Medical Devices in the US: History and Regulatory Process

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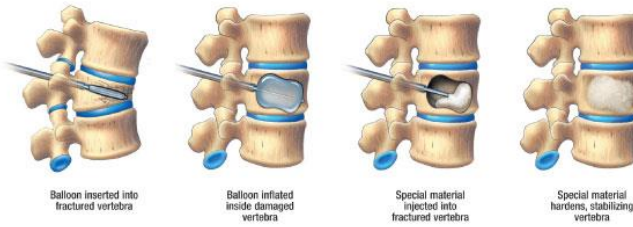
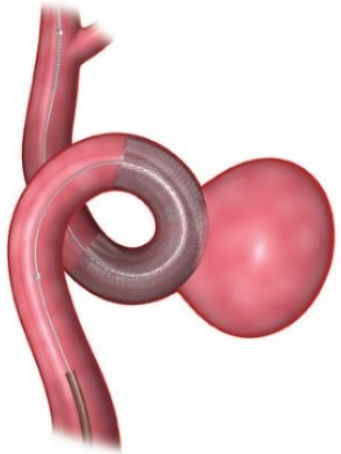
About Me / Disclosures

- Stanford Biology 1986
- Yale MD 1990
- Medicine residence (Univ Wisconsin, California-Pacific Medical Center)
- Stanford/Palo Alto VA Hospital fellowship general medicine
- Medical device industry since 1997
- Multiple clinical trials/devices
- Head of clinical affairs at SI-BONE and PROCEPT Biorobotics





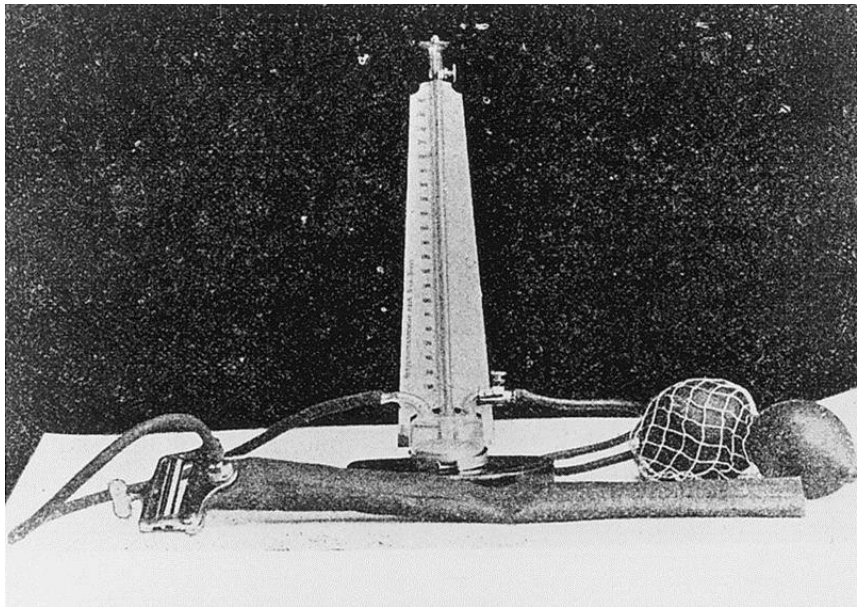
Outline

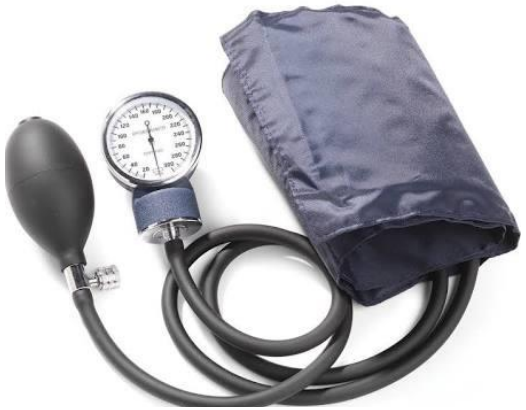
- History of medical devices
- Medical device regulations and approval process
- Medical device premarket studies
- Premarket studies vs. studies for market acceptance
- Health economics in med devices
- Postmarket surveillance and device epidemiology

History of Medical Devices

First Medical Device

- Sphygmomanometer 1881?
  - Samuel Siegfried Karl Ritter von Basch

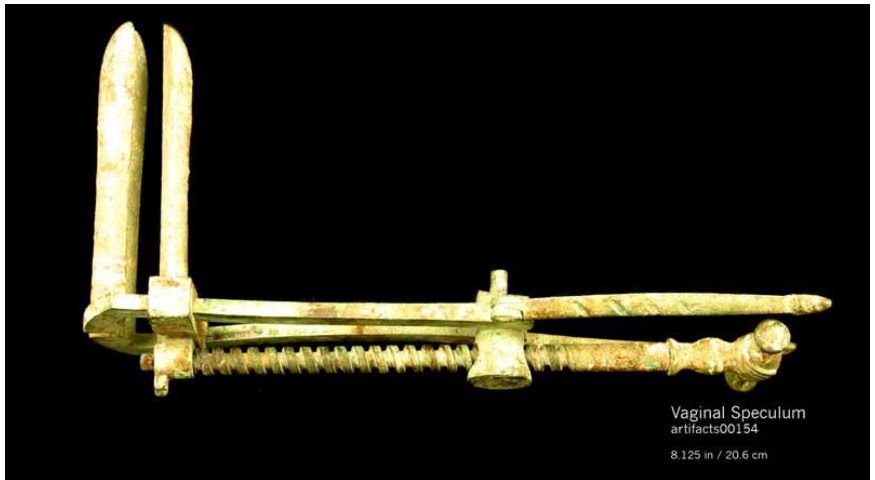




First Medical Device

- **1714**: first mercury thermometer, Daniel Gabriel Fahrenheit
- **1881**: sphygmomanometer, Samuel Ritter von Basch
- **1858**: Stethoscope, René Laënnec, a French physician

- Ancient Greeks and Romans:



Timeline

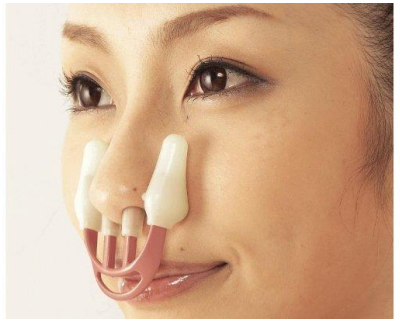
Year	Device
1881	Sphygmomanometer
1885	X-ray image
1885	Electrocardiograph
1899	Radiation therapy (yes, radiation is a type of medical device)
1939	Mammogram
1927	Respirator
1933	Defibrillator
1945	Dialysis machine
1948	Contact lens
1951	Artificial heart valve
1952	Pacemaker

First fraudulent medical device marketed in the US

- “Tractors”, Dr. Elisha Perkins (Connecticut, late 1700s)
- Two brass/iron rods, 3 inches long
  - Use: apply the points on the aching body part for about 20 minutes.
  - Claim: unusual alloys with special properties that could cure inflammation, rheumatism and pain in the head and the face.
  - "draw off the noxious electrical fluid that lay at the root of suffering"
- George Washington bought a set!
- Exposed as a fraud 1799

Medical Device Regulation in US

- Pure Food and Drugs Act, 1906
  - Purpose: ban foreign and interstate traffic of adulterated or mislabeled food and drug products
  - Took 27 years to pass
  - Did not address medical devices!
- In early 1900s, devices simple, hazards readily apparent – little overall risk
- By 1917, fraudulent med devices appearing:
  - Nose straighteners
  - Height-stretching machines
  - Heated rubber applicators as a cure for prostate gland disorders
  - Radiation health hazards of radium (Curie, 1898), radium belt to prevent appendicitis!
- 1938 update to Food and Drug Act, multiple subsequent updates (1976, 1990)



Citation:
http://www.fda.gov/aboutfda/whatwedo/history/productregulation/medicaldeviceandradiologicalhealthregulationscomeofage/default.htm

Medical Device Definition

- Section 201(h) of the Federal Food Drug & Cosmetic (FD&C) Act
- "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:
  - recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
  - **intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease**, in man or other animals, or
  - intended to **affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action** within or on the body of man or other animals and which is **not dependent upon being metabolized** for the achievement of any of its primary intended purposes."

US Medical Device Approval

Classify Your Device

Class I – Lowest Risk	• **Examples:** manual toothbrush, sutures, many simple surgical instruments. • General controls
Class II – Moderate Risk	• **Examples**: male condoms, non-invasive blood pressure monitors, catheters, screws • General controls and **special controls**
Class III – Highest Risk	• **Examples:** heart valve, most permanent implants • General controls and **premarket approval**

Combination Products

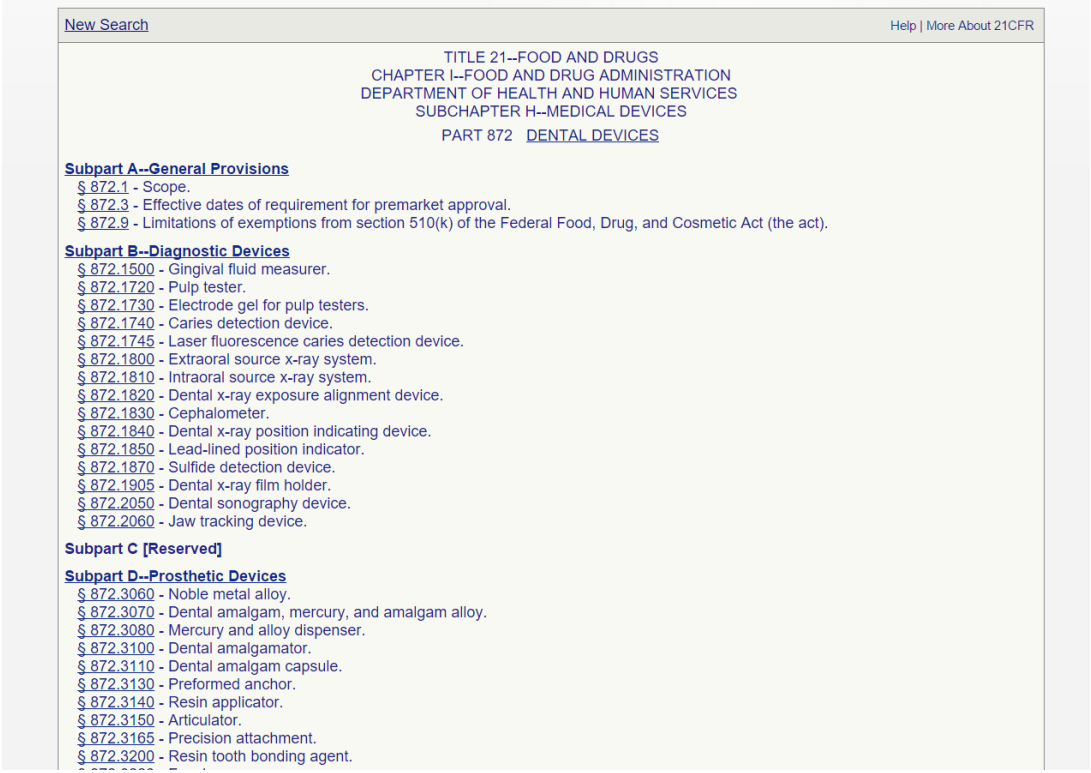
- Definition
  - Two or more regulated products (drug/device, biologic/device, drug/biologic, or drug/device/biologic) that are physically, chemically, or otherwise combined or mixed and produced as a single entity
  - Two or more separate products packaged together comprised of drug and device products, etc.
  - Drug, device, or biological product packaged separately but used together for a specific reason

- Examples
  - Device coated or impregnated with a drug or biologic
  - Drug-eluting stent; pacing lead with steroid-coated tip; catheter with antimicrobial coating; condom with spermicide
  - Skin substitutes with cellular components; orthopedic implant with growth factors
  - Prefilled syringes, insulin injector pens, metered dose inhalers, transdermal patches

- Not address today

Classify Your Device

- CFR Title 21 - Food and Drugs: Parts 1 to 1499
- FDA regulations for most device types
- http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm
- Examples:
  - (862) Clinical chemistry and clinical toxicology devices
  - (864) Hematology and pathology devices
  - (866) Immunology and microbiology devices
  - (868) Anesthesiology devices
  - (870) Cardiovascular devices
  - (872) Dental devices
  - (874) Ear, nose, and throat devices
  - (876) Gastroenterology-urology devices
  - (878) General and plastic surgery devices
  - (880) General hospital and personal use devices
  - (882) Neurological devices



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TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER H--MEDICAL DEVICES

PART 872 DENTAL DEVICES

Subpart A--General Provisions
§ 872.1 - Scope.
§ 872.3 - Effective dates of requirement for premarket approval.
§ 872.9 - Limitations of exemptions from section 510(k) of the Federal Food, Drug, and Cosmetic Act (the act).

Subpart B--Diagnostic Devices
§ 872.1500 - Gingival fluid measurer.
§ 872.1720 - Pulp tester.
§ 872.1730 - Electrode gel for pulp testers.
§ 872.1740 - Caries detection device.
§ 872.1745 - Laser fluorescence caries detection device.
§ 872.1800 - Extraoral source x-ray system.
§ 872.1810 - Intraoral source x-ray system.
§ 872.1820 - Dental x-ray exposure alignment device.
§ 872.1830 - Cephalometer.
§ 872.1840 - Dental x-ray position indicating device.
§ 872.1850 - Lead-lined position indicator.
§ 872.1870 - Sulfide detection device.
§ 872.1905 - Dental x-ray film holder.
§ 872.2050 - Dental sonography device.
§ 872.2060 - Jaw tracking device.

Subpart C [Reserved]

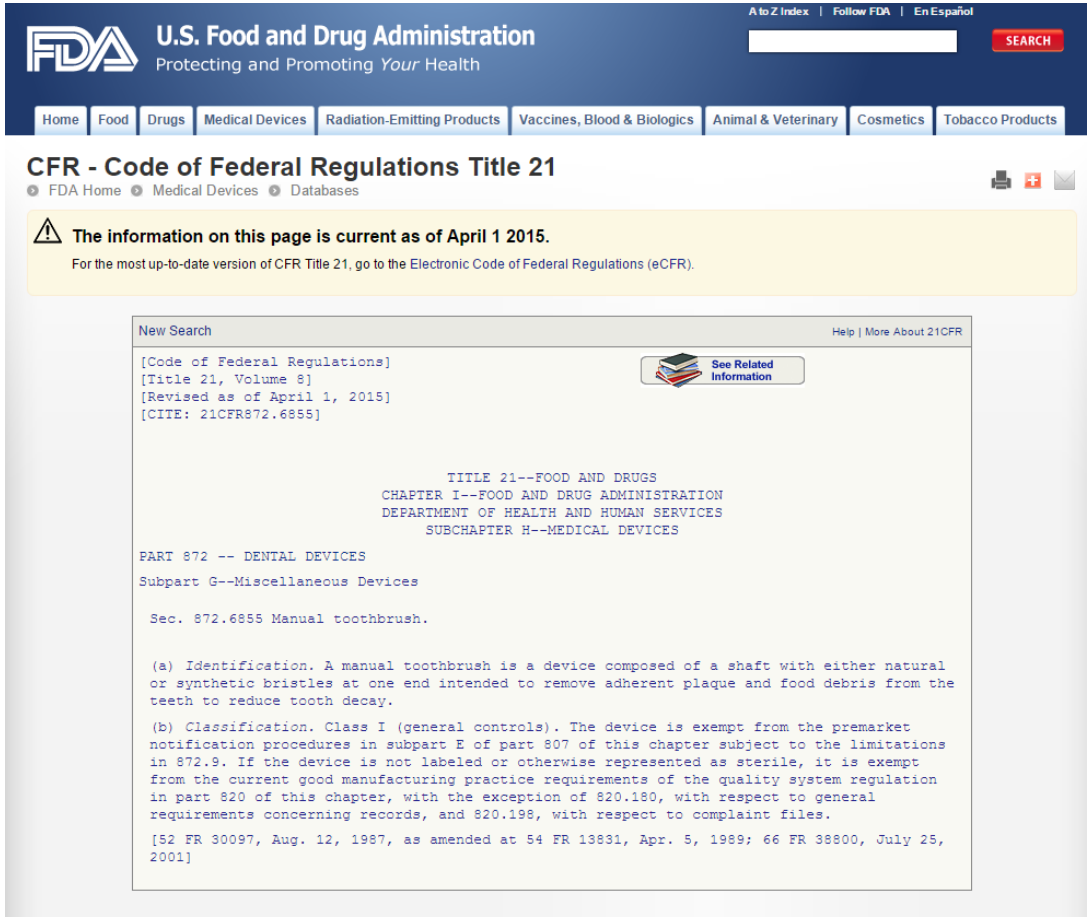
Subpart D--Prosthetic Devices
§ 872.3060 - Noble metal alloy.
§ 872.3070 - Dental amalgam, mercury, and amalgam alloy.
§ 872.3080 - Mercury and alloy dispenser.
§ 872.3100 - Dental amalgamator.
§ 872.3110 - Dental amalgam capsule.
§ 872.3130 - Preformed anchor.
§ 872.3140 - Resin applicator.
§ 872.3150 - Articulator.
§ 872.3165 - Precision attachment.
§ 872.3200 - Resin tooth bonding agent.

Premarket Submission Pathway

- 510(k) Premarket Notification
- PMA Premarket Approval
- De Novo: Evaluation of Automatic Class III Designation
- HDE Humanitarian Device Exemption

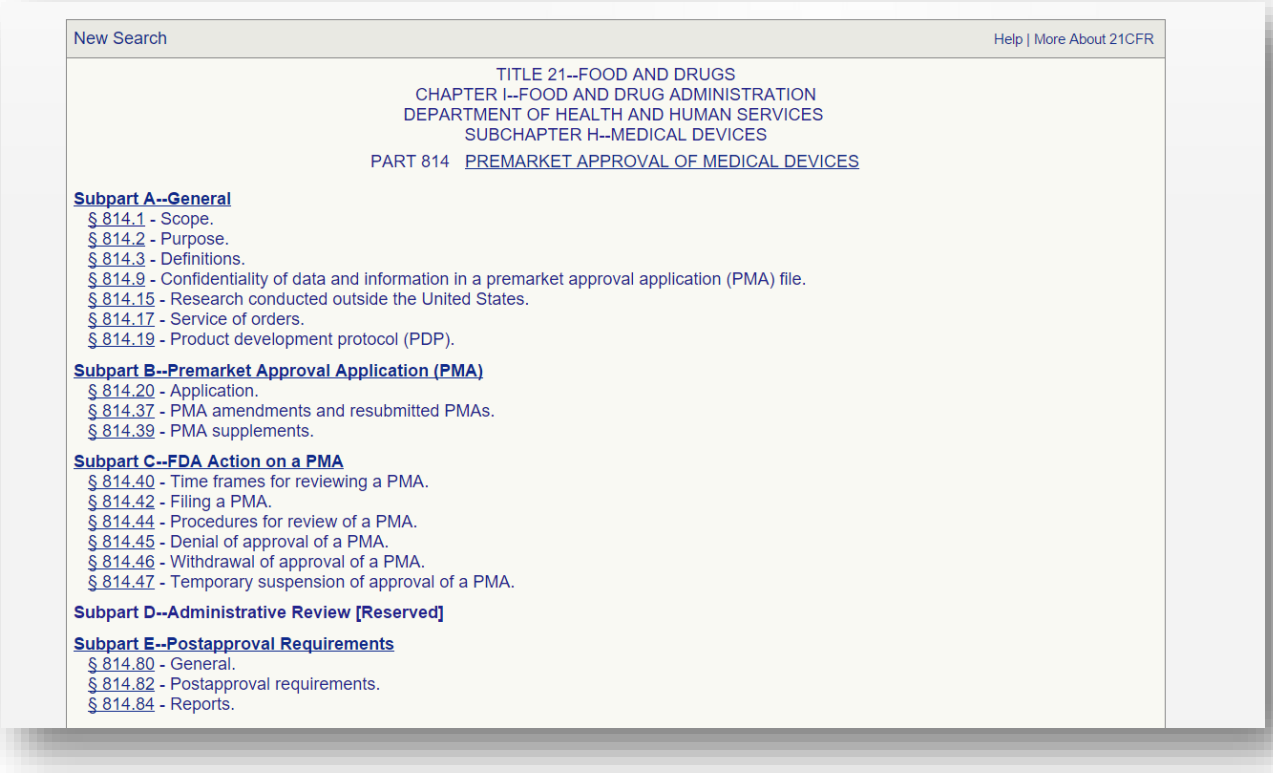
Class I (Lowest Risk) Devices

- Register establishment with FDA
- General controls
  - Regulatory requirements
  - Part of FD&C Act, sections 501, 502, 510, 516, 518, 519, and 520
  - Apply to all medical devices
- Comply and manufacture: you're in business
- You are subject to periodic FDA inspections and all aspects of medical device recalls



Class III (Highest Risk) Premarket Approval

- Broad definition:
  - Any device supporting or sustaining human life or preventing impairment of human health, or that may present a potential unreasonable risk of illness or injury for which general controls and special controls are insufficient to provide reasonable assurance of the safety and effectiveness of a device, or for which there is insufficient information to make such a determination.
- 21 CFR 814
- Examples: most permanent implants or complex devices
  - Heart valves, orthopedic devices, coronary stents, etc.
- Substantially difficult regulatory pathway



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CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER H--MEDICAL DEVICES

PART 814 PREMARKET APPROVAL OF MEDICAL DEVICES

Subpart A--General
§ 814.1 - Scope.
§ 814.2 - Purpose.
§ 814.3 - Definitions.
§ 814.9 - Confidentiality of data and information in a premarket approval application (PMA) file.
§ 814.15 - Research conducted outside the United States.
§ 814.17 - Service of orders.
§ 814.19 - Product development protocol (PDP).

Subpart B--Premarket Approval Application (PMA)
§ 814.20 - Application.
§ 814.37 - PMA amendments and resubmitted PMAs.
§ 814.39 - PMA supplements.

Subpart C--FDA Action on a PMA
§ 814.40 - Time frames for reviewing a PMA.
§ 814.42 - Filing a PMA.
§ 814.44 - Procedures for review of a PMA.
§ 814.45 - Denial of approval of a PMA.
§ 814.46 - Withdrawal of approval of a PMA.
§ 814.47 - Temporary suspension of approval of a PMA.

Subpart D--Administrative Review [Reserved]

Subpart E--Postapproval Requirements
§ 814.80 - General.
§ 814.82 - Postapproval requirements.
§ 814.84 - Reports.

Class II (Moderate Risk)

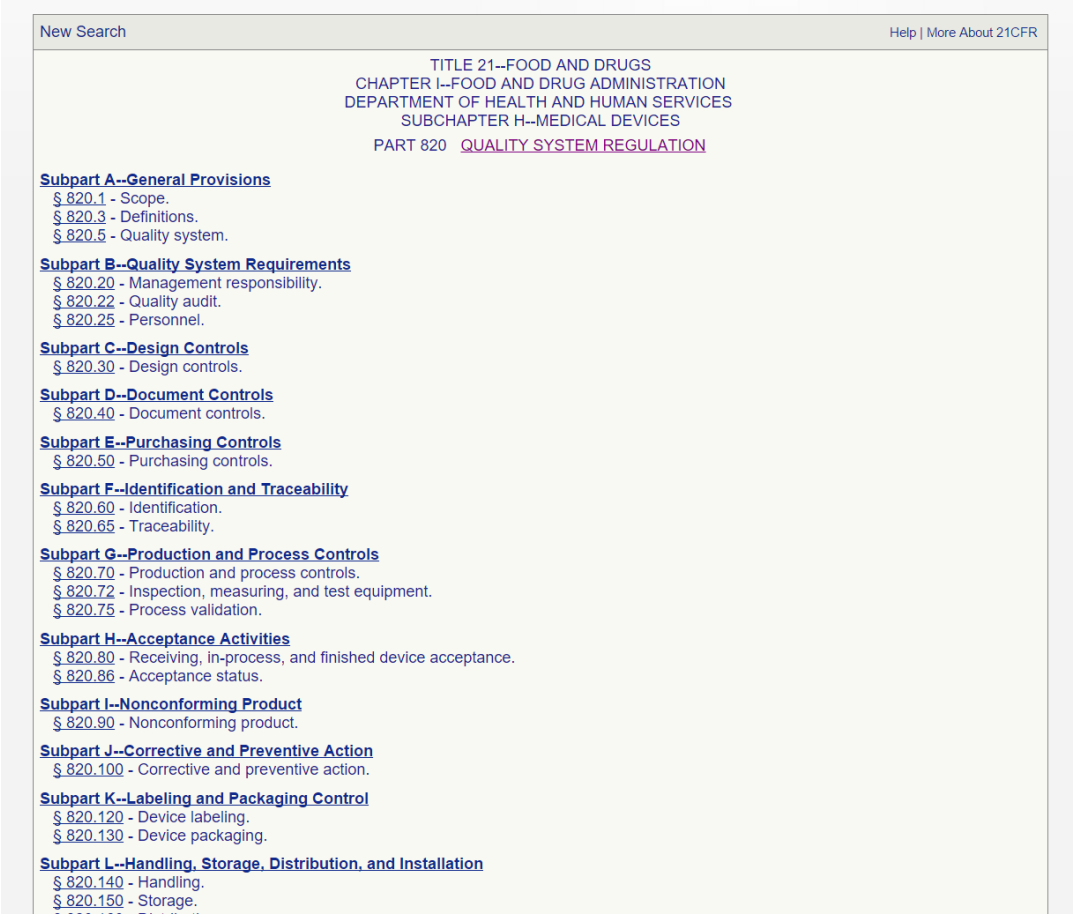
- Special controls, as general controls are insufficient
- Specific FDA requirements related to device category to assure safety and effectiveness
- AKA 510k pathway
- Special Controls
  - Performance standards
  - Postmarket surveillance
  - Patient registries
  - Special labeling requirements
  - Premarket data requirements
  - Guidelines

Market a Device without Clinical Testing – is that right?

- **Low** risk devices do not need clinical trials
  - Needle, appropriately manufactured, is low risk and likely effective for its intended use
- **High** risk devices need clinical trials for safety/effectiveness
- **Intermediate** risk devices may be marketed provided that:
  - Manufacturer establishes and proves that device can be made reliably under a **quality system**
  - Device itself meets **FDA requirements for testing**
  - They are **substantially equivalent** to previously marketed devices

Quality System Regulations

21 CFR 820	• FDA regulation applying to all devices
Purpose	• Systems to ensure safety, effectiveness and quality of medical devices
Responsibility	• Manufacturers responsible for determining which parts of QSR apply to their device
Burden	• Appropriately high



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TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER H--MEDICAL DEVICES
PART 820 QUALITY SYSTEM REGULATION

Subpart A--General Provisions
§ 820.1 - Scope.
§ 820.3 - Definitions.
§ 820.5 - Quality system.

Subpart B--Quality System Requirements
§ 820.20 - Management responsibility.
§ 820.22 - Quality audit.
§ 820.25 - Personnel.

Subpart C--Design Controls
§ 820.30 - Design controls.

Subpart D--Document Controls
§ 820.40 - Document controls.

Subpart E--Purchasing Controls
§ 820.50 - Purchasing controls.

Subpart F--Identification and Traceability
§ 820.60 - Identification.
§ 820.65 - Traceability.

Subpart G--Production and Process Controls
§ 820.70 - Production and process controls.
§ 820.72 - Inspection, measuring, and test equipment.
§ 820.75 - Process validation.

Subpart H--Acceptance Activities
§ 820.80 - Receiving, in-process, and finished device acceptance.
§ 820.86 - Acceptance status.

Subpart I--Nonconforming Product
§ 820.90 - Nonconforming product.

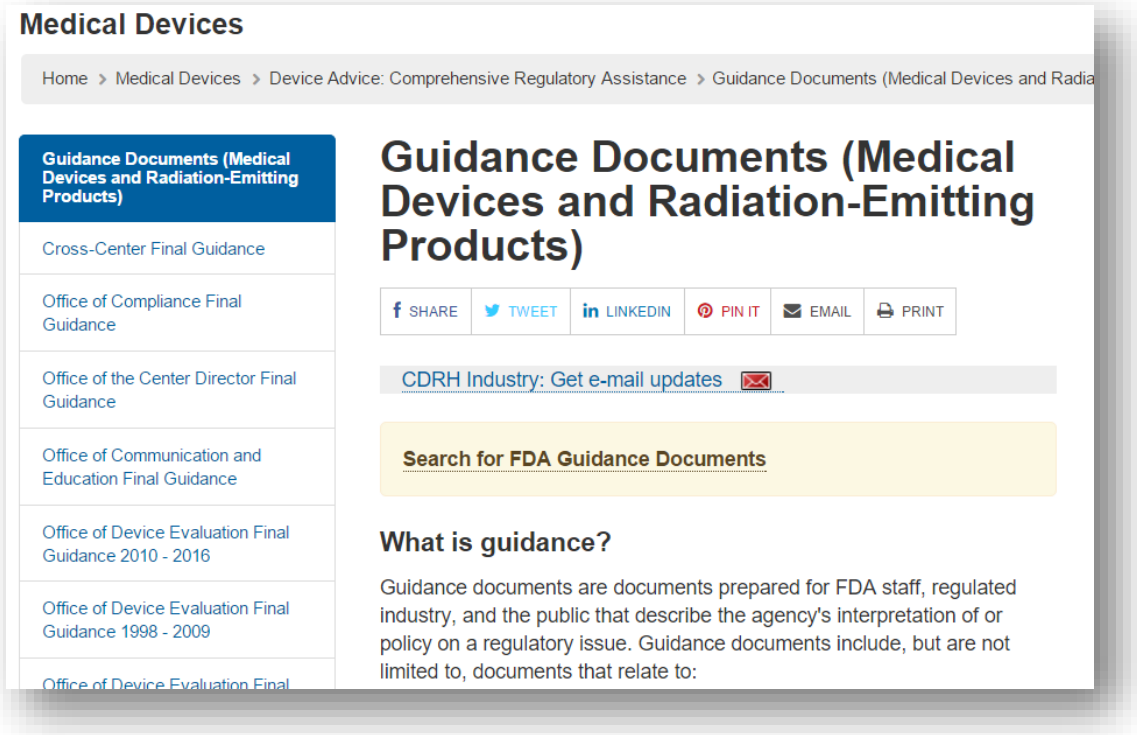
Subpart J--Corrective and Preventive Action
§ 820.100 - Corrective and preventive action.

Subpart K--Labeling and Packaging Control
§ 820.120 - Device labeling.
§ 820.130 - Device packaging.

Subpart L--Handling, Storage, Distribution, and Installation
§ 820.140 - Handling.
§ 820.150 - Storage.

Class II Guidance Documents

- Guidance documents for particular device types
- Must read / follow / provide proof that your class II device meets FDA's needs



FDA Guidance Documents

ODE Final Guidance Documents 2010 - 2016

Title	Organization	Doc #	Date
Applying Human Factors and Usability Engineering to Medical Devices - Guidance for Industry and Food and Drug Administration Staff (PDF - 918KB)	ODE	1757	02/03/16
Implanted Blood Access Devices for Hemodialysis - Guidance for Industry and Food and Drug Administration Staff (PDF - 710KB)	ODE	1781	01/21/16
Premarket Studies of Implantable Minimally Invasive Glaucoma Surgical (MIGS) Devices - Guidance for Industry and Food and Drug Administration Staff (PDF - 609KB)	ODE/DOENTD/ICIB	1400049	12/15/15
Premarket Notification Requirements Concerning Gowns Intended for Use in Health Care Settings - Guidance for Industry and Food and Drug Administration Staff (PDF - 319KB)	ODE/DAGHRICDD	1500025	12/09/15
Select Updates for Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems - Guidance for Industry and Food and Drug Administration Staff (PDF - 410KB)	ODE/DCD OSEL	1826	08/18/15
Endotoxin Testing Recommendations for Single-Use Intraocular Ophthalmic Devices - Guidance for Industry and Food and Drug Administration Staff (PDF - 419KB)	ODE/DOENTD	1836	08/17/15
Intent to Exempt Certain Unclassified, Class II, and Class I Reserved Medical Devices from Premarket Notification Requirements - Guidance for Industry and Food and Drug Administration Staff (PDF - 303KB)	ODE	1300046	08/14/15
Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling - Guidance for Industry and Food and Drug Administration Staff (PDF - 1.3MB)	CDRH/ODE CBER	1748	03/17/15

Guidance for Industry and FDA Staff

Class II Special Controls Guidance Document: Vascular and Neurovascular Embolization Devices

Document issued on: December 29, 2004

For questions regarding this document, contact:

- Peter L. Hudson, Ph.D., Plastic and Reconstructive Surgery Branch, at 240-276-3600, or by e-mail at peter.hudson@fda.hhs.gov.
- Doyle Gantt, Peripheral Vascular Devices Branch, at 240-276-4000, or by e-mail at a.gantt@fda.hhs.gov.
- Colin M. Pollard, Obstetrics and Gynecology Devices Branch, at 240-276-4155 or by e-mail at colin.pollard@fda.hhs.gov.

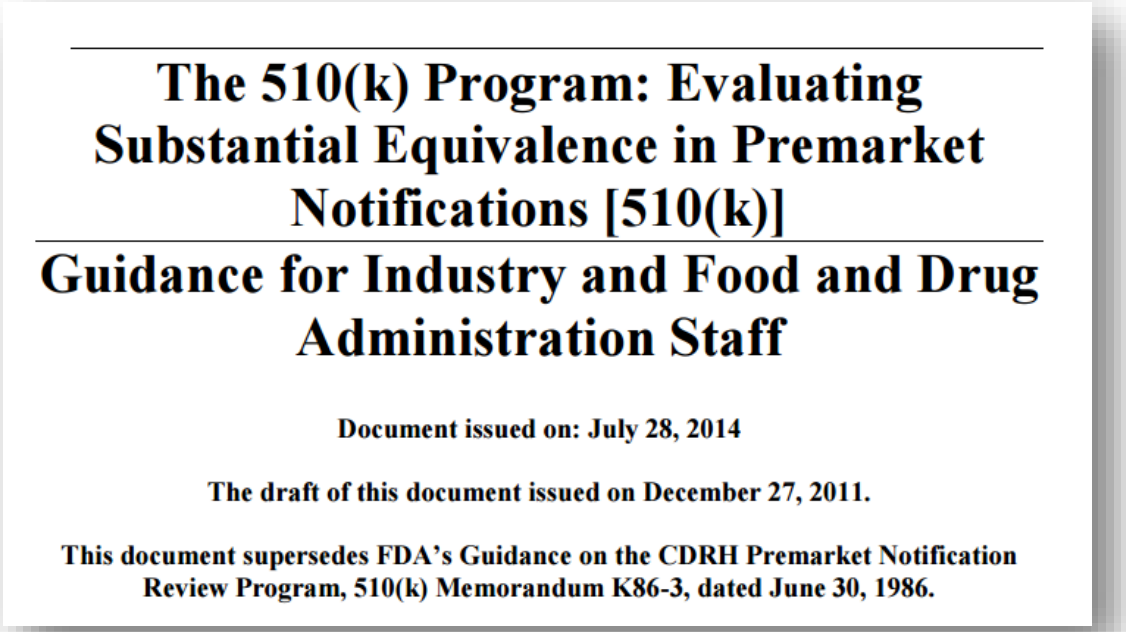
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm198577.htm

Guidance Documents Scope

- Preclinical tests:
  - Benchtop tests to verify device design and validate (confirm) that device works as intended
  - Biocompatibility testing (ISO 10993)
- Sterility testing:
  - Substantial work to ensure reliable sterility
  - Can be challenging when device very complex
- Animal testing
  - Confirm that device works as intended in suitable animal model
- Clinical testing
  - Very specific guidance on trial design
- Labeling
  - What you can and cannot claim

Class II Pathway – Substantial Equivalence: 510k regulation

- A new (i.e., post-amendments) device is automatically in Class III and must undergo premarket approval or reclassification before it can be marketed, **unless it is a type of device that was in commercial distribution prior to May 28, 1976, and is substantially equivalent to another such device**;
- Not “approval” but rather “clearance under 510(k)”



The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]

Guidance for Industry and Food and Drug Administration Staff

Document issued on: July 28, 2014

The draft of this document issued on December 27, 2011.

This document supersedes FDA’s Guidance on the CDRH Premarket Notification Review Program, 510(k) Memorandum K86-3, dated June 30, 1986.

http://www.fda.gov/downloads/MedicalDevices/.../UCM284443.pdf

Definition of Substantial Equivalence

- **Device has the same intended use as the predicate [i.e., already cleared] device** and device
  - (i) has the **same technological characteristics** as the predicate device, or
  - (ii)(I) has different technological characteristics and the information submitted that the device is substantially equivalent to the predicate device contains information, including appropriate clinical or scientific data if deemed necessary by the Secretary or a person accredited under section 523, that demonstrates that the **device is as safe and effective as a legally marketed device**, and (II) does **not raise different questions of safety and effectiveness** than the predicate device.

- “different technological characteristics” means significant change in the **materials, design, energy source, or other features** compared to the predicate

Substantial Equivalence Issues

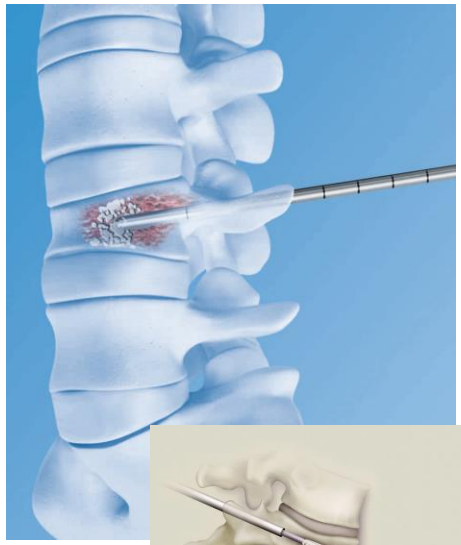
Same technological characteristics as the predicate

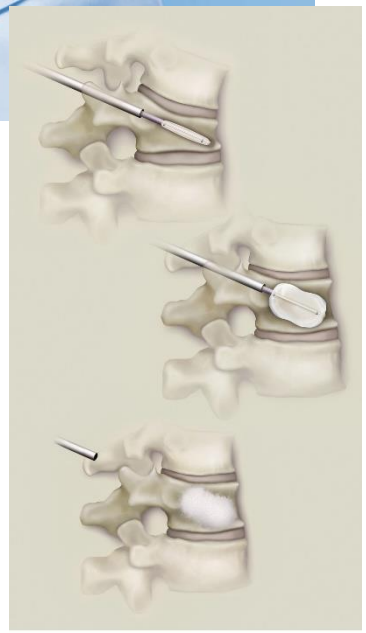
- “Me, too” device – your catheter is identical in most respects to a catheter on the market
- Challenging if your device
  - Made from different materials
  - Put in different place in body
  - Manufactured very differently
- Impossible if your device:
  - Different mech of action
  - Different energy source
  - Different application

Different technological characteristics but “as safe and effective” as a legally marketed device

- “As S/E” highly debatable
- You may not want to do a large non-inferiority clinical tria
- But FDA may require it

Vertebroplasty / Kyphoplasty





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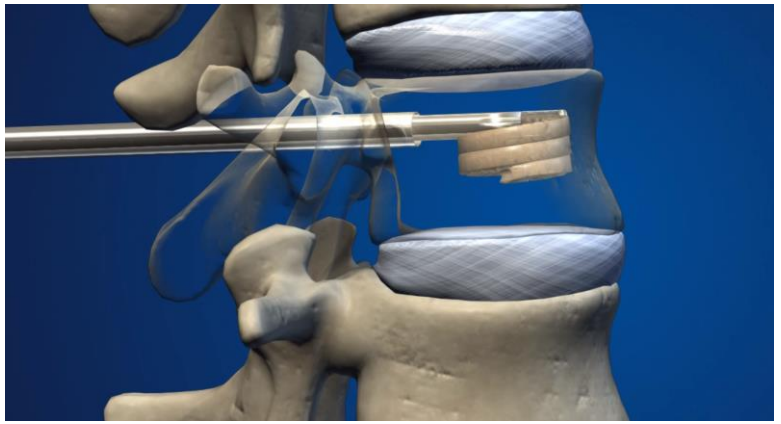
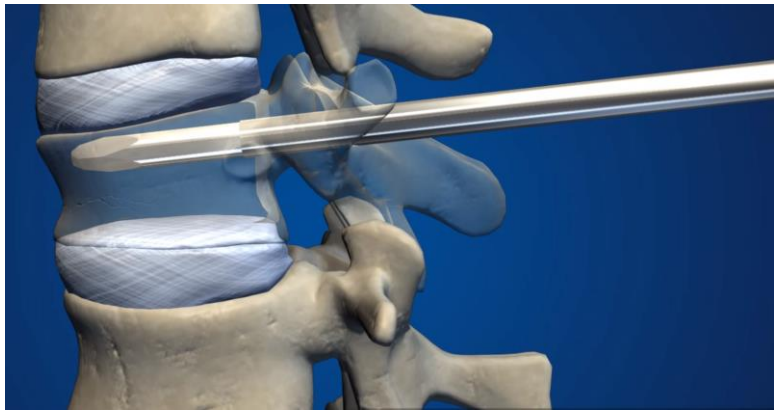
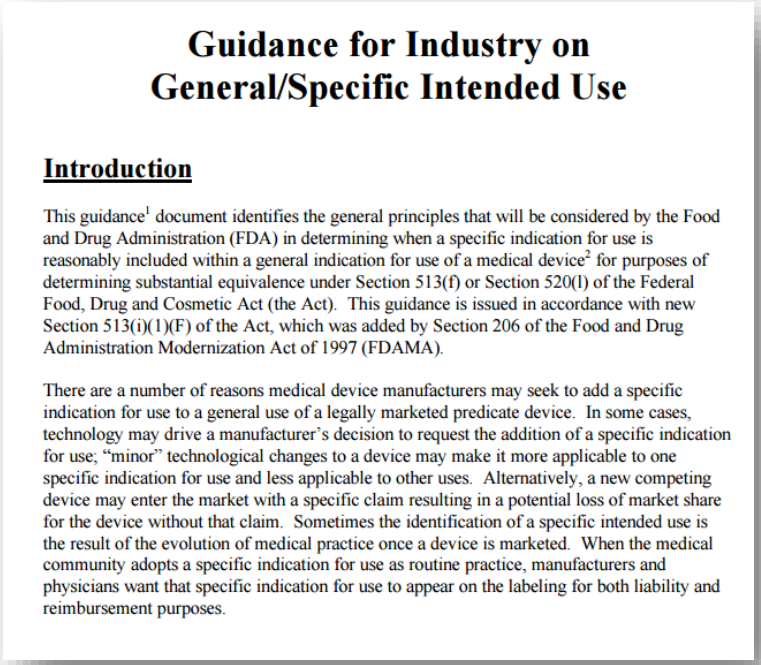




General → Specific Use

1. Risk - Does a specific use introduce new risks not associated with general use of the device?
2. Public Health Impact - Does specific use impact public health to a significantly greater degree than the general use of the device?

   Example: diagnosis vs. screening, cutting soft tissue vs. treating breast cancer
3. Knowledge base - Is there evidence that distinguishes more specific use from a new intended use?
4. Endpoints – Can performance information on general use speak to specific use? E.g., your device ablates tissue, but does it cure heart arrhythmia?
5. Tool or treatment?- A tool is used by a physician to perform a task (e.g., scalpel to cut tissue) vs. device to treat particular disease (e.g., extra corporeal shock wave lithotripter)
6. Adjunctive therapy- does a separate device need to be used to achieve the proposed therapeutic goal?
7. Design changes- how modified is the design to facilitate the specific use compared to the general use?



Guidance for Industry on
General/Specific Intended Use

Introduction

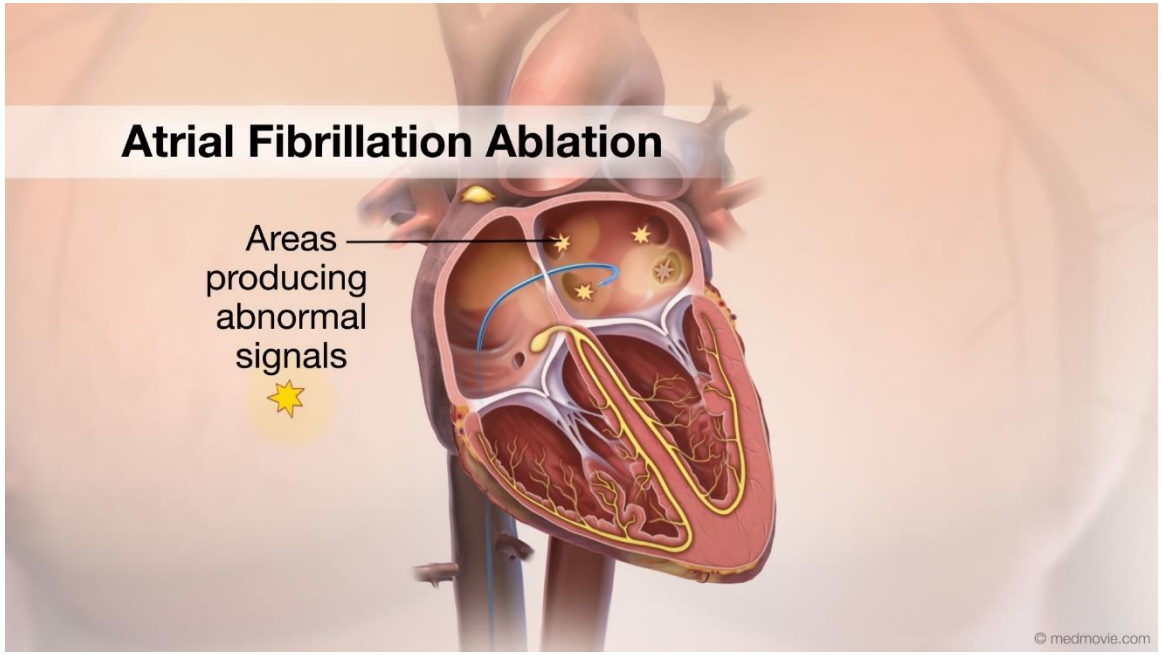
This guidance[1] document identifies the general principles that will be considered by the Food and Drug Administration (FDA) in determining when a specific indication for use is reasonably included within a general indication for use of a medical device[2] for purposes of determining substantial equivalence under Section 513(f) or Section 520(l) of the Federal Food, Drug and Cosmetic Act (the Act). This guidance is issued in accordance with new Section 513(i)(1)(F) of the Act, which was added by Section 206 of the Food and Drug Administration Modernization Act of 1997 (FDAMA).

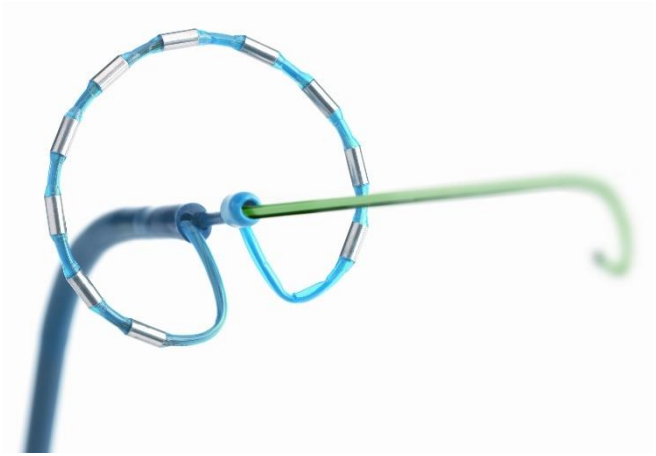
There are a number of reasons medical device manufacturers may seek to add a specific indication for use to a general use of a legally marketed predicate device. In some cases, technology may drive a manufacturer's decision to request the addition of a specific indication for use; "minor" technological changes to a device may make it more applicable to one specific indication for use and less applicable to other uses. Alternatively, a new competing device may enter the market with a specific claim resulting in a potential loss of market share for the device without that claim. Sometimes the identification of a specific intended use is the result of the evolution of medical practice once a device is marketed. When the medical community adopts a specific indication for use as routine practice, manufacturers and physicians want that specific indication for use to appear on the labeling for both liability and reimbursement purposes.

Can trigger PMA pathway instead of 510k pathway
Can trigger

General → Specific Can Trigger PMA

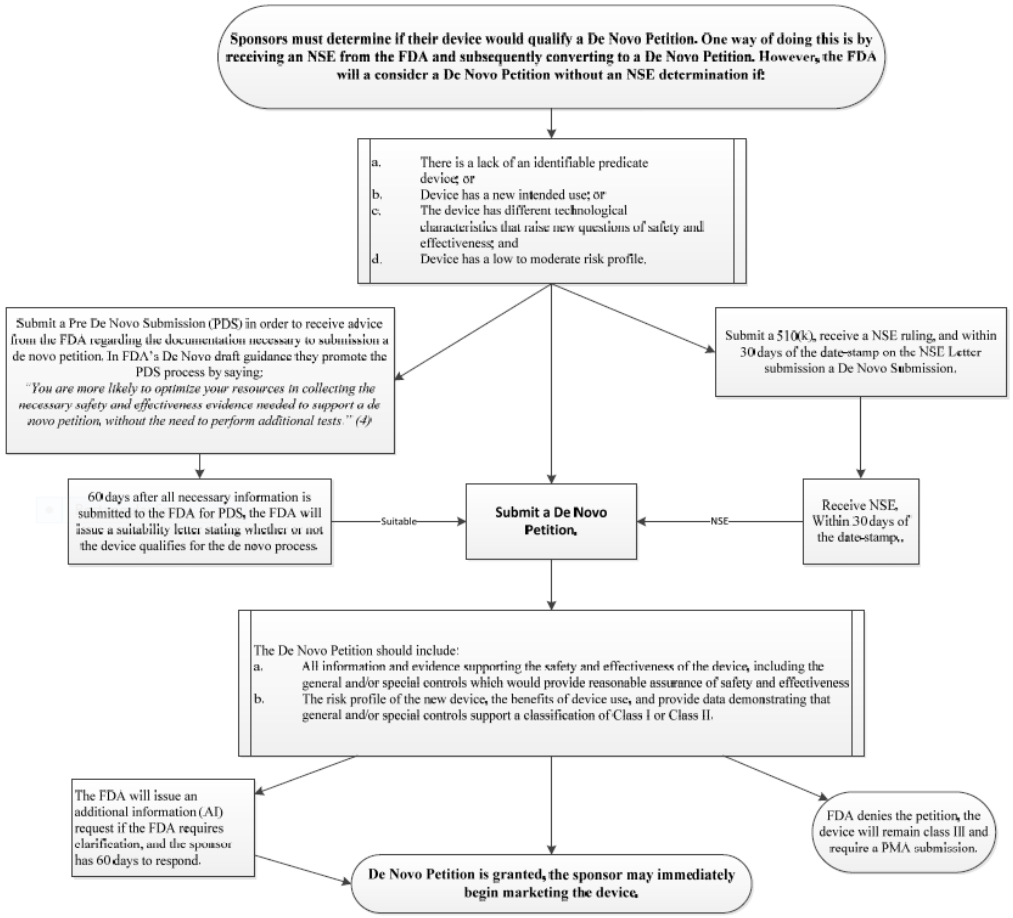
- PMA may also be required for
  - Devices with new concepts
  - Simpler (class II) devices applied to specific diseases



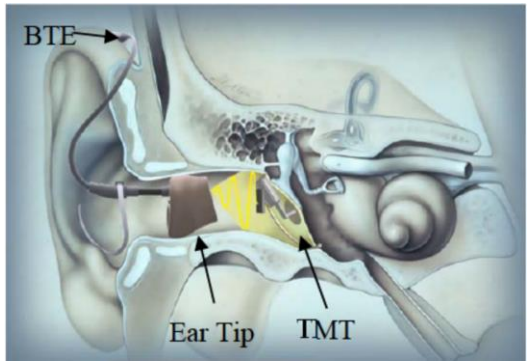


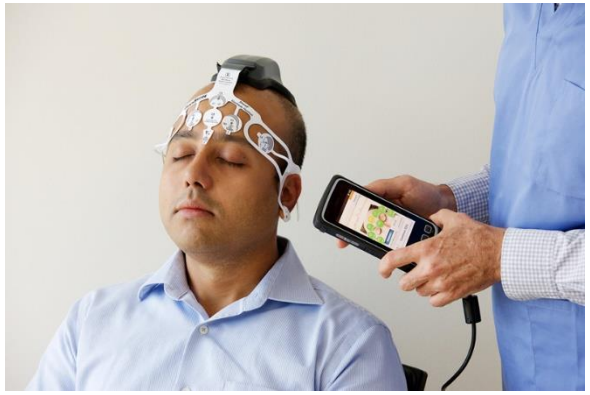
What if there is no clear pathway?

- Class II may not apply
  - Your device is moderate risk but there is no predicate
  - “De novo process” as a Class I or Class II device
  - Section 513(f)(2)



Devices cleared through de novo



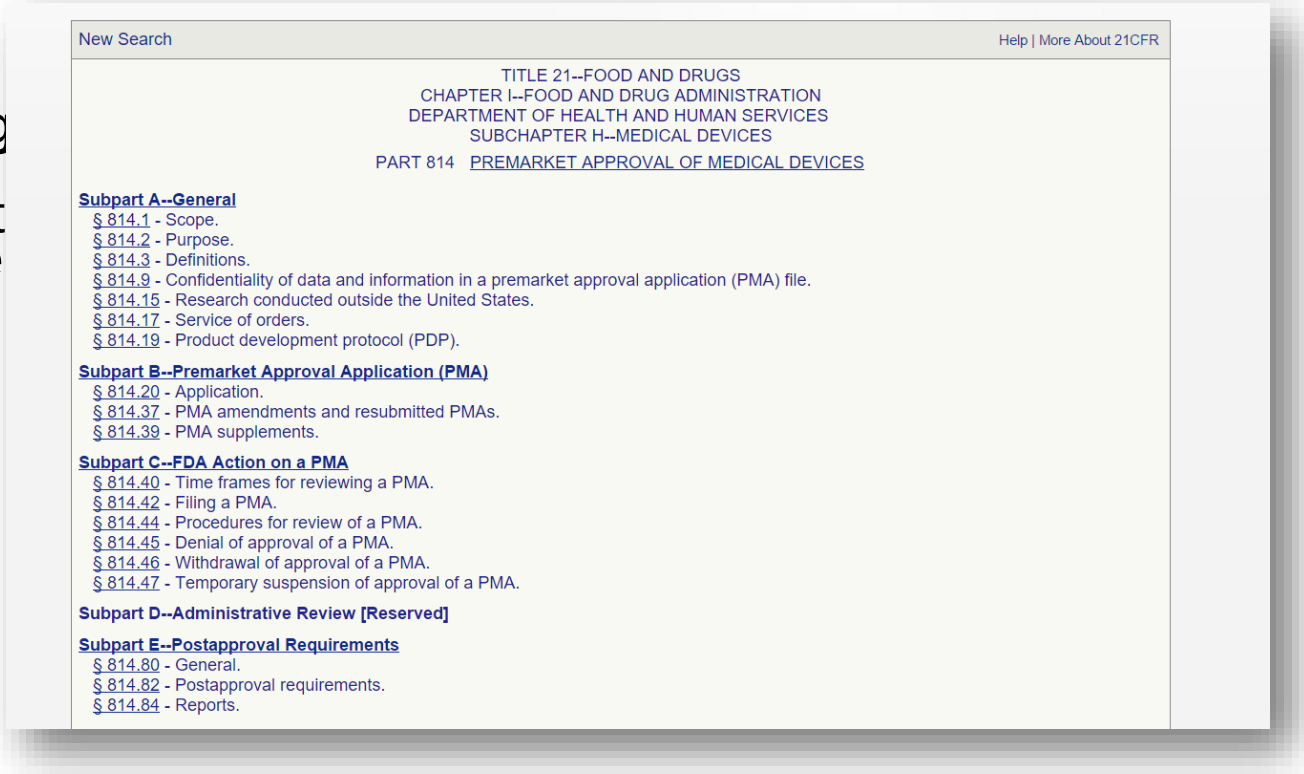


Device Name	DEN#
RELIZORB™	DEN150001
Sonablate® 450	DEN150011
EarLens™ Contact Hearing Device	DEN150002
Newa™	DEN150005
INVOcell™ Intravaginal Culture System	DEN150008
FilmArray® Meningitis/Encephalitis (ME) Panel	DEN150013
BrainScope Ahead 100, Models CV-100 and M-100	DEN140025
EnLite™ Neonatal TREC Kit	DEN140010
Esophageal Cooling Device	DEN140018
DigniCap™ Scalp Cooling System	DEN150010
Eclipse System	DEN140020
NOVA View® Automated Fluorescence Microscope	DEN140039

http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHTransparency/ucm232269.htm

Class III (Highest Risk) Premarket Approval

- Broad definition:
  - Any device **supporting or sustaining human life** or **preventing impairment of human health**, or that may present a potential unreasonable risk of illness or injury for which general controls and special controls are insufficient to provide reasonable assurance of the safety and effectiveness of a device, or for which there is insufficient information to make such a determination.
- 21 CFR 814
- Examples: most permanent implants or complex devices
  - Heart valves, orthopedic devices, coronary stents, etc.



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TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER H--MEDICAL DEVICES

PART 814 PREMARKET APPROVAL OF MEDICAL DEVICES

Subpart A--General
§ 814.1 - Scope.
§ 814.2 - Purpose.
§ 814.3 - Definitions.
§ 814.9 - Confidentiality of data and information in a premarket approval application (PMA) file.
§ 814.15 - Research conducted outside the United States.
§ 814.17 - Service of orders.
§ 814.19 - Product development protocol (PDP).

Subpart B--Premarket Approval Application (PMA)
§ 814.20 - Application.
§ 814.37 - PMA amendments and resubmitted PMAs.
§ 814.39 - PMA supplements.

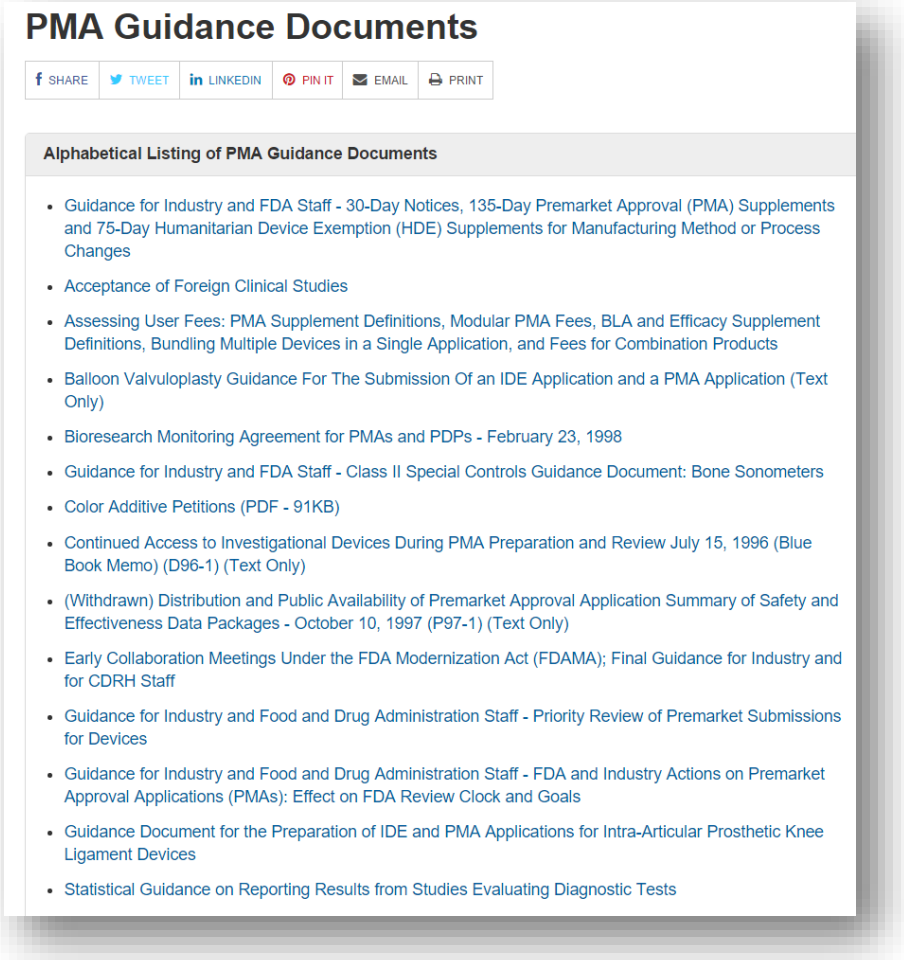
Subpart C--FDA Action on a PMA
§ 814.40 - Time frames for reviewing a PMA.
§ 814.42 - Filing a PMA.
§ 814.44 - Procedures for review of a PMA.
§ 814.45 - Denial of approval of a PMA.
§ 814.46 - Withdrawal of approval of a PMA.
§ 814.47 - Temporary suspension of approval of a PMA.

Subpart D--Administrative Review [Reserved]

Subpart E--Postapproval Requirements
§ 814.80 - General.
§ 814.82 - Postapproval requirements.
§ 814.84 - Reports.

Class III Pathway - Clinical Trials Required

- Premarket approval (PMA)
- Long list of requirements in 21 CFR 860.7
- Implies at least 1clinical trial



PMA Guidance Documents

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

Alphabetical Listing of PMA Guidance Documents

- Guidance for Industry and FDA Staff - 30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75-Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes
- Acceptance of Foreign Clinical Studies
- Assessing User Fees: PMA Supplement Definitions, Modular PMA Fees, BLA and Efficacy Supplement Definitions, Bundling Multiple Devices in a Single Application, and Fees for Combination Products
- Balloon Valvuloplasty Guidance For The Submission Of an IDE Application and a PMA Application (Text Only)
- Bioresearch Monitoring Agreement for PMAs and PDPs - February 23, 1998
- Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Bone Sonometers
- Color Additive Petitions (PDF - 91KB)
- Continued Access to Investigational Devices During PMA Preparation and Review July 15, 1996 (Blue Book Memo) (D96-1) (Text Only)
- (Withdrawn) Distribution and Public Availability of Premarket Approval Application Summary of Safety and Effectiveness Data Packages - October 10, 1997 (P97-1) (Text Only)
- Early Collaboration Meetings Under the FDA Modernization Act (FDAMA); Final Guidance for Industry and for CDRH Staff
- Guidance for Industry and Food and Drug Administration Staff - Priority Review of Premarket Submissions for Devices
- Guidance for Industry and Food and Drug Administration Staff - FDA and Industry Actions on Premarket Approval Applications (PMAs): Effect on FDA Review Clock and Goals
- Guidance Document for the Preparation of IDE and PMA Applications for Intra-Articular Prosthetic Knee Ligament Devices
- Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests

21 CFR 860.7 Definitions

- …agency relies upon only **valid scientific evidence** to determine whether there is **reasonable assurance** that the device is **safe and effective**.

- **Valid scientific evidence** is evidence from **well-controlled investigations, partially controlled studies**, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts… from which it can fairly and responsibly be concluded by qualified experts that there is **reasonable assurance of the safety and effectiveness** of a device under its conditions of use.

- reasonable assurance that …**benefits to health** from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, **outweigh any probable risks… absence of unreasonable risk of illness or injury** associated with the use of the device for its intended uses

- valid scientific evidence… **significant portion of the target population**, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide **clinically significant results**.

Subjective Interpretation vs. FDA Needs

- FDA wants to approve new medical devices
- FDA needs to preserve patient safety
- FDA therefore requires high-quality evidence of safety and effectiveness
- At least 1 “pivotal” clinical trial
- Design, sample size, assessments, etc. are negotiated

- Substantial portion of start-up investment

Typical Requirements for Premarket Medical Device Studies

- Usually control group
  - Compare experience of new device with experience of **“old” device** or **standard treatment** or **non-surgical treatment**

- No control group in unusual circumstances
  - Objective performance criteria
  - Success if demonstrate [safety] [effectiveness] at least “X”

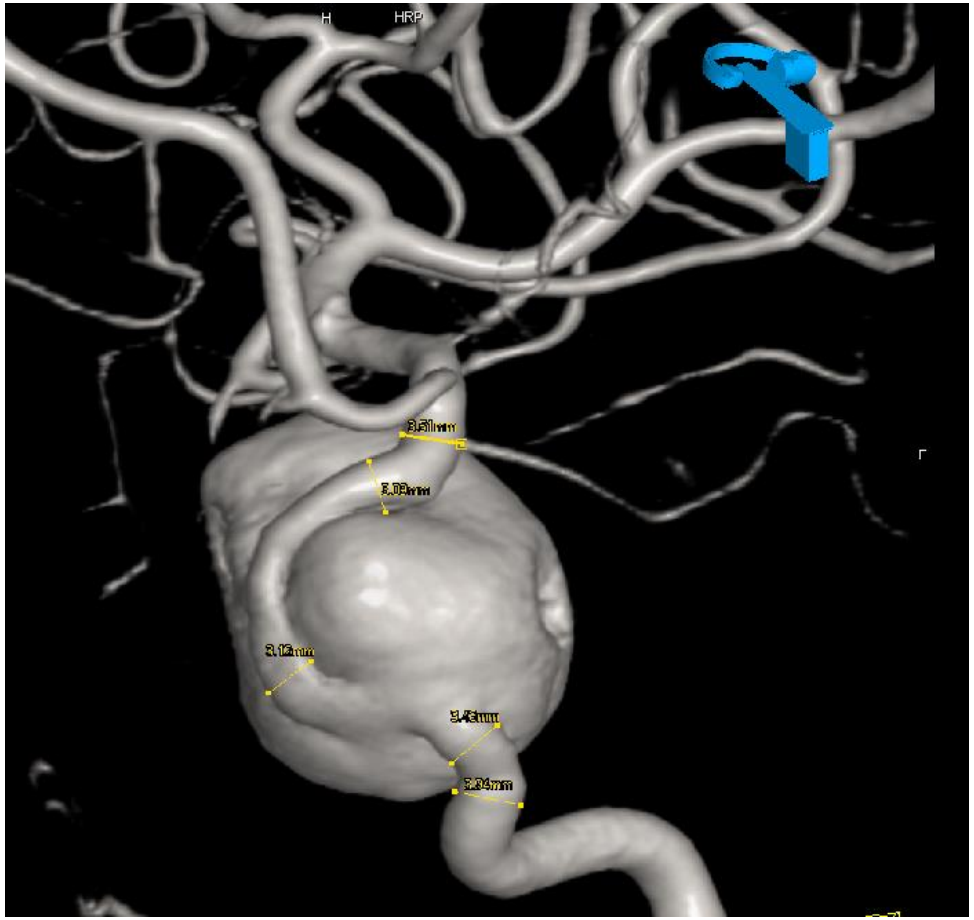
Pipeline Embolization Device

- Giant intracranial aneurysms
- Anatomic abnormality of blood vessels in brain
- Can be highly symptomatic
- High rate of spontaneous rupture → immediate death or grave disability

Five year cumulative risk of rupture
by size and location

Location	13-24mm	>25mm
Cavernous	3.0%	6.4%
ICA	14.5%	40%

Lancet 2003;362:103 *ISUIA*



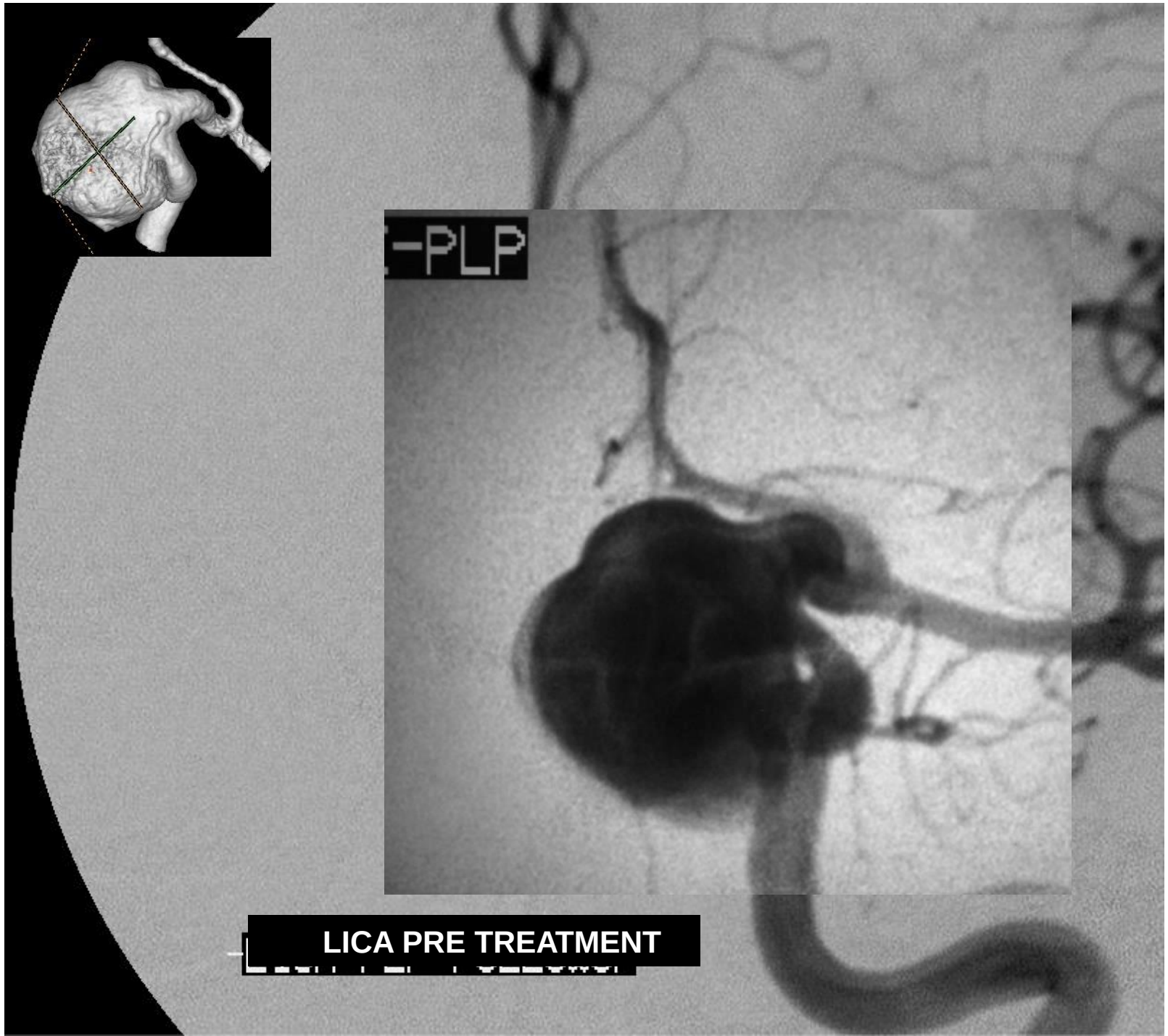
Treatments for Giant Aneurysms

- Surgery
  - Challenging
  - High risk
- Endovascular
  - Guglielmi detachable coils didn’t work well due to adverse geometry
  - Stents available but not designed for this very abnormal anatomy

Available literature in 2008 showed success rates of 15-30%

Pipeline Embolization Device

- Metal stent with high-density mesh
- Reconstruct artery from inside


-PLP
LICA PRE TREATMENT

FDA OK with single arm

- FDA agreed that
  - Available treatments not very effective
  - If we showed success rate statistically exceeded 50%, “breakthrough treatment” and approvable
  - Success rate could be judged with 6 month cerebral angiogram
  - Final success rate 74% ($p<.0001$ vs. 50%)

Other Aspects of Med Device Trials

Sham trials very difficult	• Especially when treatment is surgical • In comparison, placebo-controlled drug trial is “easy”
Surgery vs. non-surgery trials challenging	• Patients with severe problem “ready” for surgery and have exhausted medical options • Unblinding bias
Intervention significant	• Compared to “little white pill” surgical intervention usually very impactful • Patients often very sick, at high risk for death

Other Aspects of Med Device Trials

Intervention complex

- Not just “pill”
- Often many complex devices – shipping/manufacturing issues

Support staff

- Often, company members present to help surgeon use device
- Bias introduced?

Sample Sizes

- Multicenter common (10-50 sites)
- “Hundreds” – typically not “thousands”
- Enrollment challenging
  - Especially when other devices/treatments available commercially

Study Endpoints

- In many cases different from drug studies
- Often radiographic endpoints
  - Confirm “device accomplishes its technical goal”
    - Blocked something (embolization device in an aneurysm)
    - Kept something open (stent in heart artery)
    - Promoted fusion of a body part (spine implant)
- Endpoints less often just death

Physician Investigators

- Typically, busy surgeons
- Often no clinical trial infrastructure
- Often wide variation in practice
- Lack of data doesn’t prevent strong opinions
- Surgeons are good at surgery
  - Typically not good at research
  - (Internists are better researchers but they don’t use devices)

In-House Team

- In pharma, teams can be large
- Many device companies are small
- Clinical affairs teams can be very small
- Often no in-house technical expertise
  - No statistician
  - No IT support
  - Seat of the pants

International Data

- FDA prefers med device trials in US citizens
- Reluctantly accepted data from outside US
- Best to limit proportion of data not from US
- Concern that patient responses and surgical practices are “different” in Europe

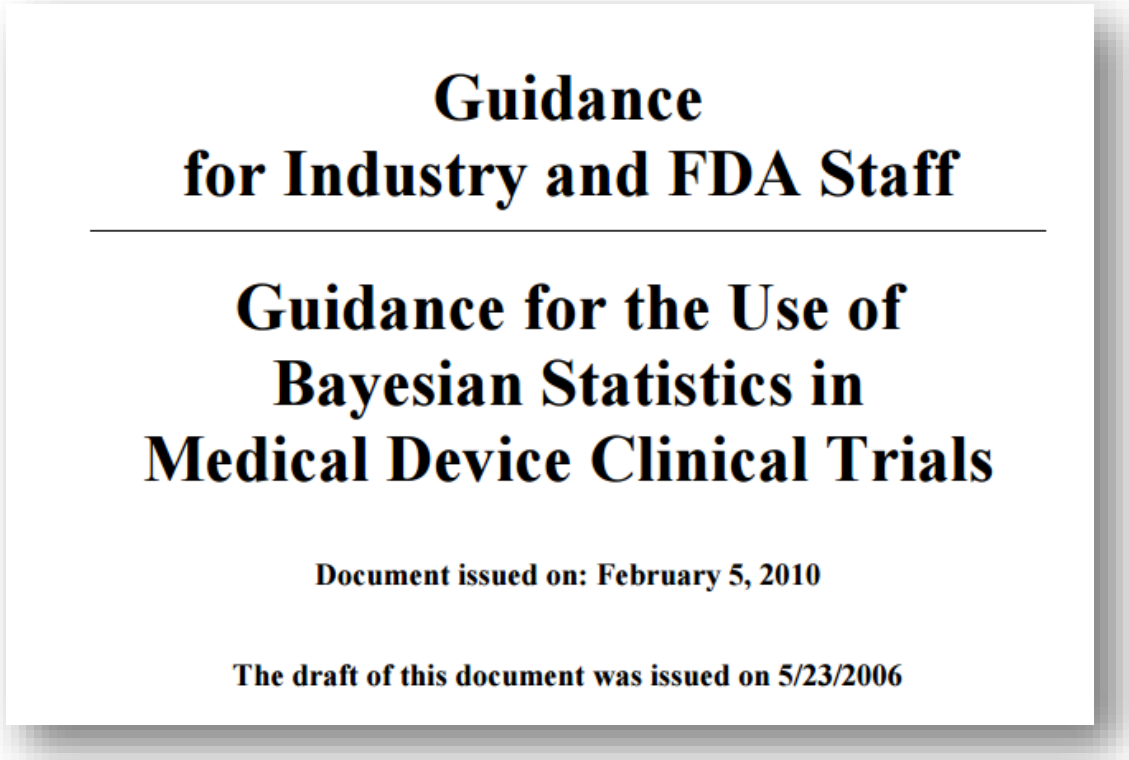
Statistical Rigor

- <1980s: Wild West
  - Loose power calculations
  - Single-arm studies
  - Poorly defined endpoints
- 1990s: increasing rigor
- 2000s-present: highly rigorous

- Great concern regarding
  - Statistical techniques
  - Impact of missing data
  - Define EVERYTHING up front
    - Do what you said you were going to do
    - No posthockery allowed

Increasing Acceptance of Flexible (Adaptive) Trial Designs

- Bayesian statistics first explored in late 1990s
- Bayesian paradigm uniquely suited to devices



Guidance
for Industry and FDA Staff

Guidance for the Use of
Bayesian Statistics in
Medical Device Clinical Trials

Document issued on: February 5, 2010

The draft of this document was issued on 5/23/2006

Bayesian Paradigm

- Bayesian stats: degrees of belief
- Pathobiology of disease often quite clear
- Mech of action of a device is very clear
  - Holds open
  - Closes off
  - Holds together
  - Zapping and frying
- Strong prior beliefs based on “surgical knowledge”
- Trials are therefore “confirmatory” as opposed to “establishing knowledge”
- Allows flexibility

Adaptive Design

- Planned changes to trial conduct while the trial is happening

"Play the winner"	• "For the last few patients, treatment A was better" • "You get treatment A"
Interim sample size calculations	• "Based on what I know now, wow many more will I need?"
Predictive calculations	• "Based on what I know now, how likely will trial be a success?"
Longitudinal modeling	• "Based on how patients have done up until now, how will remaining patients do?"
Dose response	• "Based on accumulating data, is the likelihood that dose A is ineffective high? If so, terminate that arm"

Adaptive Designs Promote Efficiency

- Enroll only right amount
- Select only treatments (or doses) that are most promising
- Gain insight into your trial as it’s happening

- FDA OK with this provided you
  - Confirm test performance characteristics before study starts
  - Follow the rules
  - Preserve Type 1 error

Bayesian Interim Analyses to Stop Enrollment

Advantages

- When effect size not known but suspect large
- Early cessation of enrollment = save $ and time

Disadvantages

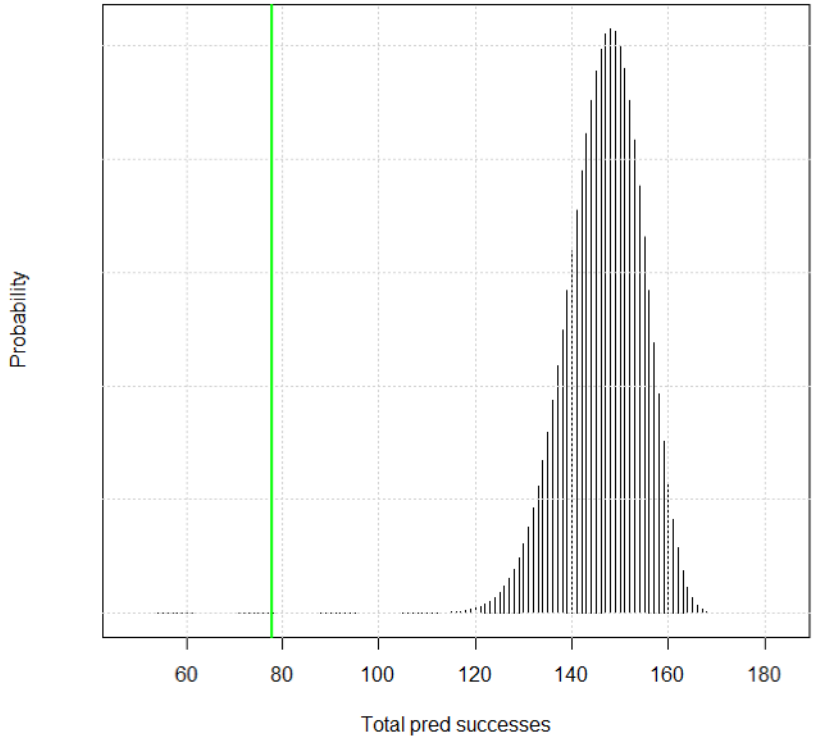
- Depends on enrollment
- Sometimes cannot take advantage of

Always carefully explore Type 1 error rate before implementing

Adjust for Type 1 error (e.g., prob = 0.98XX not 0.975)

Prospective Single-Arm Study
Stop enrollment?

- Dec 2013
- 184 enrolled
- 48/60 (80%) success rate
- Predicted success rate high
- Stop enrolling
- Follow all to primary endpoint
- Single calculation
- No statistical penalty



Predictive distribution for # of successes at trial end

Plan Device Study Carefully

- Design may work for FDA approval
- But market may find the study too small or wrong design
- Customers (surgeons) may find the study great… but insurance companies want better
- Insurance companies often apply “drug approach” to devices
  - Want gold Cadillac studies, which could be impossible
- US trials may not work for EU
- EU trials may not work for US

One design doesn’t fit all…

Trial Design May Not Work For Everyone

- Insurers may want longer follow-up
- May challenge control group
- Technology changes
  - By the time your study done, control treatment might be different
- Not “real world” – maybe your trial used world’s experts
- Design trial for all audiences, even if it’s beyond what FDA would want

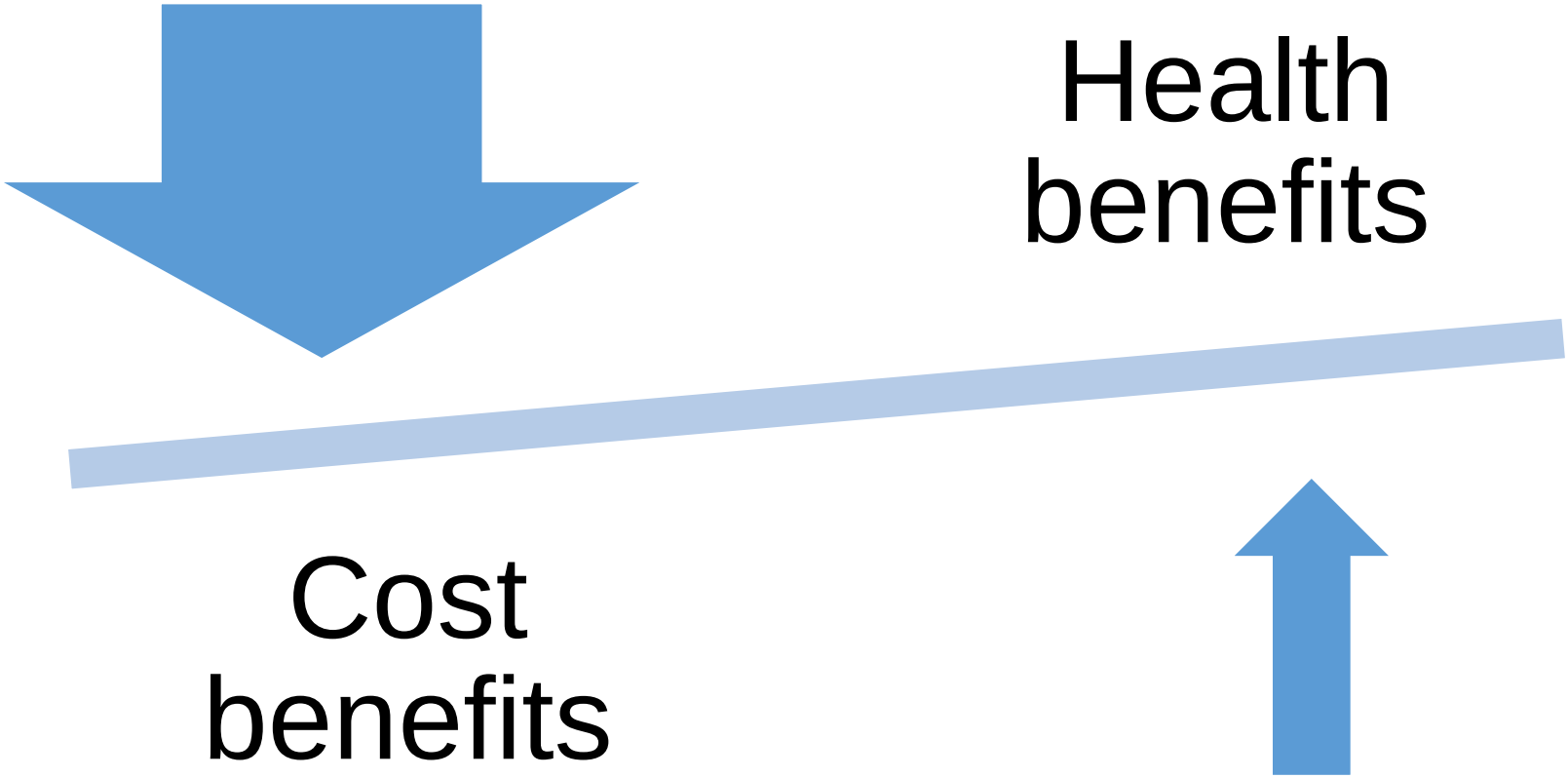
Regulatory approval studies: US vs. EU vs. Elsewhere

Health Economics in Medical Devices

Similar Question: Health Value for $

- QALYs often used
- Incremental cost for QALY
  - Incremental cost effectiveness ratio
  - How much does it cost to improve quality of life by about 1 year of full health?
- Difference: med device interventions can be very expensive
- Many questions about how to do this:
  - Compare with no treatment? Best available treatment? Non-surgical treatment?

Insurers demand value



Embed Cost Analysis in Clinical Trials

- At each study visit assess:
  - Quality of life → health state utility
  - Healthcare costs
  - Perhaps even indirect cost measures (work status, days out of work)
- Standard calculation of
  - Difference in QALY
  - Difference in cost
  - Incremental cos effectiveness ratio with measure of uncertainty

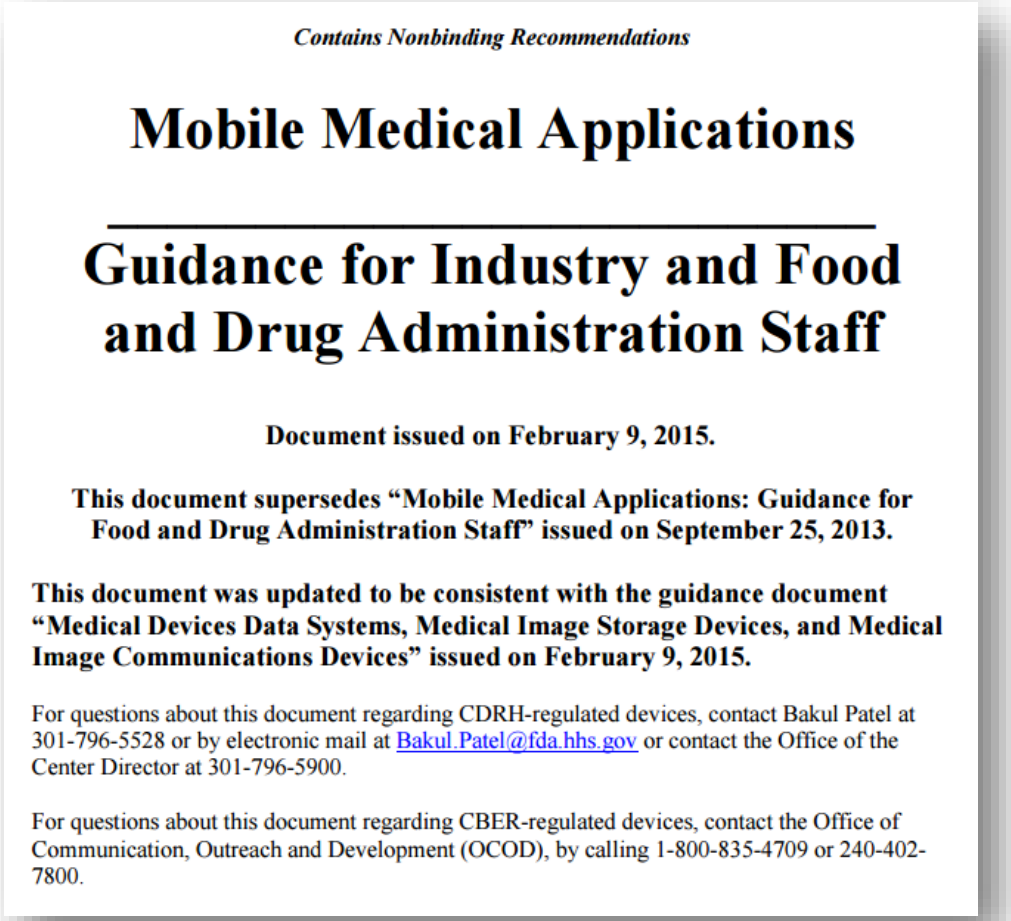
Postmarket surveillance and device epidemiology

Your iPhone can be a Medical Device

- FDA increasingly involved

FDA Guidance

- “Mobile medical app” is a mobile app that **meets the definition of device** in section 201(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) - 7 - 4 ; and either is intended:
  - to be used as an accessory to a regulated medical device
  - to transform a mobile platform into a regulated medical device



Contains Nonbinding Recommendations

Mobile Medical Applications

Guidance for Industry and Food and Drug Administration Staff

Document issued on February 9, 2015.

This document supersedes “Mobile Medical Applications: Guidance for Food and Drug Administration Staff” issued on September 25, 2013.

This document was updated to be consistent with the guidance document “Medical Devices Data Systems, Medical Image Storage Devices, and Medical Image Communications Devices” issued on February 9, 2015.

For questions about this document regarding CDRH-regulated devices, contact Bakul Patel at 301-796-5528 or by electronic mail at Bakul.Patel@fda.hhs.gov or contact the Office of the Center Director at 301-796-5900.

For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach and Development (OCOD), by calling 1-800-835-4709 or 240-402-7800.

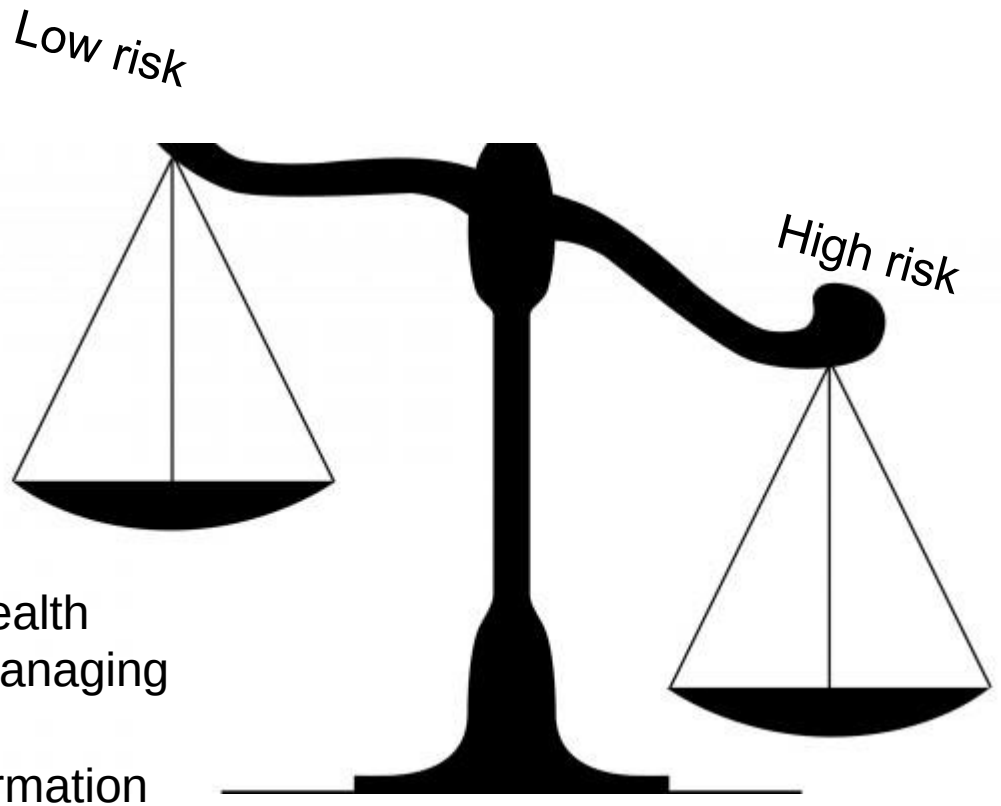
http://www.fda.gov/downloads/MedicalDevices/.../UCM263366.pdf

Perspective

It’s a device if it is designed to perform a medical device function

Responsible party is software company, not Apple

FDA wants to regulate high risk devices only



- General information about health
- General information about managing health condition
- Tools to organize health information
- Tools to automate simple tasks for HCP

- Control inflation of a medical balloon
- Retrieve/display patient-specific CT scan
- Patient-specific calculations or diagnosis

Mobile Apps FDA Wants to Regulate

- Sensor connected to a mobile platform to measure and display EKG
- Microphone to amplify heart sounds (electronic stethoscope)
- Accelerometer to measure physiologic parameters during CPR
- Sensor to measure eye movements to diagnose balance disorders

Regulatory pathway can be unclear for mobile apps

- Many in vitro diagnostic tests are class III devices
  - Require trial proving test characteristics are adequate

- Same for mobile apps – sleep apnea

Mandatory Post-Market Studies

- After device approval, FDA will often request further studies
- Done in post-market setting
- Answer residual questions about use outside of clinical trials
- Controversial
  - Less motivation (sponsor and physician)
  - Harder to enroll as device may be available commercially

Post-Market Surveillance

- System for reporting of adverse events related to device problems
  - Medical Device Reporting
  - MAUDE
- Denominator data only
- How to measure impact of new med tech use in community

Systems in Development

US market approval vs. EU and other countries

What We Talked About

- History of medical devices
- Medical device regulations and approval process
- Medical device premarket studies
- Premarket studies vs. studies for market acceptance
- Health economics in med devices
- Mobile medical devices
- Postmarket surveillance and device epidemiology

Thanks for listening!
Questions?