FDA Regulatory Process for CAUTI Medical Devices: Premarket Review Processes

Ángel A. Soler-García, Ph.D.

Microbiologist/Senior Lead Reviewer

Division of Reproductive, Gastro-Renal, and Urologic Devices (DRGUD)
Urology and Lithotripsy Devices Branch (ULDB)
Office of Device Evaluation (ODE)
Center for Devices and Radiological Health (CDRH)

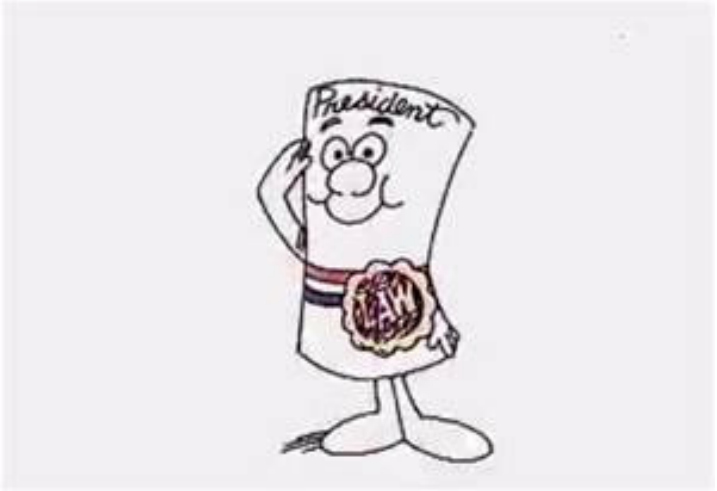
Disclosures:

Outline I

- FDA and CDRH Overview
- Combination Products
- Premarket Review Processes
- Substantial Equivalence and Antimicrobials
- Clinical Data and Investigational Device Exemptions
- FDA Feedback and Pre-Submission
- Take Home Message

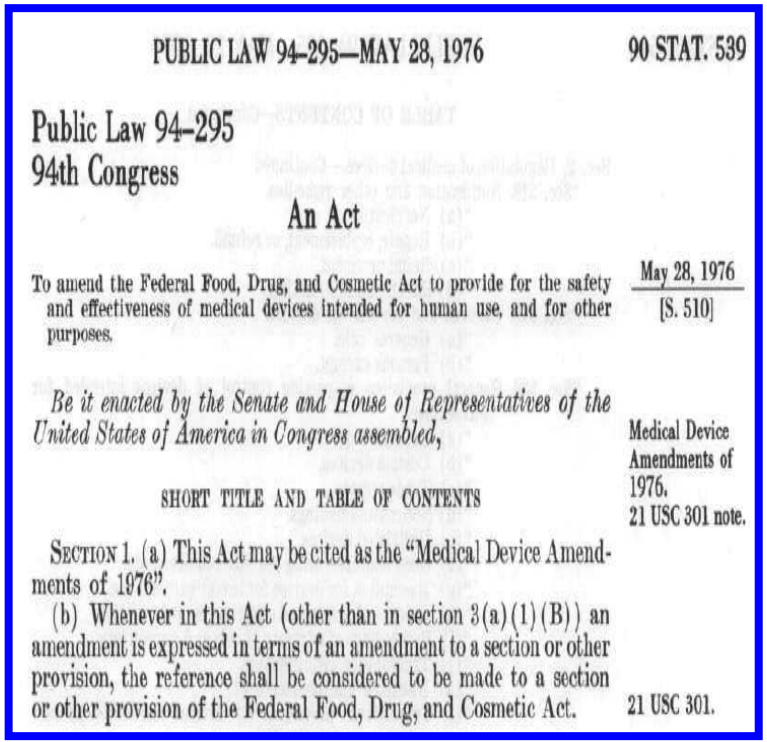
FDA Statutory Authority

- FDA's authority is granted by Congress.
  - Without statutory authority, FDA has no jurisdiction.



FDA Regulatory Mandates

- **1938** Federal Food, Drug, and Cosmetic Act (FD&C)
- **1968** Radiation Control for Health & Safety Act (RCHSA)
- **1976** Medical Device Amendment of 1976
- **1988** Clinical Laboratory Improvement Amendments (CLIA)
- **1990** Safe Medical Devices Act (SMDA)
- **1992** Mammography Quality Standards Act (MQSA)
- **1992** Medical Device Amendments
- **1997** Food & Drug Administration Modernization Act (FDAMA)
- **2002** Medical Device User Fee and Modernization Act (MDUFMA)
- **2004** Project Bioshield Act
- **2005** Medical Device User Fee Stabilization Act (MDUFSA)
- **2007** Food and Drug Administration Amendments Act (FDAAA)
- **2012** Food and Drug Administration Safety and Innovation Act (FDASIA)
  - Medical Device User Fee and Modernization Act (MDUFMA III)
- **2016** 21st Century Cures Act



PUBLIC LAW 94-295—MAY 28, 1976 90 STAT. 539

Public Law 94-295
94th Congress

An Act

To amend the Federal Food, Drug, and Cosmetic Act to provide for the safety and effectiveness of medical devices intended for human use, and for other purposes.

May 28, 1976
[S. 510]

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

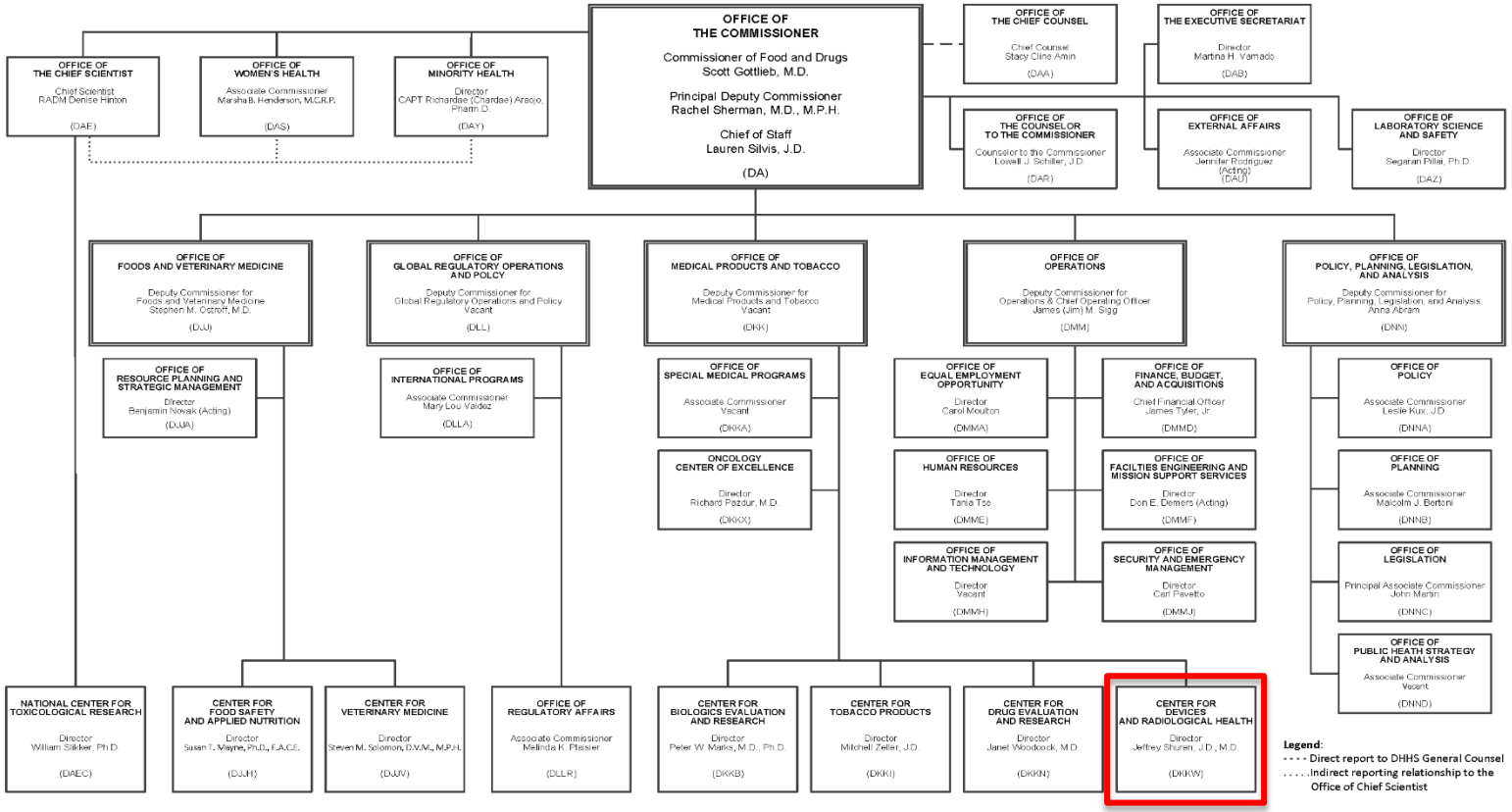
Medical Device Amendments of 1976.
21 USC 301 note.

SHORT TITLE AND TABLE OF CONTENTS

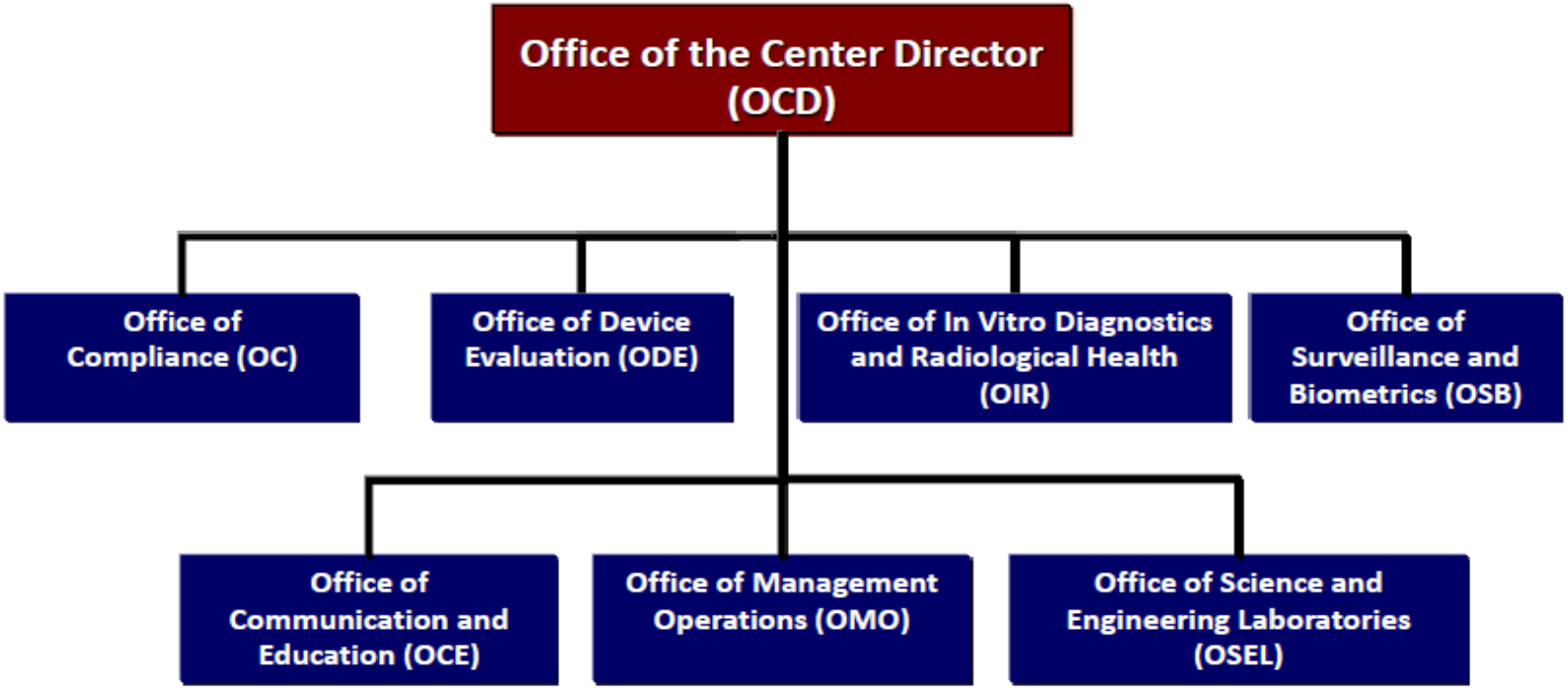
SECTION 1. (a) This Act may be cited as the "Medical Device Amendments of 1976".

(b) Whenever in this Act (other than in section 3(a)(1)(B)) an amendment is expressed in terms of an amendment to a section or other provision, the reference shall be considered to be made to a section or other provision of the Federal Food, Drug, and Cosmetic Act. 21 USC 301.

FDA Overview



Center for Devices and Radiological Health (CDRH)



Centers and Regulatory Responsibilities

Center	Regulates	Definition	Examples
CDRH	• Medical devices • Radiation emitting products	Section 201(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) defines a medical device as any healthcare product that does not achieve its principal intended purposes by chemical action or by being metabolized.	• Catheter • Stents • Endoscopes • X-ray machines • Mammography
CDER	• Over-the-counter and prescription drugs • Biological therapeutics • Generic drugs • Fluoride toothpaste* • Antiperspirants* • Dandruff shampoos* • Sunscreens*	Product is considered a drug is its primary intended use is achieved through chemical action or being metabolized by the body	• Aspirin • Beta Blockers • Polymyxin B Sulfate
CBER	• Blood and blood products • Blood banking equipment	"biological product" means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound	• Vaccine

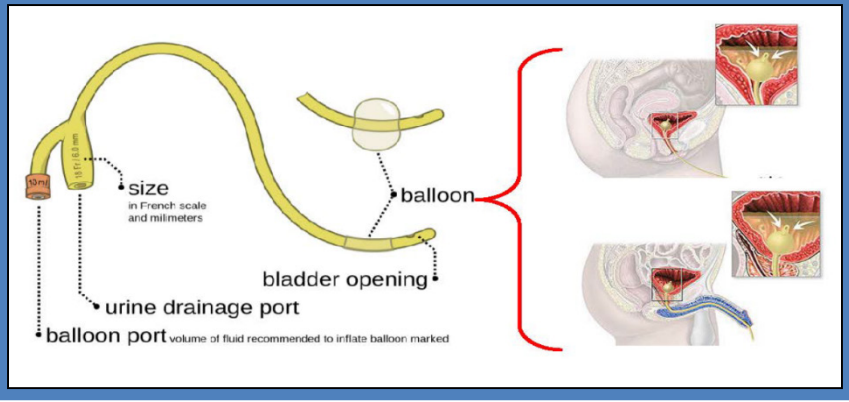
Combination Product

- It is a product composed of two or more different types of medical products (i.e., a combination of a drug, device, and/or biological product with one another). The medical products are referred to as “constituent parts” of the combination product.
- The FDA Office of Combination Products (OCP) covers the regulatory life cycle of combination products.
- OCP can be reached at either 301-796-8930 or combination@fda.gov

How Combination Products are Evaluated?

- Combination Products are assigned to a “Lead Center” having primary responsibility for their review.
- The Lead Center is selected base on the “primary mode of action” (PMOA) of the combination product.
- The PMOA refers to the single mode of action of a combination product that provides the greatest contribution to the product’s intended effects.

Combination Product Example

Characteristics	Foley Catheter with Silver Coating
	
Constituents	Foley Catheter (device) and Silver Coating (drug)
PMOA	Drainage of urine from the bladder (device)
Secondary MOA	Killing of microorganisms (drug)
Lead Center	CDRH

CDRH Risk Base Classification

	Class I	Class II	Class III
Risk level	Low	Moderate	High
Sufficient information for controls?	General	General & Special	Insufficient
Premarket review?	Mostly exempt	510(k) De Novo	PMA
Examples	Tongue depressor, stethoscope	Catheter with antimicrobial coating, Endoscopes	Cardiac ablation catheters, coronary artery stents

Premarket Submission

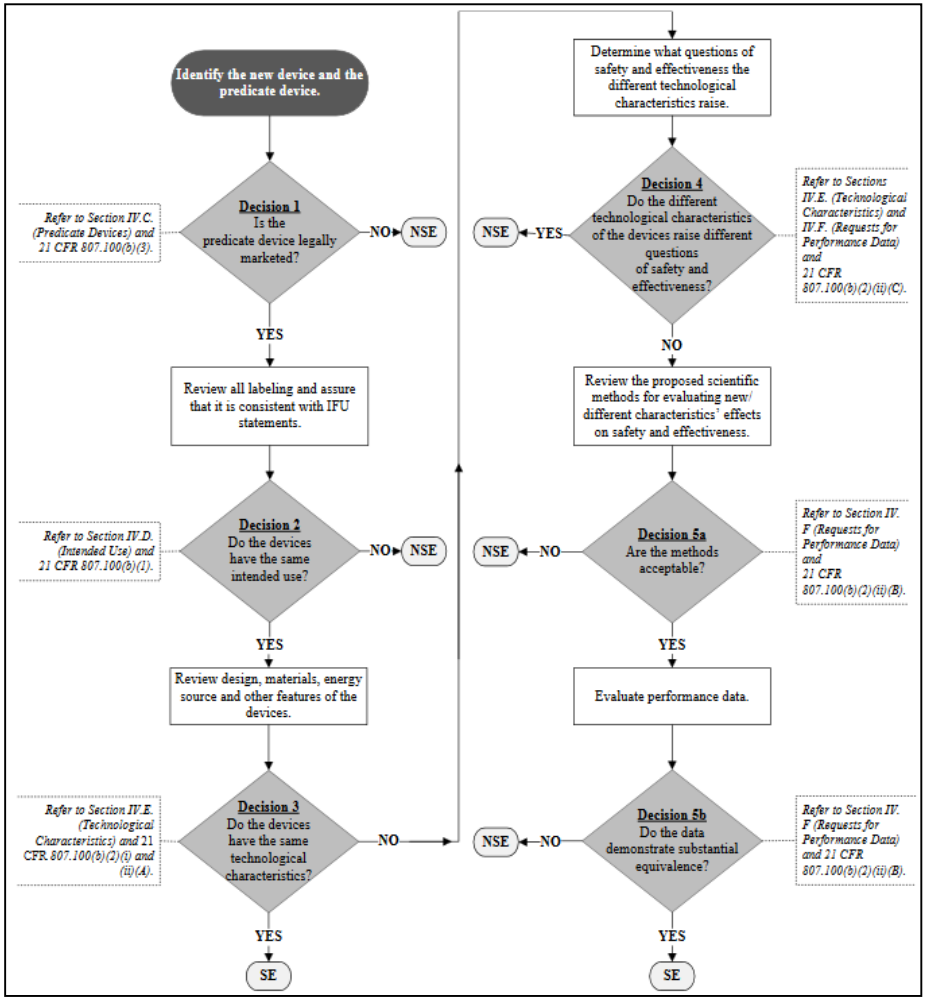
	Class II		Class III
Premarket Path	510(k)	De Novo	PMA
Predicate?	Identified	None	None
Appropriate for …	"me also"	Innovative lower risk	High risk
Regulatory standard	"substantial equivalence"	Controls provide reasonable assurance for reclassification	Reasonable assurance of safety and effectiveness
Permission	"cleared'	"granted"	"approved"
Clinical data?	10-15%	Most	Almost always
Time to approval	4-6 months	6-9 months	1-2 years
2019 User Fees	$10, 953.00	$96,644.00	$322,147.00

What is Substantial Equivalence?

- Demonstration that a new device (subject device), as compared to a legally marketed device (predicate device), has…
  - the same intended use **and**
  - the same technological characteristics,
  - **Or** differences in technological characteristics do not raise different questions regarding safety and effectiveness

Guidance document: The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)] (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284443.pdf)

510(k) Decision-Making Flowchart



Determination of Substantial Equivalence

Key Elements of Substantial Equivalence	Corresponding Decision Point in Flowchart
Predicate Device	1 . Is the predicate device legally marketed?
Intended Use	2. Do the devices have the same intended use?
Technological Characteristics	3. Do the devices have the same technological characteristics? 4. Do the different technological characteristics of the devices raise questions of safety and effectiveness?
Performance	5a. Are the methods acceptable? 5b. Do the data demonstrate substantial equivalence?

Guidance document: The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)] (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284443.pdf)

Antimicrobial Agent

- Any substance that kills or inhibits the growth of microorganisms.
- These substances may or may not meet the statutory definition of a drug in section 201(g) of the Food Drug and Cosmetic Act, depending on their mechanism of action and intended use

510(k)-Cleared Antimicrobial Coatings on Urological Catheters

- Silver
- Nitrofurazone
- Minocycline and rifampin

Foley Catheter with Antimicrobial Coatings - 510(k) Decision Making

Key Elements of Substantial Equivalence	Corresponding Decision Point in Flowchart	Foley Catheter with Silver, Nitrofurazone, or Minocycline/ Rifampin
Predicate Device	1	Yes
Intended Use	2	Yes
Technological Characteristics	3 & 4	Yes
Performance	5 a & b	Yes
510(k) Appropriate		Yes

Foley Catheter with Antimicrobial Coatings - 510(k) Decision Making

Key Elements of Substantial Equivalence	Corresponding Decision Point in Flowchart	Foley Catheter with None or Different Antimicrobial Coating
Predicate Device	1	Yes
Intended Use	2	Yes
Technological Characteristics	3 & 4	No
Performance	5 a & b	No
510(k) Appropriate		No

Examples of Different Questions

- What is the appropriate antimicrobial release profile?
- What is the antimicrobial safety and effectiveness at the specified range of concentrations?
- What is the safe and effective dose of the antimicrobial agent?
- What are the toxicity risks not present in the predicate product?
- What are the antimicrobial resistance (AMR) risks not present in the predicate product?

Regulatory Pathway Outcomes

- A subject device with an antimicrobial would not be able to be found substantially equivalent to a predicate with no antimicrobial.
- A subject device with different antimicrobial agent than that present in the predicate device would not be able to be found substantially equivalent.
- Therefore, the 510(k) regulatory pathway won't be appropriate.
- Depending on the device characteristics, an alternative regulatory pathway such as De Novo or PMA should be considered.

Clinical Data and Investigational Device Exemption (IDE)

- Clinical data to support a premarket application depends on the risk of the device and the type of application.
  - Clinical studies are most often conducted to support a PMA
  - Most of De Novos and only a small percentage of 510(k)s require clinical data to support the application.
- The investigational device exemption (IDE) is a regulatory submission that allows clinical investigation of medical devices to collect safety and effectiveness data.
  - All clinical evaluations of investigational devices, unless exempt, must have an approved IDE before the study is initiated.

Feedback and Pre-submission

- Prospective applicants of future premarket submissions may request feedback from the FDA through **Pre-Submission program**.
- Detailed information regarding the program can be found in the 2017 FDA 's guidance document, ***"Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff"*** (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf.)
- There is no user fee associated with the Pre-Submission program

Division of Industry and Consumer Education (DICE)

- DICE provides education regarding medical device laws, regulations, guidances, and policies, covering both premarket and postmarket topics.

- Web Resources:
  - **Device Advice** (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm)
  - **CDRH Learn** (https://www.fda.gov/Training/CDRHLearn/default.htm)

- DICE staff can be reached by email (dice@fda.hhs.gov) or phone at 1(800) 638-2041 or (301) 796-7100 between the hours of 9:00 am – 12:30 pm and 1:00 pm – 4:30 pm Eastern Time.

Take Home Message

- The FDA uses a risk-based process for the premarket evaluation of medical devices.
- Highest risk devices undergo the most rigorous review.
- For FDA Feedback, take advantage of the Pre-Submission Program.

Thank you!


FDA
U.S. Department of Health and Human Services
Food and Drug Administration