

Developing Drug Products Containing Nanomaterials: CDER CMC Perspective

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Disclaimer

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

Overview



- Introduction of 2022 CDER/CBER Nanomaterials Guidance
- CMC Considerations for Nanomaterial Product Development
- Discussion of Two Case Studies
- Early Development Advice

Goals for this talk

- Clarify high level takeaways of the guidance
- Facilitate drug development with fewer regulatory issues
- Set the stage for the next speakers

Poll Question from Registration



When developing a new product that contains nanomaterials, what factors should be considered:?

- A. The function of the nanomaterial
- B. Potential risks to patients
- C. Route of administration
- D. All of the above

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

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.



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

- Focuses on identifying and managing new risks
 - FDA doesn't judge nanomaterial product a priori as harmful or benign
 - Same standards of safety, efficacy, and quality
 - Characterization and intent of nanomaterial
 - Risk-based approach
 - Discriminating in vitro release method with clinical relevance



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- No new regulatory requirements
 - Characterization is key through development
 - Bridging physical/chemical properties to clinical outcome
 - Addresses lifecycle control

- CMC Review Considerations:
 - Adequacy of analytical methods and characterization
 - In vitro evaluation to determine impact of particle size on product performance
 - Process risks and control strategy for nanomaterial products
 - Excipients can require same level of risk assessment/mitigation



- A note on analytical methods
 - Standardized methods are under development
 - Complementary methods
 - Reporting of results
 - Method suitability
 - Sample preparation
 - Sampling strategy
 - Dissolution/In vitro drug release



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- Nonclinical and Generics
 - Defer to other speakers
- Clinical Considerations for 505(b)(2):
 - Plasma exposure may not be sufficient due to endocytosis or EPR
 - Describes low, medium, and high-risk products, requiring different clinical evidence of exposure/response
 - Characteristics of the nanomaterial, route of administration, and frequency of use can influence clinically significant changes.

Risk/Benefit analysis



Product design reflects study's purpose



- Objectives from your study?
- Critical physical/chemical attributes of your drug product?
- Clinical supply characterized, controlled, and stable?
- Knowledge gaps: how are you mitigating residual risk?

Drug Development and Lifecycle Control



- Bridge the gaps
- Critical quality attributes
- Retain samples for bridging
- Monitor and characterize even if not controlled

Early Formulation Development



KEEP
THINGS
SIMPLE

- Use conventional excipients within demonstrated level¹
- Novel excipients and human/animal derived excipients require evaluation
- Dose according to the active moiety²
- Justify novel technology (e.g., nanotechnology, device combinations)

¹<https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm>

²<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM379753.pdf>

Stability

- At least a month of long-term and accelerated data
- Commitment to follow prescribed protocol
- Consider an Accelerated Stability Assessment Program (ASAP)
- *Demonstrate you understand your product:*
 - *What is critical for it to perform as designed,*
 - *How to maintain its integrity.*



Q. Chan et. al. J. Pharm. Innov. 2012, 7:214-224.

K. Waterman et. al. *Pharmaceutucial Research* 2007, 24:780-790.

K. Waterman *Pharmaceutical Outsourcing* 2012,

Case Study 1

- Series of related products
- Seemingly simple formulation
- Similar manufacturing processes
- Manufacturing Process critical
- Identified potential excipient issues even though they are compendial



Case Study 2

- Product still under development under IND
- Complex design targeted, precision medicine
- Chemistry adaptable to platform
- Control of multiple CQAs necessary early in development



pIND Meetings are a gift



Best, free advice; don't waste it.

- FDA is not a developing your product
- Seek to reach agreements
 - Impurity limits and justifications
 - Data necessary to launch a clinical study
 - Mitigation strategy for known residual risks
 - Link study objective to product design
 - Demonstrate rational drug product design
 - Current and future data packages



Additional CDER Resources

- Nanotechnology database
- Nanotechnology Reviewer Network (NRN)
- Internal regulatory research

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

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](#)
- [GUIDANCE DOCUMENT: Content and Format of Investigational New Drug Applications \(INDs\) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products - Guidance for Industry; NOVEMBER 1995](#)

Summary

- Introduced 2022 Nanomaterial Guidance
- Drug development using risk/benefit paradigm
- Case studies
- Encourage interaction with FDA



Closing Thought

You know your product better
than anyone
and you know our concerns.

Demonstrate that understanding
in the language of risk/benefit



Questions?

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