Drug Products Containing Nanomaterials: A Regulatory Perspective

Katherine Tyner, PhD
FDA Liaison to the EMA
Europe Office | US FDA
7 December 2022

Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

Regulatory Differences and Similarities

EMA

- 27 EU Member States
- Use of Network Resources
  - Small EMA Staffs
- Clinical trials are not authorized by EMA
- Some generics
- Definitions

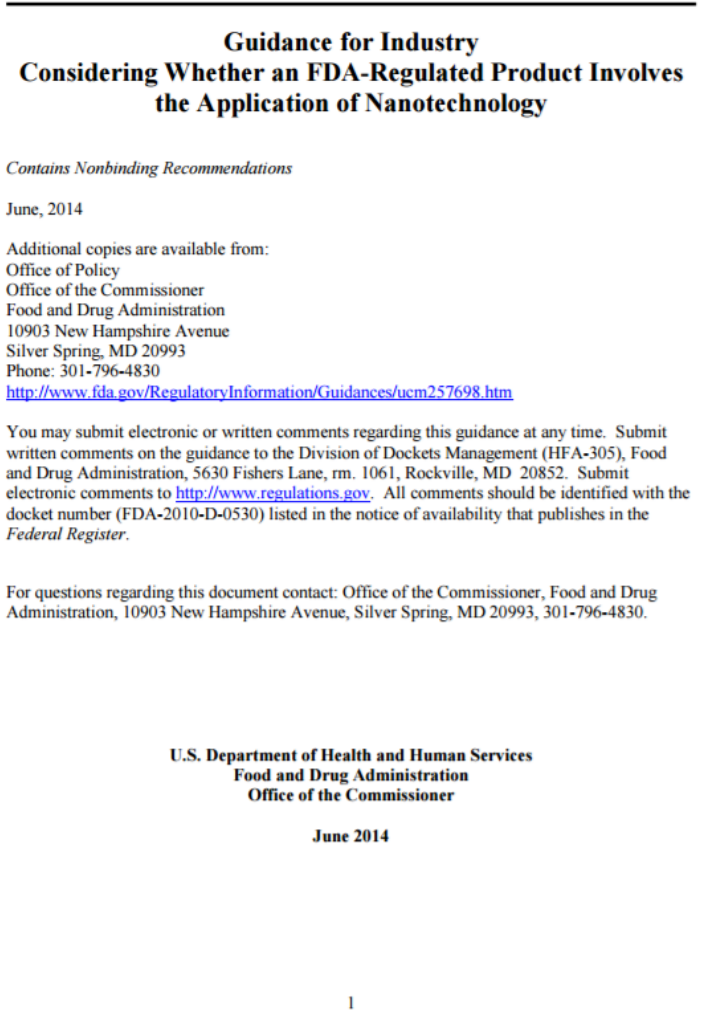
FDA

- 1 Country
- Everything In-House
  - Large FDA Staffs
- Clinical trials are regulated by FDA
- All generics
- Definitions

Different regulatory processes produce the same scientific questions

US FDA Nanotechnology Regulatory Framework

- No regulatory definition of nanotechnology or related terms
  - E.g., no definition for “Nanomedicine”
- Regulations and law do not separate nanotechnology products
  - Same regulatory pathways
  - Do not categorically judge products as intrinsically benign or harmful
- FDA regulatory framework and review processes adequately identify and manage potential risks associated with the use of nanomaterials in products



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

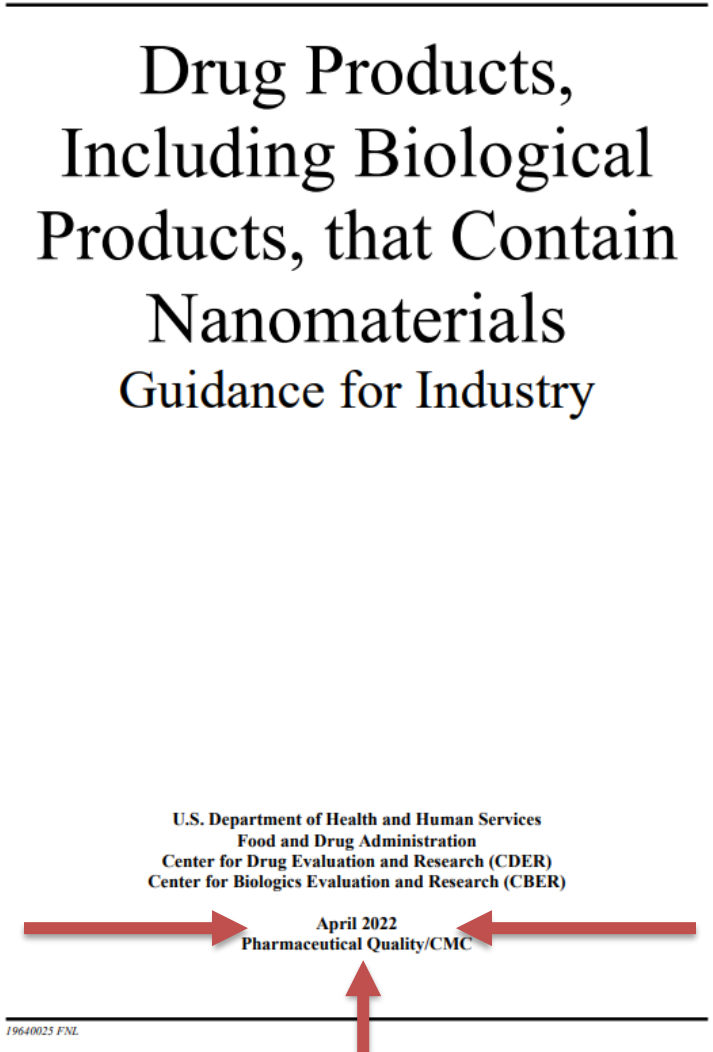
June 2014

1

2014 FDA Guidance

- Deliberate and purposeful manipulation and control of dimensions
- External dimensions or internal surface structure 1-100 nm
- Properties attributable to the dimensions
- Addressed on a case-by-case basis using FDA's existing review processes.

2022 CDER/CBER Guidance


Drug Products, Including Biological Products, that Contain Nanomaterials

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2022
Pharmaceutical Quality/CMC

19640025 FNL

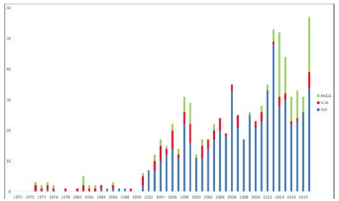
- Focuses on identifying and managing new risks
- Same standards of safety, efficacy, and quality
- Risk-based approach for characterization and intent of nanomaterial

Risk/Benefit Analysis

Nanomaterials in Drug Products: Examples

Platform	Example		
	Name	NDA Approval	Indication
Liposome	DOXIL® (Doxorubicin)	1995[1]	Cancer
Inorganic nanoparticle	FERRLECIT® (Sodium ferric gluconate complex)	1999[2]	Anemia
Protein -based	ABRAXANE® (Paclitaxel)	2005	Cancer
Polymer -based	MACUGEN® (Pegaptanib sodium)	2004	Macular degeneration.
Emulsion	RESTASIS® (Cyclosporine)	2002[4]	To increase tear production
Lipid complex	AMPHOTEC® (Amphotericin B)	1996	Invasive aspergillosis
Nanotube	SOMATULINE DEPOT® (Lanreotide acetate)	2007	Acromegaly
Nanocrystal	TRICOR® (Fenofibrate)	2004[3]	Hypercholesterolemia
Micelle	TAXOTERE® (Docetaxel)	1996	Cancer

[1] First ANDA approval in 2013
[2] First ANDA approval in 2011
[3] First ANDA approval in 2011
[4] **First ANDA approval in 2022**



Nanotechnology – A Decade of Progress and Innovation: A Report by the U.S. Food and Drug Administration
https://www.fda.gov/media/140395/download

Generic Drug Products

New Drug Application (NDA)

Brand Name Drug

NDA Requirements

1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing

6. Animal Studies
7. Clinical Studies
8. Bioavailability

Abbreviated NDA (ANDA)

Generic Drug

ANDA Requirements

1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing

6. Bioequivalence

A **complex generic drug product** is (*among others*) a product with:

- a complex active ingredient(s) (e.g., peptides, polymeric compounds, complex mixtures of APIs, naturally sourced ingredients)
- a complex formulation (e.g., liposomes, colloids)
- a complex route of delivery (e.g., locally acting drugs such as dermatological products and complex ophthalmological products and otic dosage forms that are formulated as suspensions, emulsions, or gels)
- a complex dosage form (e.g., transdermals, metered dose inhalers, extended release injectables)

Product Specific Guidances

- outline the information and types of studies recommended to support the approval of generic
- product referencing a specific RLD product.
- PSGs are posted on a quarterly basis
- as of Oct 2022, there are 23 for a complex ophthalmic or injectable product containing nanotechnology

Regulatory Needs

- Early discussions on novel formulations

- (continued) Regulatory Research
- Standards

Example: Suggested Minimal Characterization of Nanomaterials in Drug Products 2013

- Agglomeration/aggregation
- Chemical composition
- Crystal structure/crystallinity
- Particle size/size distribution
- Purity
- Shape
- Surface area
- Porosity
- Surface charge
- Surface chemistry (composition and reactivity)
- Endotoxin content
- Solubility
- Stability
- Concentration
- Zeta potential
- Surface energy
- Catalytic properties
- Dustiness
- Oleophilicity/hydrophilicity
- Grain size
- Photocatalytyic activity
- Octanol-water partition coefficient
- Redox potential
- Radical formation potential

Card and Magnuson, J. Food Sci., 74, vi-vii, 2009; MinCHAR project; www.characterizationmatters.org
http://www.toxicology.org/isot/ss/nano/docs/Ostraat_guest_presentation.pdf

Attributes of Nanomaterials

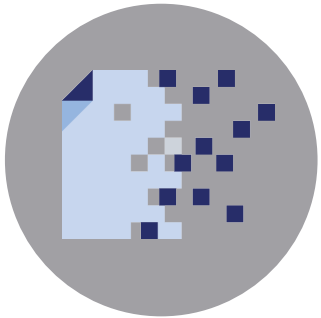
ALWAYS

- **Chemical composition**
- **Average particle size**
- **Particle size distribution**
- **General shape and morphology**
- **Stability, both physical and chemical**

SOMETIMES

- Assay and distribution of any active ingredient
  - Associated with the nanomaterial and free in solution
- Structural attributes that relate to function
- Surface properties
- Coating properties
  - Including how coatings are bound to the nanomaterial
- Porosity
- Particle concentration
- In vitro release
- Crystal form
- Impurities
- Sterility and endotoxin levels

Why Are Standards Important?



Consistency + **Predictability** + **Credibility**

= Science Based Decisions

FDA Nanotechnology Standard Participation

- ASTM International
  - E56 Committee on Nanotechnology
- International Organization for Standardization
  - TC 229 Nanotechnologies
- United States Pharmacopeia (USP)
  - USP Joint Sub-committee on Nanotechnology

Acknowledgements

- Olen Stephens
- Xiaoming Xu
- Erin Woods
- Darby Kozak
- Anil Patri
- FDA Nanotechnology Task Force
- CDER Nanotechnology Working Group

U.S. FOOD & DRUG ADMINISTRATION

Questions?

Katherine Tyner, PhD
FDA Liaison to the EMA
Europe Office | US FDA
December 7, 2022


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Resources

- GUIDANCE DOCUMENT: Drug Products, Including Biological Products, that Contain Nanomaterials - Guidance for Industry; APRIL 2022
- GUIDANCE DOCUMENT: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology - Guidance for Industry; JUNE 2014
- GUIDANCE DOCUMENT: Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation; APRIL 2018
- PRODUCT SPECIFIC GUIDANCES:Product-Specific Guidances for Generic Drug Development | FDA
- Center for Drug Evaluation and Research Nanotechnology Programs | FDA
- Complex Generics News | FDA
- FDA NanoDay Symposium 2022 - 10/11/2022 | FDA