics in food
- EFSA Panel on Contaminants in Food Chain (CONTAM) 2016
  - Presence of Micro and Nanoplastics in Food Chain with particular focus on sea food
- German Risk Assessment Institute (BfR): Methods
- Joint Research Center (JRC): Methods for analysis of micro and nanoplastics – topic for GSRS19

Future is already here

- **FDA approved pill with sensor that digitally tracks if patients have ingested their medication**
  - **Nov 2017**
  - **https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm584933.htm**



- **FDA approved 3D printed tablet in 2015**

- **https://www.webmd.com/children/news/20150804/fda-approves-first-pill-made-by-3d-printing**
- **https://www.fda.gov/Drugs/NewsEvents/ucm588136.htm**

Summary

- FDA investments in Nanotechnology is modest at $ 11 M per year
- Investments from USG and Industry resulted in gradual increase in product submissions containing nanomaterial
- Increase in manufacturing facilities across the globe is resulting in increased imports of regulated products
- It is critical for FDA to engage in collaborations with other US Government agencies and Global regulators in Nanotechnology
  - Regulatory science research
  - Coordination
  - Predict emerging challenges for preparedness, staff training
- Collaborative consensus standards minimizes multiple iterations of submissions and facilitate faster regulatory review

Thank you