

Science and Regulatory Issues Relevant to Devices Containing Nanoscale Materials

Subhas G. Malghan, PhD

Office of Science and Engineering Laboratories

Center for Devices and Radiological Health

Food and Drug Administration

Presentation at the

NanoBusiness Alliance Washington DC Roundtable

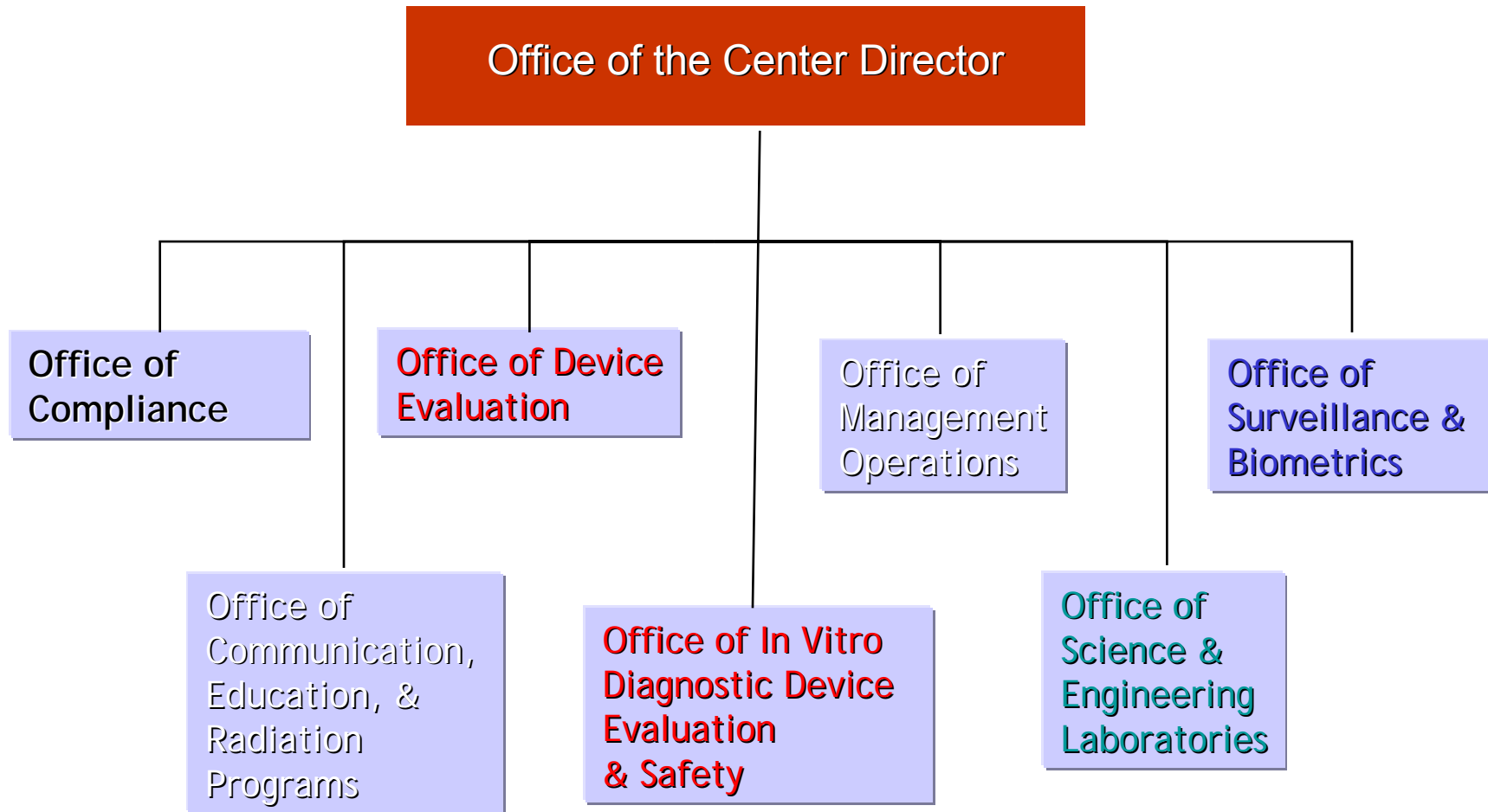
March 17, 2010

Outline

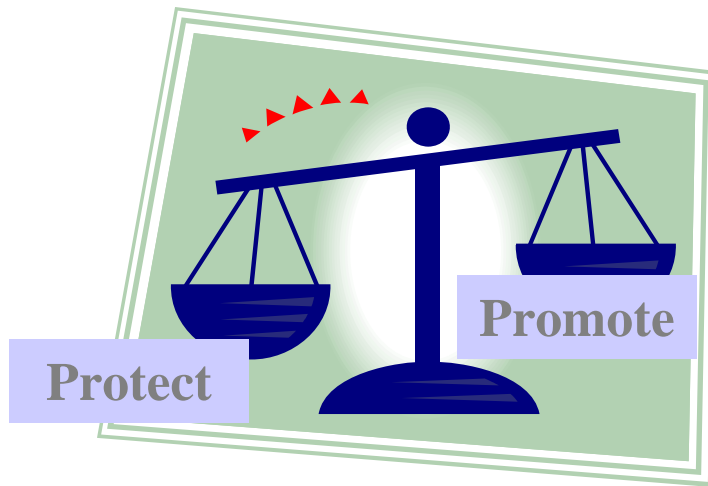
Science and Regulatory Issues Relevant to Devices:

- 1. Regulatory pathways of translating devices to the clinic**
- 2. Challenges/issues**
 - + Science**
 - + Technology**
 - + Regulatory**

CDRH Organization



CDRH (FDA) Mission



CDRH **promotes and protects** the health of the public by ensuring the **safety and effectiveness** of medical devices and the safety of radiological products

*(throughout the total product life cycle **and** fostering innovation)*

Medical Device Classification- Risk-Based Paradigm

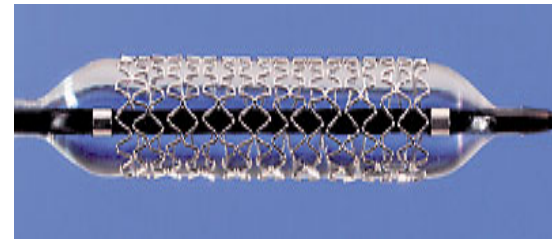
Medical devices are classified and regulated according to their degree of risk to the public



Class I



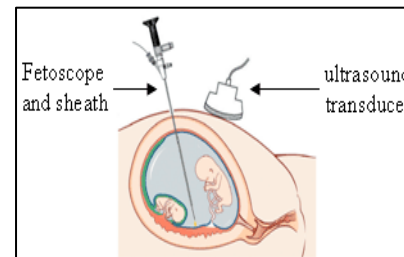
Class II - 510(k)



Class III - PMA



De Novo



HDE

Regulatory Basis

Current medical device regulations can adequately address devices produced using nanoscale materials.

- **The medical device regulations are based on risk management, and**
- **This risk management approach is in principle suitable to address all kinds of risks, including the risks associated with medical devices manufactured using nanoscale materials.**

Regulatory Landscape – Science challenges

I. Science

**Mechanistic understanding of
nanomaterials behavior from
physical, chemical and
biological aspects**

Regulatory Landscape – Science and Regulatory challenges

I. Science

**Mechanistic understanding of
nanomaterials behavior from
physical, chemical and
biological aspects**

II. Regulations

**Existing regulations are
sufficient to ensure safety
and efficacy**

Regulatory Landscape – Science and regulatory challenges

I. Science

Mechanistic understanding of nanomaterials behavior from physical, chemical and biological aspects

II. Regulations

Existing regulations are sufficient to ensure safety and efficacy

III. Issues

- Does the product contain **nanomaterials**?
- When does the **nanomaterials** presence of NP change the product classification?

Regulatory Landscape – Ready and addressing multiple issues

I. Science

Mechanistic understanding of nanomaterials behavior from physical, chemical and biological aspects

II. Regulations

Existing regulations are sufficient to ensure safety and efficacy

III. Issues

- **Does the product contain nanomaterials?**
- **When does the presence of nanomaterials change the product classification?**

IV. Current review process

Case-by-case review

FDA Regulatory Science

1. Mechanistic understanding of **nano scale materials** behavior from physical, chemical and biological aspects
2. Advancing our knowledge regarding the characterization of **nanoscale materials**
3. What is the minimum level of characterization needed?

Knowledge and data to address potential questions related to:

- Characterization methods
- Physico-chemical stability
- Physical, chemical and biological interaction
- In-vitro and in-vivo behavior
- ADME, biocompatibility and toxicity
- Guidance preparation
- Standards development

Materials Science Challenges

- **Challenges**
 - **Lab innovation → Commercial product**
 - **Materials manufacturing and scale-up**
 - **Production of medical grade materials**
 - **Multidisciplinary S&E expertise**
- **Easier path**
 - **Develop NT for existing applications to improve products; e.g., drug delivery**
 - **Simple to manufacture products come to market first; e.g., powders, colloids, coatings (catheters)**

Regulatory Issues

Premarket

- Does the product contain nano-scale particles?
- When does the presence of nanoscale change the product classification?

Postmarket

- Can existing Quality System Regulation (QSR) requirements for process validation address issues for manufacturing nanoscale materials containing products?

Current Review Process

- **Primary focus is on product safety and efficacy**
- **Case-by-case evaluation**
- **Application of standards**

Risk management challenges in case-by-case evaluation

- Understanding **general risks** of products using nanoscale materials
- Greater **need for understanding risks** of:
 - free nanoscale materials because of potential for altered biological (toxicological) behavior
 - solid materials with surface nanoscale features as in surface coatings, or with other nanotopographical features
- **Guidances (at present)** may play an important role here by describing known risks, and possibly providing solutions to manage these risks.
- There is a need for **collection of data** at the pre- and post- market level on:
 - risk observed in premarket review
 - risks experienced at the postmarket level, incl manufacturing
- **Future guidances** and/or regulatory pathways can be developed with better predictability and precision.

Use of consensus standards in review of nanotechnology products

- Required to produce a range of characterization data to gain better understanding of safety and efficacy issues
 - Physical
 - Chemical
 - Biological (ISO 10993)
 - + Proof of efficacy
 - + Sterility and depyrogenation
 - + Toxicity and biocompatibility

Reproducibility and role of standards

- **GLP/GMP/QSR requirements**
- **Use of consensus standards in establishing batch-to-batch reproducibility**
- **Use of reference nanoscale material standards for calibration and biocompatibility studies (fate, behavior, and effects)**

Use of Guidances, standards, and test methods in review of 510(k) products

- **Blue book memorandum #G95-1 (guidance), "Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part-1: Evaluation and Testing,"**
- **#G95-1 Includes:**
 - **a flow chart entitled "Biocompatibility Flow Chart for the Selection of Toxicity Tests for 510(k)s."**
 - **an FDA-modified matrix that designates the type of testing needed for various medical devices.**

Initial Evaluation Tests for Consideration

Device Categories		Biological Effect																	
Body Contact (see 4.1)	Contact duration (see 4.2)	<table border="1"> <tr> <td>Cytotoxicity</td> <td>Sensitization</td> <td>Irritation</td> <td>Acute toxicity</td> <td>Chronic toxicity</td> <td>Gentoxicity</td> <td>Implantation</td> <td>Hemolysis</td> </tr> </table>										Cytotoxicity	Sensitization	Irritation	Acute toxicity	Chronic toxicity	Gentoxicity	Implantation	Hemolysis
	Cytotoxicity											Sensitization	Irritation	Acute toxicity	Chronic toxicity	Gentoxicity	Implantation	Hemolysis	
	A-limited (24h)																		
	B-prolonged (24h to 30 days)																		
C-permanent (>30days)																			
Implant devices	Tissue/ bone	A	x	x	x	o									
		B	x	x	o	o	o	x	x	.									
		C	x	x	o	o	o	x	x	.									
	Blood	A	x	x	x	x	.	.	x	x									
		B	x	x	x	x	o	x	x	x									
		C	x	x	x	x	x	x	X	x									

X = ISO Evaluation Tests for Consideration

O = Additional Tests which may be applicable

Note + Tissue includes tissue fluids and subcutaneous spaces

Note ^ For all devices used in extracorporeal circuits *See Table 2 for Supplementary Evaluation Tests

(Updated April 12, 1996)

FDA Regulatory Scene

– Ready and addressing multiple challenges

I. Science

Mechanistic understanding of nanoscale particles behavior from physical, chemical and biological aspects

II. Regulations

Existing regulations are sufficient to ensure safety and efficacy

III. Issues

- **Does the product contain nanoscale particles (NP) ?**
- **When does the presence of NP change the product classification?**

IV. Current review process

- **Focus on safety and efficacy of product**
- **Case-by-case review**
- **Application of standards**

Summary

- **Primary Focus**
 - Promoting nanotechnology and protecting public health
- **Challenges remain in nanotechnology**
 - Mechanistic understanding, methods, standards,
- **Gaps remain in developing test methods and standards**
 - Identification and assessment of nanoscale materials in products
 - + characterization methods
 - + biocompatibility and toxicity assessment

Need more information?

FDA/CDRH websites:

<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>