Developing Drug Products Containing Nanomaterials: CDER CMC Perspective

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FDA NanoDay Symposium – October 11, 2022

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

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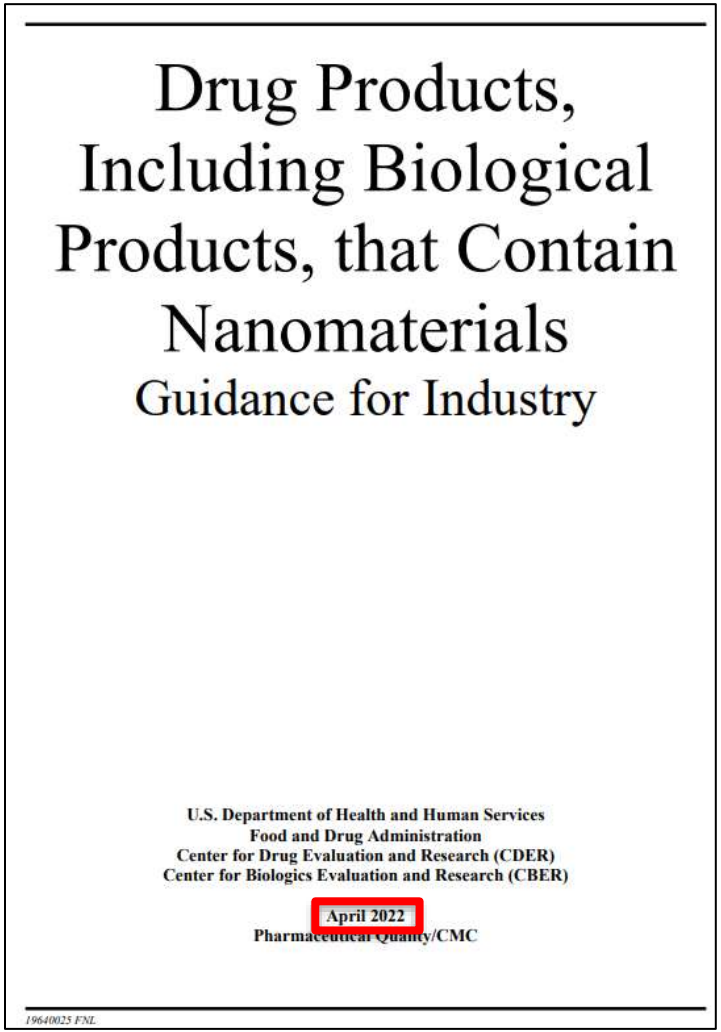
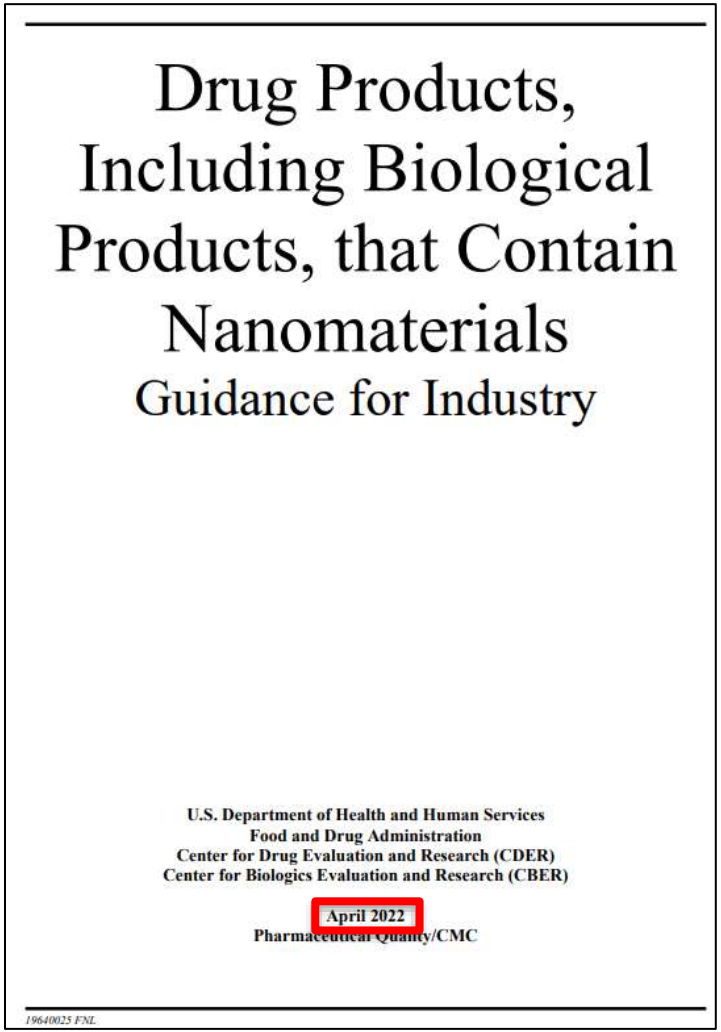
2014 FDA Guidance

- 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.



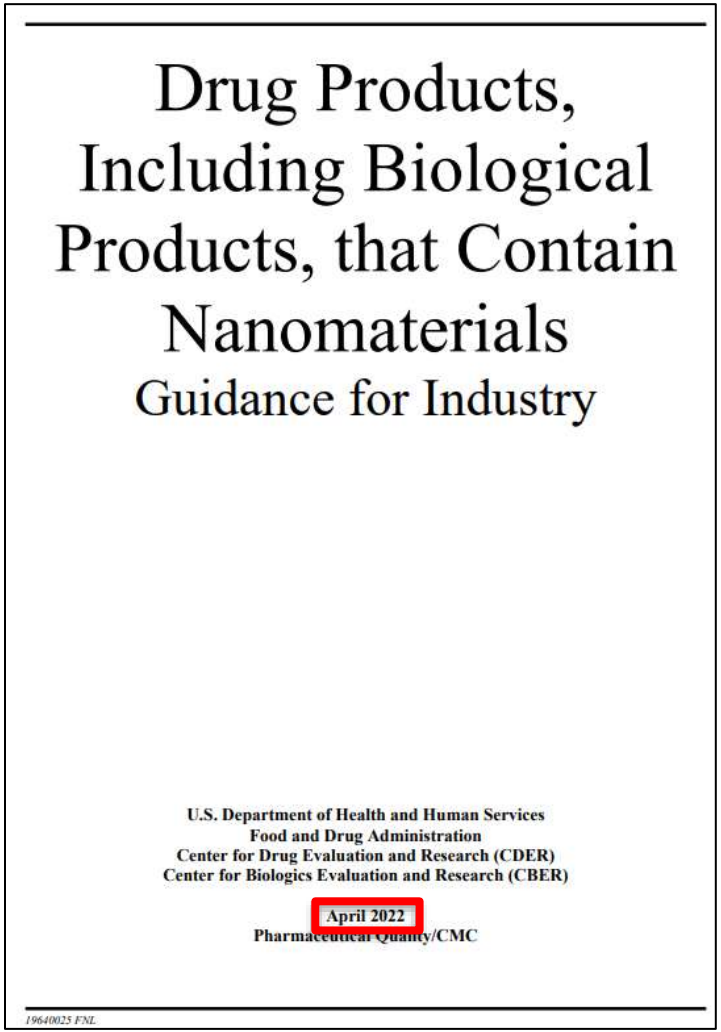
- Focuses on identifying and managing new risks
  - FDA doesn't judge nanomaterial product a priori as harmful or benign
  - Same standards of safety, efficacy, and quality
  - Characterization and intent of nanomaterial
  - Risk-based approach
  - Discriminating in vitro release method with clinical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



- 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



- 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

- Use conventional excipients within demonstrated level[1]
- Novel excipients and human/animal derived excipients require evaluation
- Dose according to the active moiety[2]
- 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. *Pharmacetucial 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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