QEEN II

Washington D.C.
October 9-10, 2018

Fostering U.S. -International Collaboration in Integrating Exposure in Nanomaterial Risk Evaluation

Global Collaborations in Regulatory Science and Standards Development

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

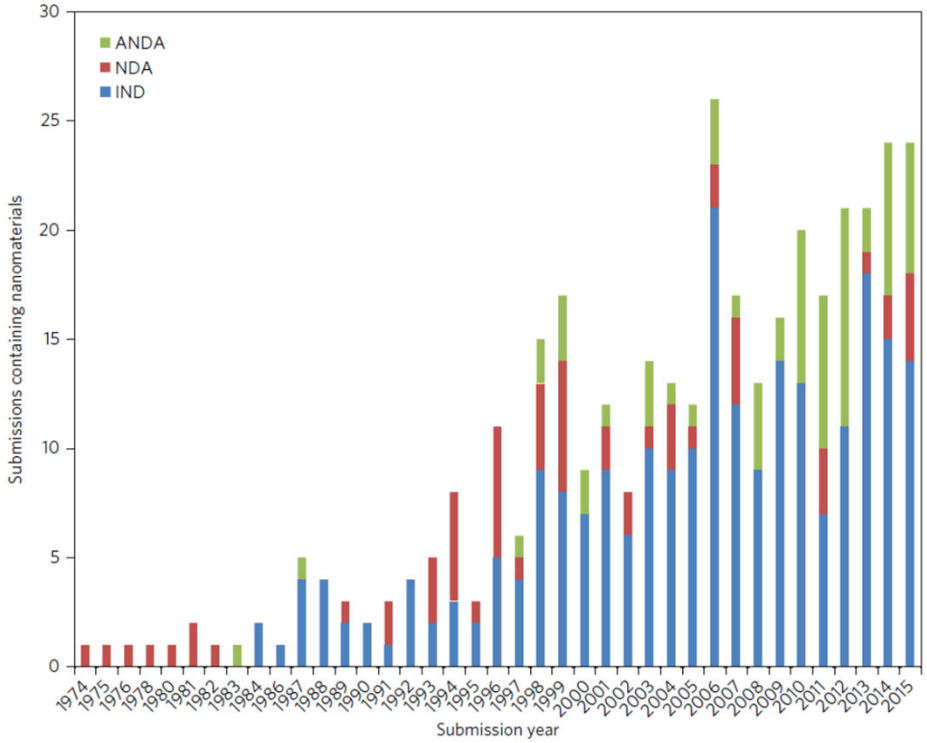
Globalization

- Production of FDA-regulated goods and materials outside of the U.S. has exploded over the last decade.
- FDA-regulated products originate from more than:
  - 150 countries
  - 130,000 importers
  - 300,000 facilities outside of the U.S.
- Drugs and Devices
  - Today, nearly 40 percent of finished drugs and 50 percent of medical devices used by Americans are made elsewhere
  - Approximately 80 percent of the manufacturers of active pharmaceutical ingredients (APIs) used in the U.S. are located abroad.
- Increase in FDA Registered Drug Facilities – Global trends

Reference: https://www.fda.gov/internationalprograms/fdabeyondourbordersforeignoffices/default.htm

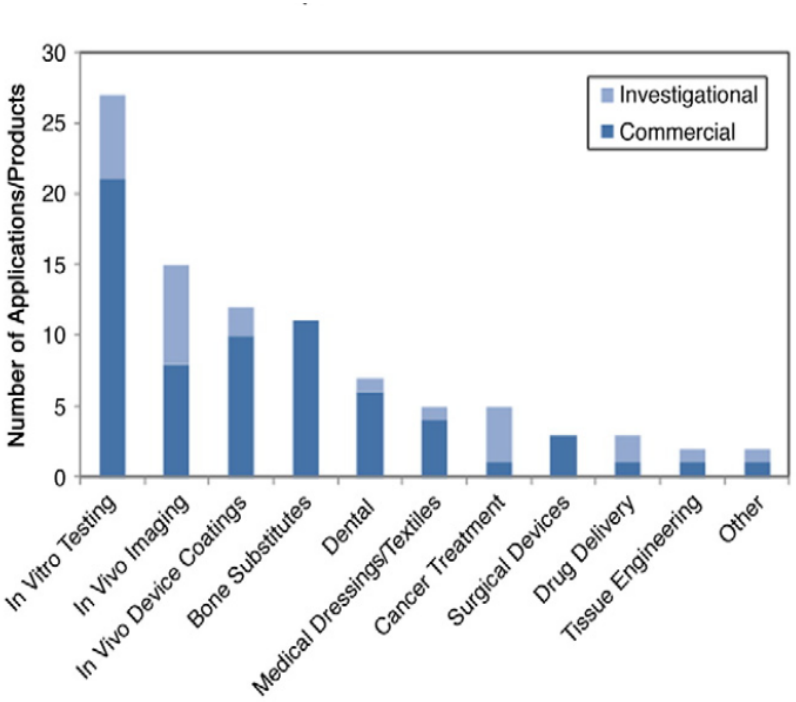
FDA Landscape of drug products and devices

Drug products containing Nanomaterial



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

Nanotechnology in medical devices

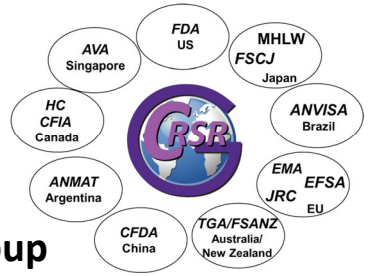


Data from CDRH/FDA

Increase in the submissions and complexity of drug products containing nanomaterials
Standards facilitate regulatory review and approval

International Coordination & Collaboration

- **Global Summit on Regulatory Science – Nanotechnology Working Group**
  - GSRS16 – Nanotechnology Standards and Applications (2016)
  - Global Regulatory, Research, SDOs; 20 countries
  - Prioritized list of standards – white paper
  - GSRS19 – Nanotechnology Summit at JRC in Ispra, Italy, September 2019.

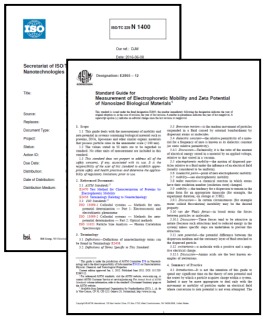


- **International Pharmaceuticals Regulators Program (IPRP) – Nano Working Group**
  - Non-confidential information sharing
  - Regulatory harmonization & collaboration
  - Standards
  - Training

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

- **US-EU Communities of Research**
  - Nanomedicines CoR (New)

- **Standards development**
  - ISO TC229
  - ASTM E56



- **Health Canada, Canadian Food Inspection Agency, FDA**
  - Regulatory training, standards

- **Indo-US Science and Technology Forum (IUSSTF) (FDA, CPSC, NIH with DBT, DST, CDSCO, ICMR)**
  - Indo-US Regulatory Science Symposium (2018)
  - Nanobiotechnology
  - Regulatory research capacity building

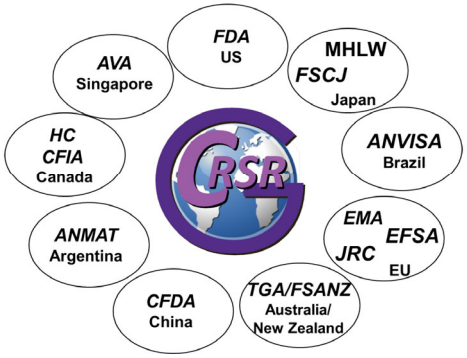
Challenges

- Communication – Nanotoxicology vs Nanomedicine community
- Development of appropriate standards with regulatory relevance
  - Fit for purpose – RMs & Documentary
- Differences in regulations across the globe – Harmonization
- Definition of Nanotechnology/Nanomaterial
- Capacity building


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Global Coalition for Regulatory Science Research (GCRSR)

- Is an international coalition of global regulatory bodies
- Facilitates and promotes the development of regulatory science research as a tool for advancing regulatory science applicable to the public health impacts of safe food and medical products
- Established in 2013



Working Groups

- Established working groups to address specific areas of need for translation of emerging technologies for global regulatory application:
  - Nanotechnology WG
  - Bioinformatics WG
  - Emerging technologies WG
  - Cross-training WG

Nanomedicines Working Group

- Africa
- ANVISA
- China
- COFEPRIS
- EMA
- EU/JRC
- FDA
- Health Canada
- HSA
- MFDS
- MHRA
- MHLW / PMDA
- NAFDAC
- RIVM
- Swissmedic
- TFDA
- TGA

Objectives:

- Non-confidential information sharing, regulatory harmonization or convergence focused on nanomedicines / nanomaterial in drug products and borderline and combination products.
- Regulatory cooperation, including work-sharing, in specific areas (see work plan) of nanomedicines / nanomaterial in drug products with other related international bodies.
- Collaboration of training organization between international regulators
- Promotion of potential consensus finding on standards

https://www.i-p-r-f.org/index.php/en/working-groups/nanomedicines-working-group/

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 ← Wednesday afternoon session at CLINAM

https://us-eu.org/

Standards Development Organizations

ISO TC 229 Nanotechnologies

65 Published Standards
43 Standards under development

Working Groups

- WG1: Terminology and nomenclature
- WG2: Measurement and Characterization
- WG3: Health, Safety and Environmental
- WG4: Material specifications
- WG5: Products and applications

https://www.iso.org/committee/381983.html

ASTM Internation E56

18 Published Standards
7 New work items

Subcommittees

E56.01 Informatics and Terminology
E56.02 Physical and Chemical Characterization
E56.03 Environment, Health and Safety
E56.04 Intellectual Property issues
E56.05 Liaison and International Cooperation
E56.06 Nano-Enabled Consumer Products
E56.07 Education and Workforce Development
E56.08 Nano-Enabled Medical Products

https://www.astm.org/COMMITTEE/E56.htm

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

Summary

- Global increase in FDA regulated products & registered facilities
- Gradual Increase in drug products containing nanomaterial
  - Increase in complexity
- International collaborations in regulatory science and cross training are key for harmonization
- Development of relevant standards enable clinical development of nanomaterial

A list of Standards Needs: Conclusions from GSRS15, October 2015, Parma

Participants: FDA, NIST, EMA, EFSA, ECHA, OECD, NMI, EC, NanoReg, JRC

- **Pristine Nanomaterials**
  - ***Reference Materials***
    - Liposomes
    - Quantitative surface coatings (species, coverage)
    - Number concentration in aqueous solution
    - Multi-modal by size (same nanomaterial)
    - Shape (needs to be specified)
  - ***Documentary Standards***
    - DLS standard test method with specifications for regulatory use
    - Surface coating: composition and stability measurement method
    - Surface coating: zeta potential measurement method
    - Guidance document for tiered approach for methods to measure size and size distribution
    - Asymmetric Flow/Sedimentation Field Flow Fractionation (ISO/PWI, Japan)
    - Electron microscopy technical specification: SEM (ISO/PWI 19749 USA); TEM (ISO/PWI USA/Japan); cryogenic TEM; and low-voltage TEM
  - ***Other needs***
    - Updated public database of reference materials: *hosted by BAM or NIST?*

A list of Standards Needs: Conclusions from GSRS15, October 2015, Parma

- **NMs in Complex Matrices**
  - ***Reference Materials***
    - Simulated body fluids (no nanomaterials)
    - (Specific) nanomaterial in (specific) media
    - Controlled agglomeration nanomaterial
  - ***Documentary Standards***
    - Drug substance release rate from a liposome
    - Quantitation of nanomaterials in blood
    - Quantitation of NMs in tissue
    - Guide for sample preparation for variety of methods, *e.g.*, SEM, TEM, ICP-MS (will be material-dependent)
    - Speciation: relative and total concentrations (e.g., ions, complex NMs)
    - Migration of nanomaterials in food packaging materials
    - Guideline for harmonization performance criteria

Margaret A. Hamburg is Commissioner of the U.S. Food and Drug Administration.

EDITORIAL

Advancing Regulatory Science

ENSURING THE SAFETY AND QUALITY OF FOOD AND MEDICAL PRODUCTS HAS NEVER BEEN MORE complicated. Societies around the world face increasingly complex challenges that require harnessing the best available science and technology on behalf of patients and consumers. This effort requires a strong field of regulatory science to develop new tools, standards, and approaches that efficiently and consistently assess the safety, efficacy, quality, and performance of products. Yet, despite being a critical component of the scientific enterprise, regulatory science has long been underappreciated and underfunded.

Today, we are neither effectively translating scientific discoveries into therapies nor fully applying knowledge to ensure the safety of food and medical products. We must bring 21st-century approaches to 21st-century products and problems. Toxicology is a prime example. Most of the toxicology tools used for regulatory assessment rely on high-dose animal studies and default extrapolation procedures and have remained relatively unchanged for decades, despite the scientific revolutions of the past half-century. We need better predictive models to identify concerns earlier in the product development process to reduce time and costs. We also need to modernize the tools used to assess emerging concerns about potential risks from food and other product exposures.

The U.S. Food and Drug Administration (FDA) is prepared to lead the way in strengthening regulatory science and transforming toxicology. But this will require collaborations and partnerships with academia, industry, and other government agencies. Fortunately, this work has already begun. For example, the FDA and the European Medicines Agency have recently worked to characterize novel biomarkers that identify drug-induced kidney toxicity in preclinical animal models, and several of these biomarkers have now been qualified for regulatory use. And last year, the FDA and the U.S. National Institutes of Health (NIH) launched a new NIH-FDA Regulatory Science Initiative to encourage new research in the field; we recently awarded our first set of grants—$9.4 million over 3 years to support four research projects. The FDA will continue to make targeted investments in such collaborations, including, if resources are available, Centers of Excellence in Regulatory Science housed in academic settings and focused on collaborative, multidisciplinary, multisectoral regulatory science research.

With an advanced field of regulatory science, new tools, including functional genomics, proteomics, metabolomics, high-throughput screening, and systems biology, can replace current toxicology assays with tests that incorporate the mechanistic underpinnings of disease and of underlying toxic side effects. This should allow the development, validation, and qualification of preclinical and clinical models that accelerate the evaluation of toxicities during

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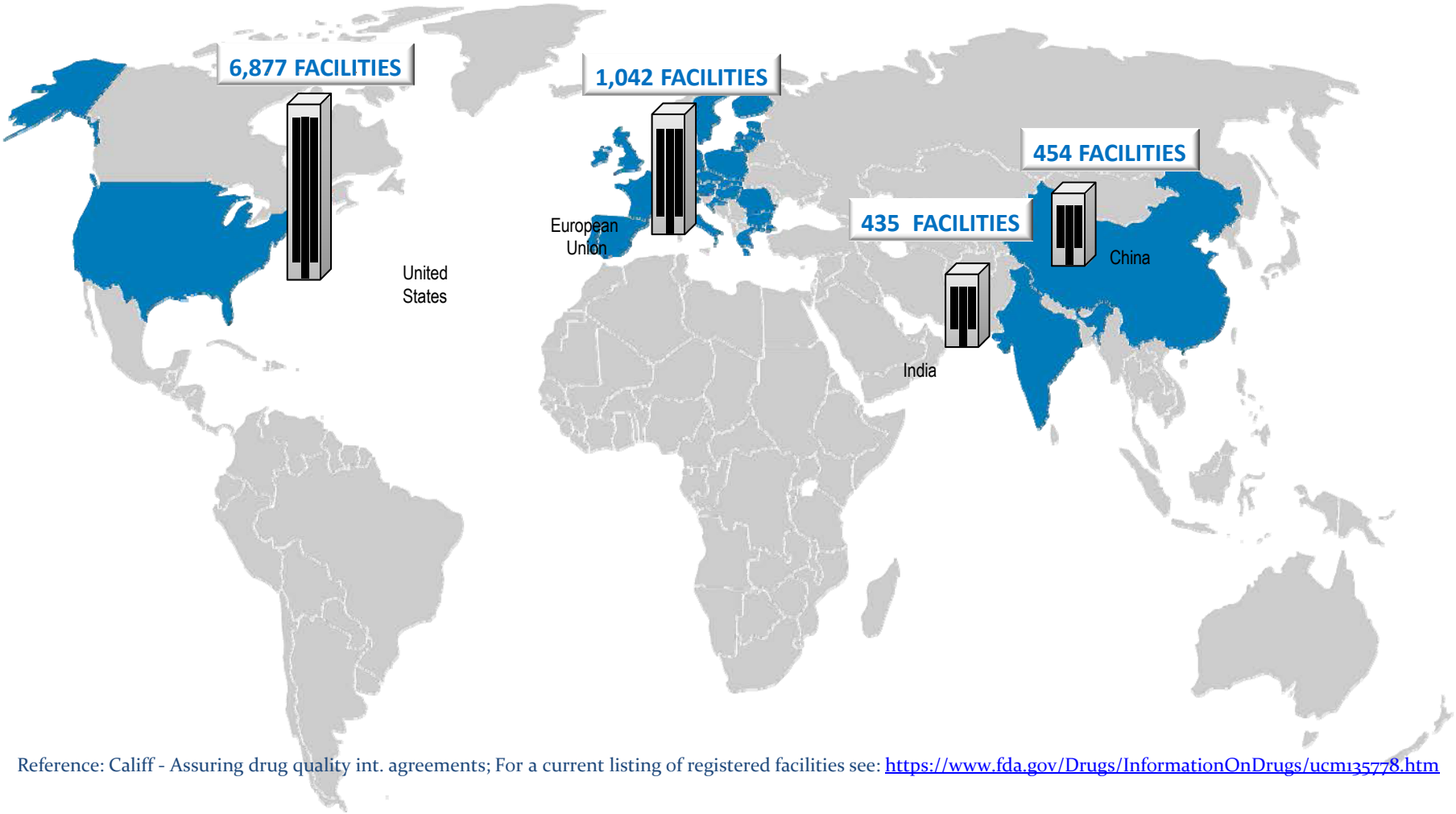
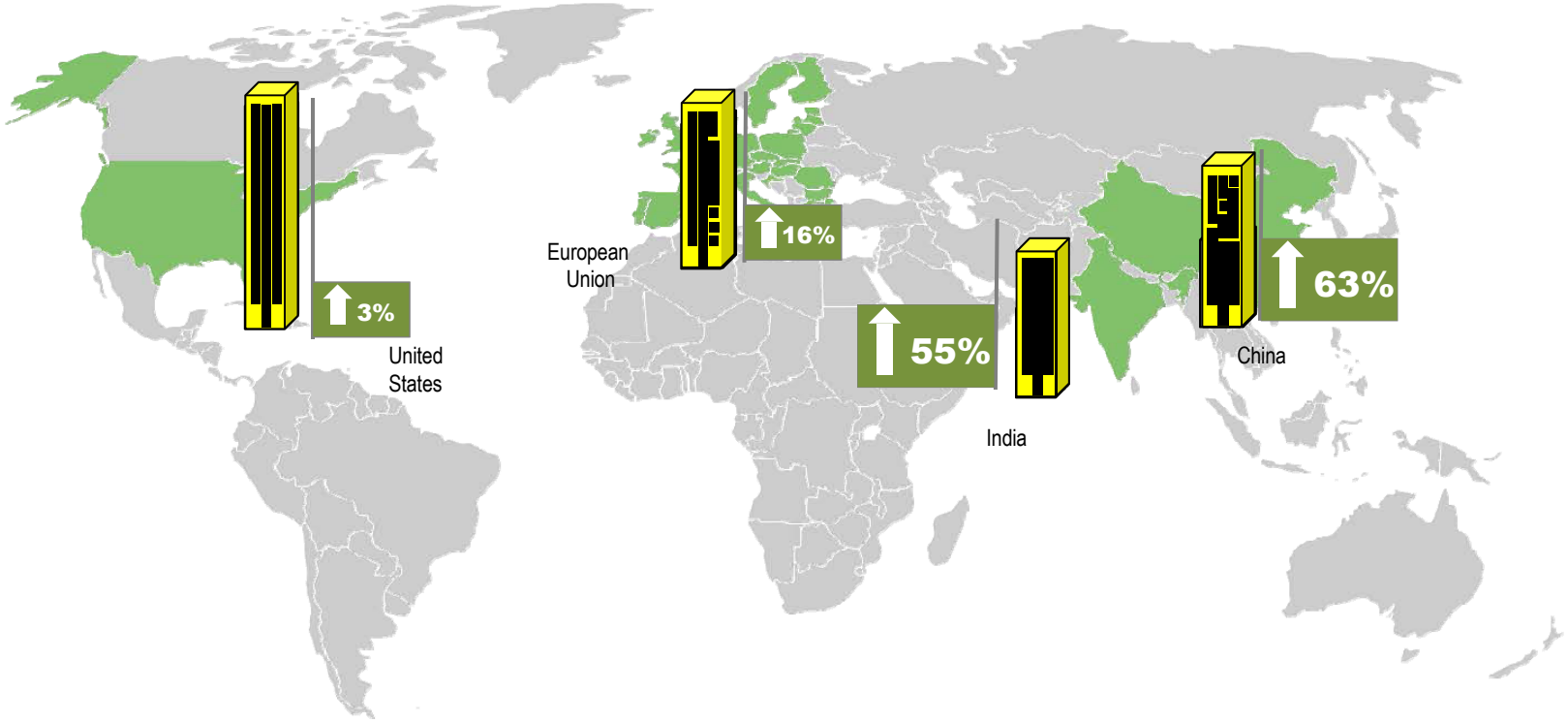
FDA Registered Drug Facilities 2011



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

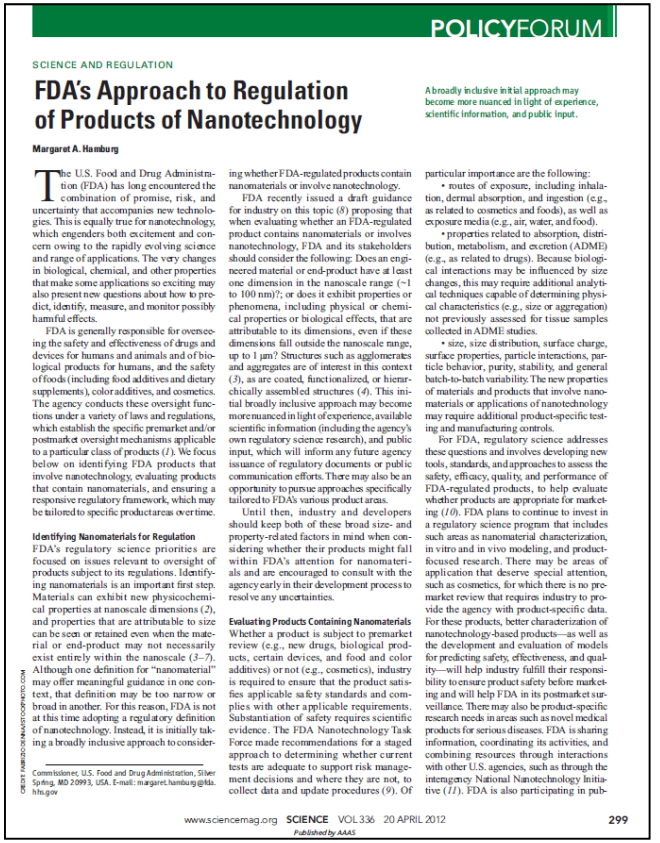
FDA Registered Drug Facilities 2015



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

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 productareas overtime.

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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