# Regulatory Science Aspects of Products Containing Nanoscale Materials

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# Outline

**What does CDRH (FDA) do in regulation of devices containing nanoscale materials:**

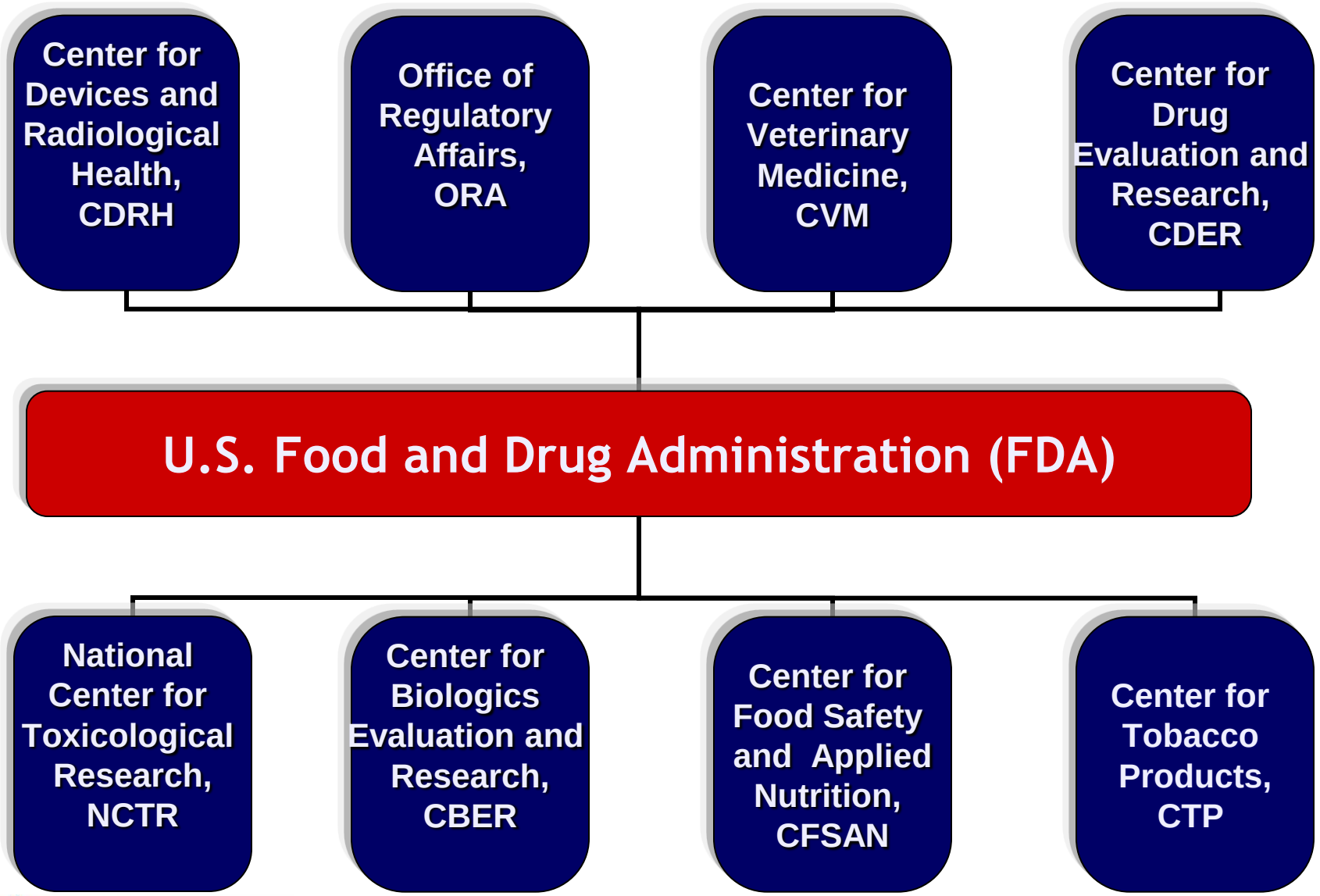
1. **Regulatory pathways of translating devices to the clinic**
2. **Regulatory science challenges/issues**

# FDA Mission

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.

FDA is also responsible for 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.

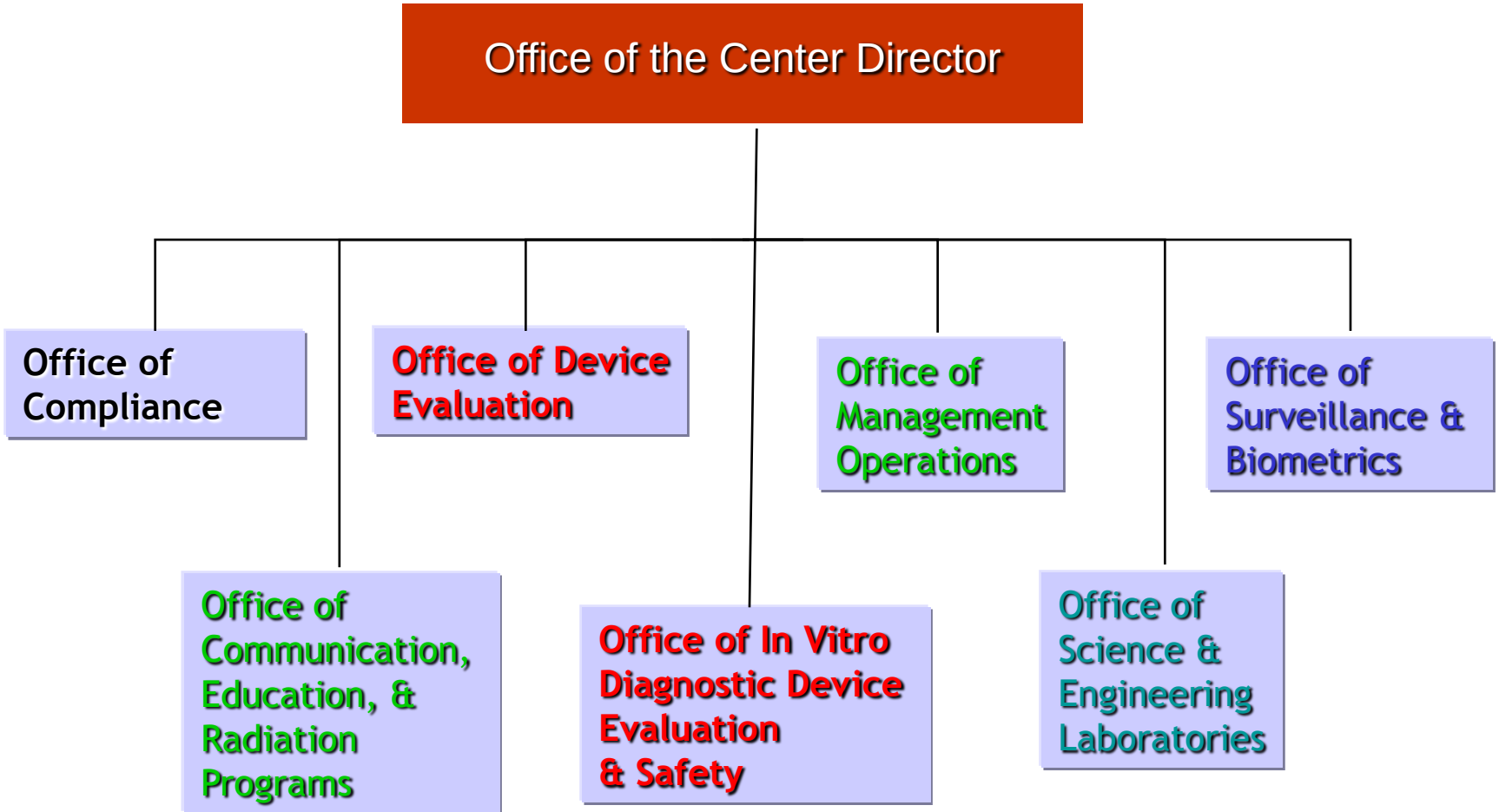



United States Department of Health & Human Services

FDA

C·D·R·H Center for Devices and Radiological Health

# CDRH Organization

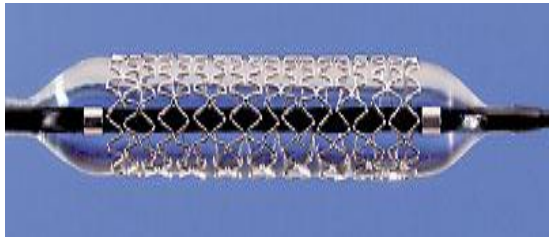


# Medical Device Classification-
# Risk-Based Paradigm

**Medical devices are classified and regulated according to their degree of risk to the public**

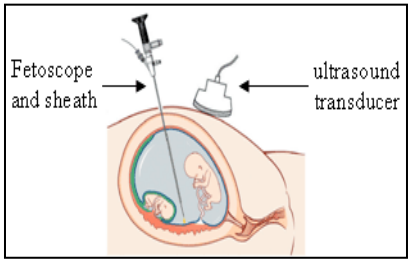
**Class I**

**Class II - 510(k)**



**Class III - PMA**

***De Novo***




**HDE**

# Medical Devices Classification

**Based on level of regulation necessary to protect the public**

- **Class I**
  - General Controls (GC)

General Controls include:
- Prohibition against adulterated or misbranded devices
- Premarket notification (510(k)) requirements
- Banned devices
- Good Manufacturing Practices (GMPs)
- Listing of device types
- Record keeping
- Repair, replacement, refund

- **Class II**
  - Special Controls + GC
  - premarket notification (510(k)

Special Controls include:
- Labeling
- Guidance
- Tracking
- Design Controls
- Performance Standards
- Postmarket Surveillance

- **Class III**
  - Premarket Approval

- Most complex, highest risk
  - Establish safety and effectiveness
  - Bench - Animal – Human testing
  - May include post-approval study requirements

# Three Steps to Obtaining Marketing Clearance from CDRH

## STEP ONE

- Ensure the product is a medical device, meets the definition of a medical device in section 201(h) of the FD&C Act.

## STEP TWO

- Classify Your Device, i.e., determine which one of the three classes the device may fall into.
- CDRH Classification identifies the level of regulatory control necessary to assure the safety and effectiveness of a medical device.
- Classification of the device will identify, unless exempt, the marketing process.
- Manufacturer must obtain FDA clearance/approval for marketing.

# Three Steps to Obtaining Marketing Clearance from CDRH (cont)

## STEP THREE

- **Select the appropriate marketing application.**
- **Develop data and/or information necessary to submit a marketing application, and to obtain FDA clearance to market.**
- **Develop clinical performance data to obtain clearance to market.**
- **Conduct trial in accord with FDA's Investigational Device Exemption (IDE) regulation.**

# Other Requirements Besides Marketing Clearance (cont.)

- **Postmarket Surveillance Requirements Require Compliance with:**

  **- Quality System Regs (Good Manufacturing Practices, GMPs)**

  **+ The QS regulation covers the design, packaging, labeling and manufacturing of a medical device.**

  **- Medical Device Reporting (MDR) Regs**

  **+ The MDR regulation is an adverse event reporting program.**

# We discussed

- **Role of FDA and Centers**
- **Regulatory pathways of bringing devices to market**

# Basis for Regulation of Nanotechnology

- **Current regulations are flexible so as to incorporate new emerging fields such as nanotechnology. For example:**

  **- Medical device regulations are based on risk management, and**

  **- This risk management approach is in principle suitable to address all kinds of risks, including risks associated with medical devices manufactured using nanoscale materials.**

- **Similar analysis may be made for other FDA regulated products**
- **Additional steps may be needed in the future**

# Regulatory Landscape

**I. Regulatory Science**

Characterization and mechanistic understanding of nanoscale materials behavior from physical, chemical and biological aspects

**II. Regulations**

Current regulations are adequate to ensure safety and efficacy

**III. Issues**

- Does the product contain nanoscale materials
- When does the presence of nanoscale materials change the product classification

**IV. Review process**

Case-by-case versus class-based review

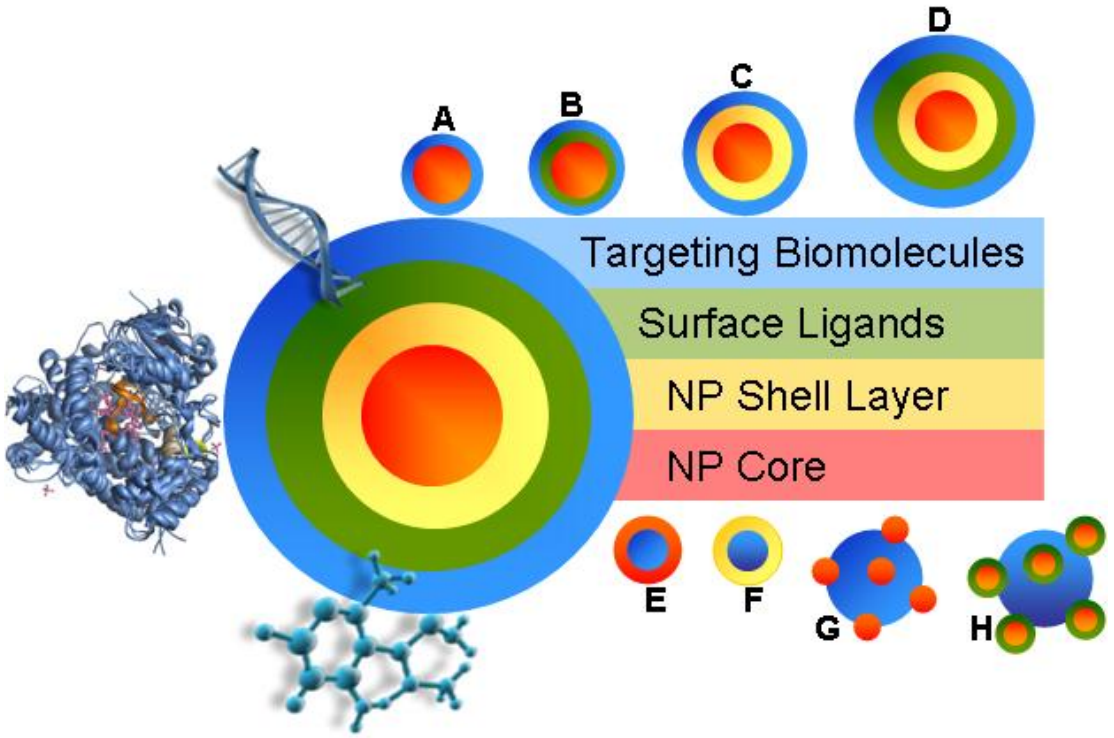
# Regulatory Science

## Driving Forces

1. Mechanistic understanding of nanoscale materials behavior from physical, chemical and biological aspects
2. The dynamic nature of nanoscale materials in biological systems
3. Advancing our knowledge regarding the characterization of nanoscale materials
4. Minimum level of characterization needed

## Specific activities

- Characterization methods
- Mechanisms of transport, and mechanisms of accumulation, degradation, and release and data
- In-vitro and in-vivo behavior
- ADME, biocompatibility and toxicity
- Guidance preparation
- Standards development




Schematic of potential NP-bioconjugate components and configurations:
A. Biomolecule interacting with NP core; B. Biomolecule interacting with NP core via intermediate ligands; C. Biomolecule interacting with NP shell layer that surrounds the NP core; D. Biomolecule interacting with NP shell layer—NP core via intermediate ligands; E. Porous NP core containing entrapped biomolecules; E. Porous/hollow NP core containing entrapped biomolecules surrounded by a NP shell layer; F. NP core smaller than much larger biomolecule; G. NP core smaller than much larger biomolecule attached via intermediate ligands. (H) NP core (or NP core/NP shell structures) particles smaller in size than the much larger biomolecule attached via intermediate ligands. *Ref. Techniques for the Characterization of Nanoparticle-Bioconjugates; Kim E. Sapsford, et al.*

# Characterization and Use of consensus standards in review of nanotechnology products

- **Sponsors required to produce a range of characterization data to gain better understanding of safety and efficacy issues**

  **1. Physical**

  **2. Chemical**

  **3. Biological**

**Minimum level of characterization**

# Characterization Data

1. Physical properties evaluation determines physical characteristics of materials used in the device.
    - Size distribution, aggregation, methods and standards used, repeatability
    - Aspect ratio of particles
    - Specific surface area
    - Stability as a function of storage time
2. Chemical and surface chemical properties evaluation describe the material and its "potential" to undergo chemical change or reaction by virtue of its composition.
    - Overall Composition
    - Impurities, especially those that may affect its behavior
    - Surface charge and surface properties

# Characterization Data (cont.)

3. Biological properties evaluation determines potential toxicity resulting from contact of materials in the device with the body.

- The device material has the potential to produce adverse local or systemic effects; therefore, evaluation of a new device requires data from systematic testing to ensure that the benefits exceed any potential risks.

  - proof of efficacy
  - sterility and depyrogenation
  - toxicity and biocompatibility

- An appropriate set of tests include those in ISO-10993

  - Interference of nanoscale particles

# Examples of tests included in ISO-10993

- toxicity (acute, sub-chronic and chronic)
- irritation to skin, eyes and mucosal surfaces
- sensitization
- hemocompatibility
- effects on reproduction and developmental
- genotoxicity
- carcinogenicity
- neurotoxicity
- immunotoxicity
- inflammation (ASTM F04)
- cytotoxicity (ASTM F04)

**"Ultimately, the specific clinical application and the materials used in the manufacture of the device determine the appropriateness of tests."**

# Summary

- **Primary Focus**

  - Protecting public health and promoting nanotechnology

- **Challenges remain in nanotechnology**

  - Mechanistic understanding, methods, standards, data

- **Gaps remain in developing test methods and standards**

  - Identification and assessment of nanoscale materials in products

    + characterization methods

    + biocompatibility and toxicity assessment

# More information available at FDA Websites

http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/default.htm
http://www.fda.gov/Training/CDRHLearn/default.htm
Overview of Regulatory Requirements: Medical Devices
- Quality System Regulation 21 CFR Part 820 Basic Introduction
- Device Establishment Registration and Listing
- Overview of the Premarket Notification Process – 510(k)
- Bioresearch Monitoring (BIMO)

http://www.fda.gov/cdrh/devadvice/
http://www.fda.gov/cder/drug/default.htm
Investigational New Drug Application (21 CFR Part 312)
Applications for FDA Approval of a Biologic License (21 CFR Part 601
http://www.fda.gov/ScienceResearchSpecialTopics/Nanotechnology/default.htm