MEDICAL DEVICE REGULATORY BASICS

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for BioDesign in Society undergraduate course (BME221)
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Learning Goals

- To understand the basic goals of the FDA and how the agency is organized
- To learn about the FDA medical device classification system and how it relates to the two main regulatory pathways for medical devices: 510(k) and PMA.
- To develop an understanding of requirements for regulatory approval in Canada and outside North America.

BIOCATALYST DEVELOPMENT

FDA Mission

- "To protect and promote the public health"
- "…protect the safety of the food supply, give the public access to safe and effective medical products, find novel ways to prevent illness and promote health, and be transparent in explaining our decision-making…"

Dr. Margaret Hamburg

Top FDA official since May 2009

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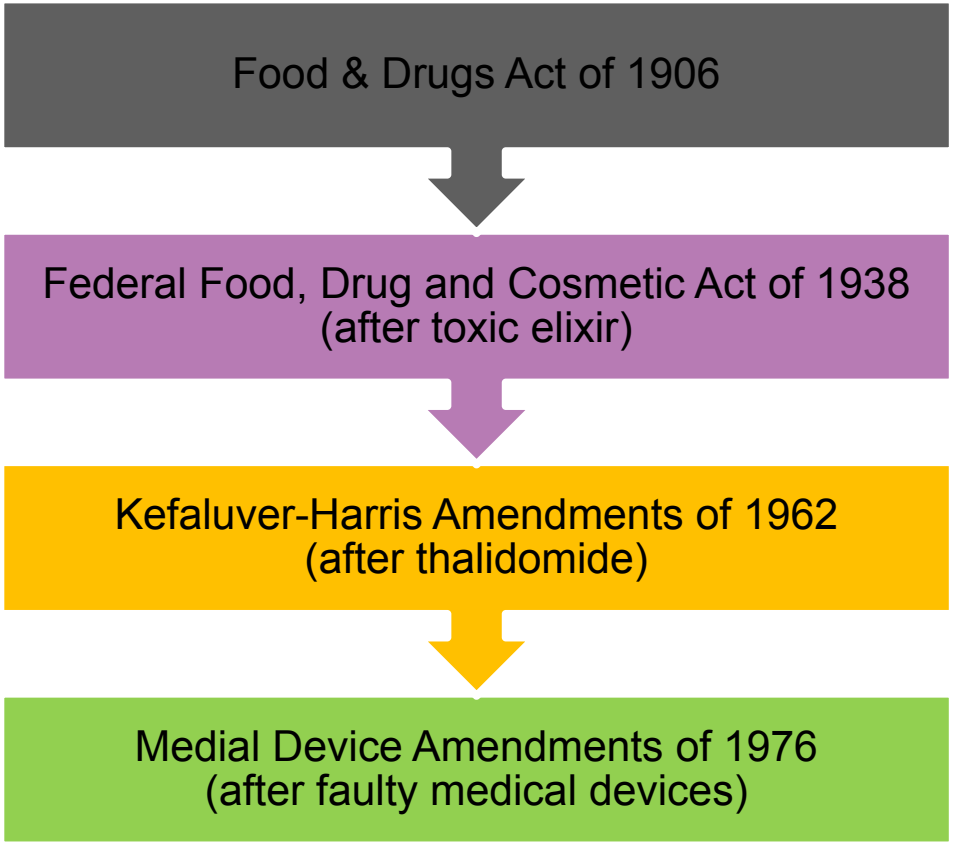
Some history of the FD&C Act



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Medical device amendments

Medical device amendments 1976	• Risk-based classification system
Safe medical devices act 1990	• Formally codifed 510(k) process and sharpened definition of substantial equivalence
Medical device amendments 1992	• Clarified 4 provisions: tracking, postmarket surveillance, reporting, repair/replacement/refund
Medical Device User Fee and Modernization Act (MDUFMA) 2002	• Driven by need to speed up 510(k) clearances and approval process for PMAs; introduced user fees, third party inspections

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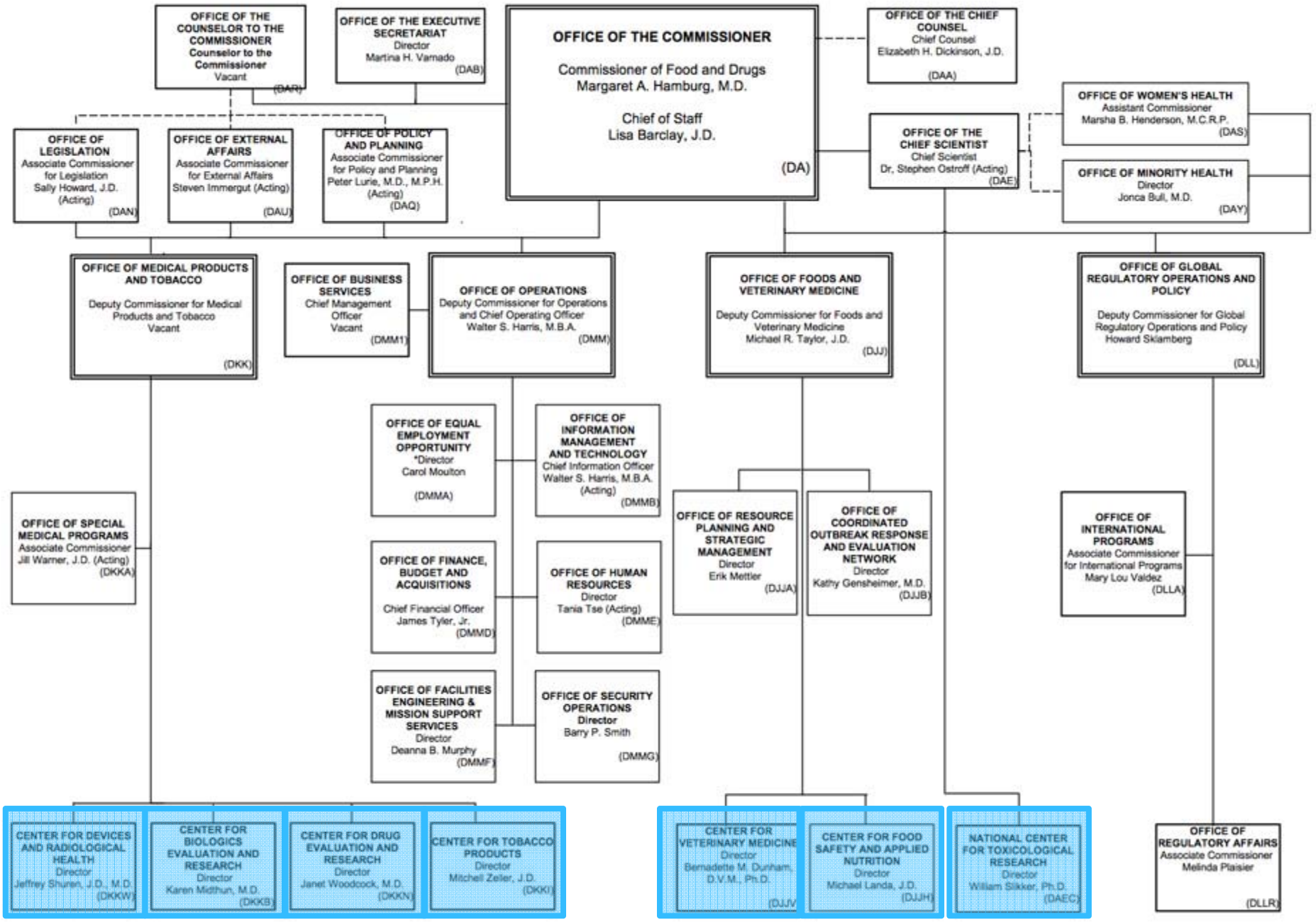
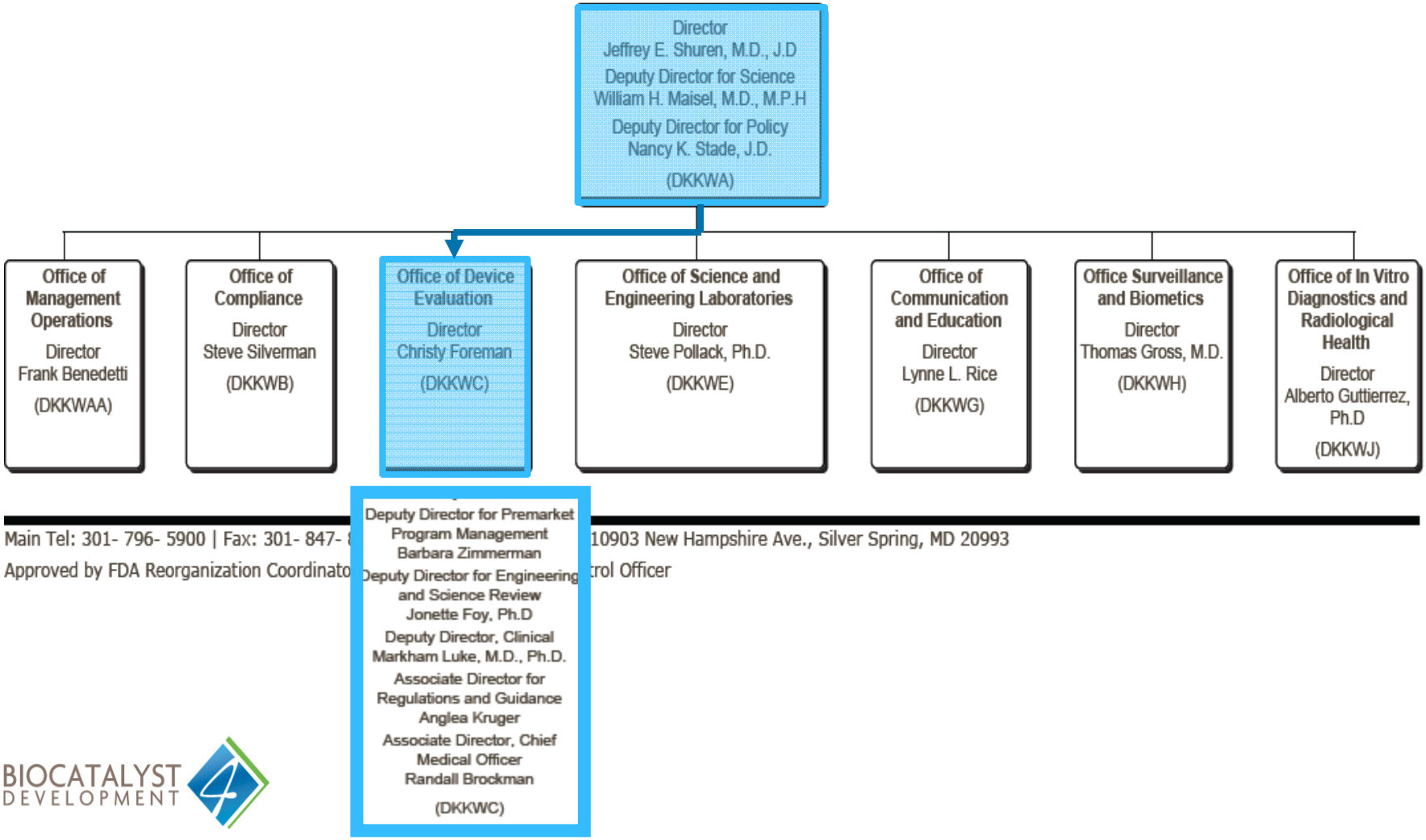
FOOD AND DRUG ADMINISTRATION



*Director Reports to the Agency Head

Center for Devices and Radiological Health



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Helpful resources

- www.fda.gov
- Laws and Regulations:
  - Food, Drug and Cosmetic Act (FD&C) Act
  - Medical Device User Fee and Modernization Act (MDUFMA)
  - Code of Federal Regulations 21(CFR 21)
- Guidance documents
  - Device advice: regulatory assistance
  - cGMP issues for devices
- FDA product classification database

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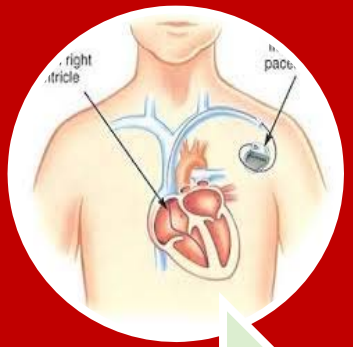
FDA: Classification of devices



INCREASING RISK
Increasing level of regulatory control

Class I

General controls
No approval required – listing on FDA website

Class II

General controls
Special controls
510(k) notification unless exempt

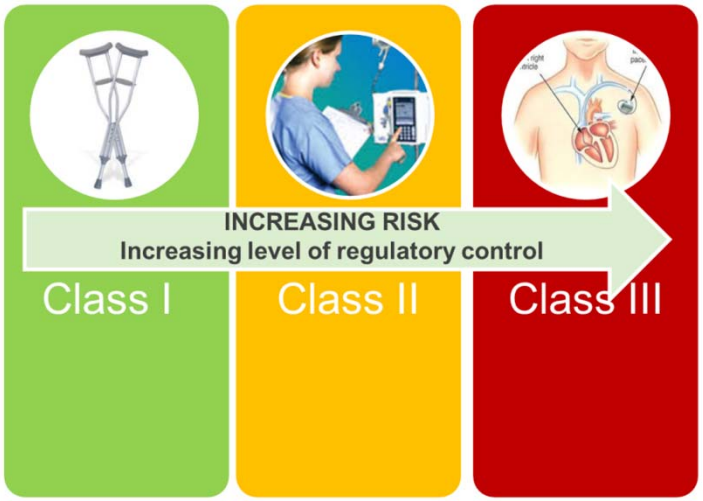
Class III

General controls
Special controls
Pre-market approval

BIOCATALYST DEVELOPMENT

General controls (all classes)

- Establishment registration and device listing (21CFR 807)
- Compliance with Good Manufacturing Practice (cGMP) (21CFR 820: The Quality System Regulation
- Labeling in accordance with 21CFR 801 or 809 (for in vitro diagnostic devices)
- Submission of 510(k), unless exempt or PMA required



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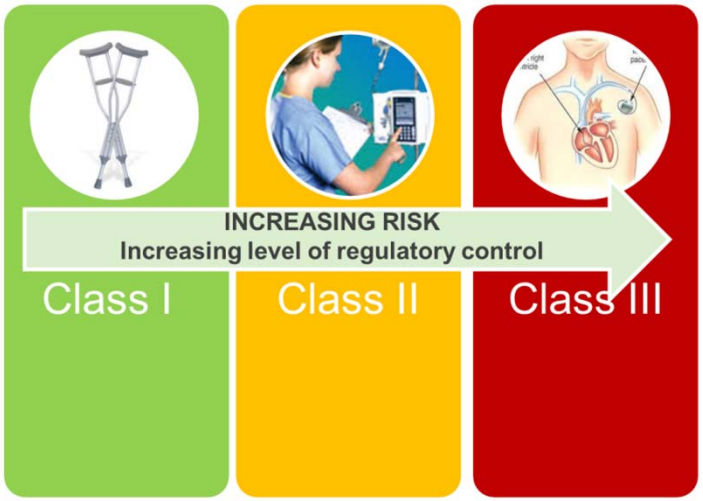
Special controls (Class II & III)

- May include:
  - Special labeling requirements
  - Recommendation to follow certain FDA guidances
  - Mandatory performance standards
  - Human clinical trials
  - Post-market surveillance requirements



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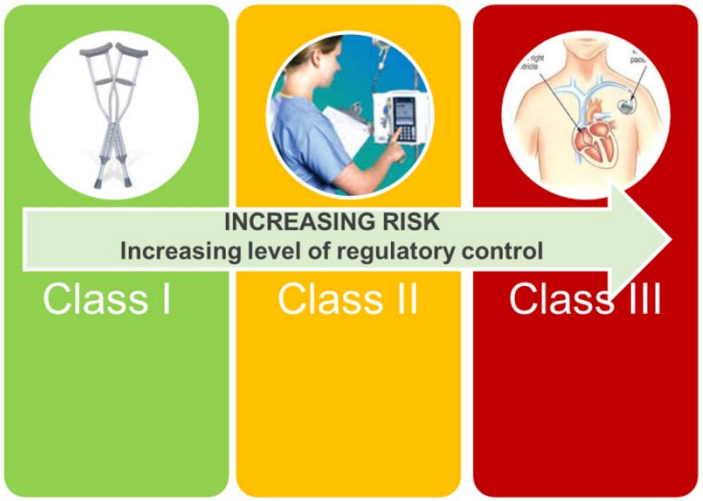
Pre-market approval (Class III)

- Typically these devices
  - Support or sustain human life
  - Important in preventing impairment to health
  - High risk of an adverse event
- Are not "substantially equivalent" to a legally marketed Class I or Class II predicate device
- Require human clinical trials substantiating and documenting safety and effectiveness



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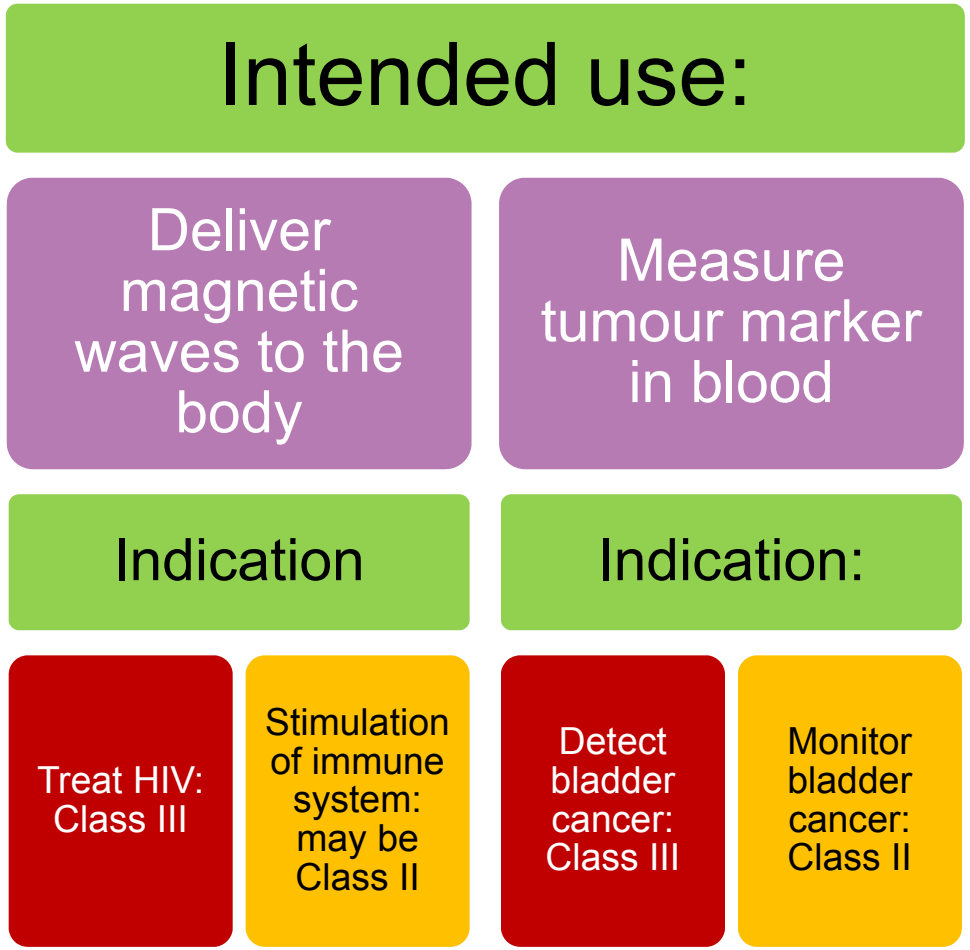
Determining classification

- Intended use: *What device is designed to do*
- Indication for use: *Disease or condition you plan to diagnose, cure, mitigate, treat, or prevent*



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Substantial equivalence (SE)

Same Intended use	• As predicate device
Same Technological characteristics or if different	• Different = significant change in the materials, design, energy source, or other features of the device from those of the predicate device
Same Safety/effectiveness and does not raise different safety/effectiveness questions	• Performance data may be necessary to support SE claim; depending on the device could be non-clinical and clinical testing • Does not raise different questions

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Finding a Predicate Device

- Go to FDA's **product classification** database
  - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm
- Search for your device using the most basic description
- If you know the **device medical specialty panel** you can also go directly to the listing for that panel and find devices that appear similar to your device
- Read the description carefully and find the device that is most similar to yours and the corresponding regulation (CFR)
- The CFR gives a general description including the intended use, the class to which the device belongs (i.e., Class I, II, or III), and information about marketing requirements

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- **16 medical specialty panels**
  - Anesthesiology
  - Cardiovascular
  - Clinical Chemistry and Clinical Toxicology
  - Dental
  - Ear, Nose, and Throat
  - Gastroenterology and Urology
  - General and Plastic Surgery
  - General Hospital and Personal Use
  - Hematology and Pathology
  - Immunology and Microbiology
  - Neurology
  - Obstetrical and Gynecological
  - Ophthalmic
  - Orthopedic
  - Physical Medicine
  - Radiology

De novo classification

If no predicate Class I or II device

- Automatic Class III designation under Section 513(f)(1) of the FD&C Act
- **BUT** – can apply for de novo classification under 513(f)(2);
- draft guidance August 2014

Low to moderate risk

- Explain risks/benefits
- Explain how risks can be mitigated by application of general and special controls

Adequate data

- To provide reasonable assurance of safety/effectiveness

BIOCATALYST DEVELOPMENT

Traditional 510(k) submission

- Includes a statement that device is similar to one or more legally marketed predicate device
- Additional supporting information to document substantial equivalence
  - Side-by-side technical comparison
  - Consideration of impact of any technical differences on safety/effectiveness
  - Summary of safety/effectiveness data
    - Generally laboratory tests: biocompatibility, engineering, bench performance, design verification, voluntary standards tests
    - Sometimes clinical studies

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Alternative 510(k) approaches

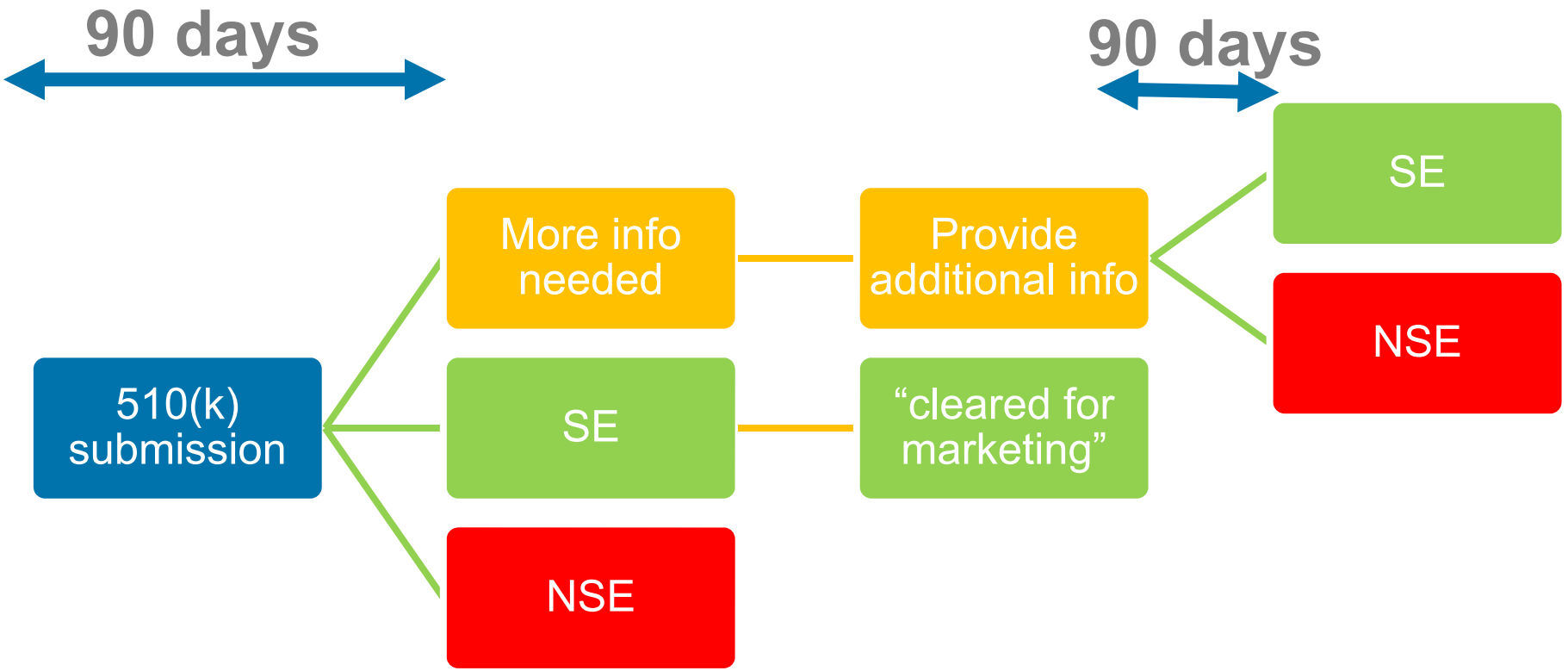
March 1998

Two optional new approaches for obtaining clearance

Modification of existing device	Special controls/recognized consensus standards
Does not affect the device's intended use or alter the device's fundamental scientific technology	Manufacturer prepares Summary Report
Design validation	How wasthe guidance document and/or special control(s) were used during device development and testing

BIOCATALYST DEVELOPMENT

510(k) Review process



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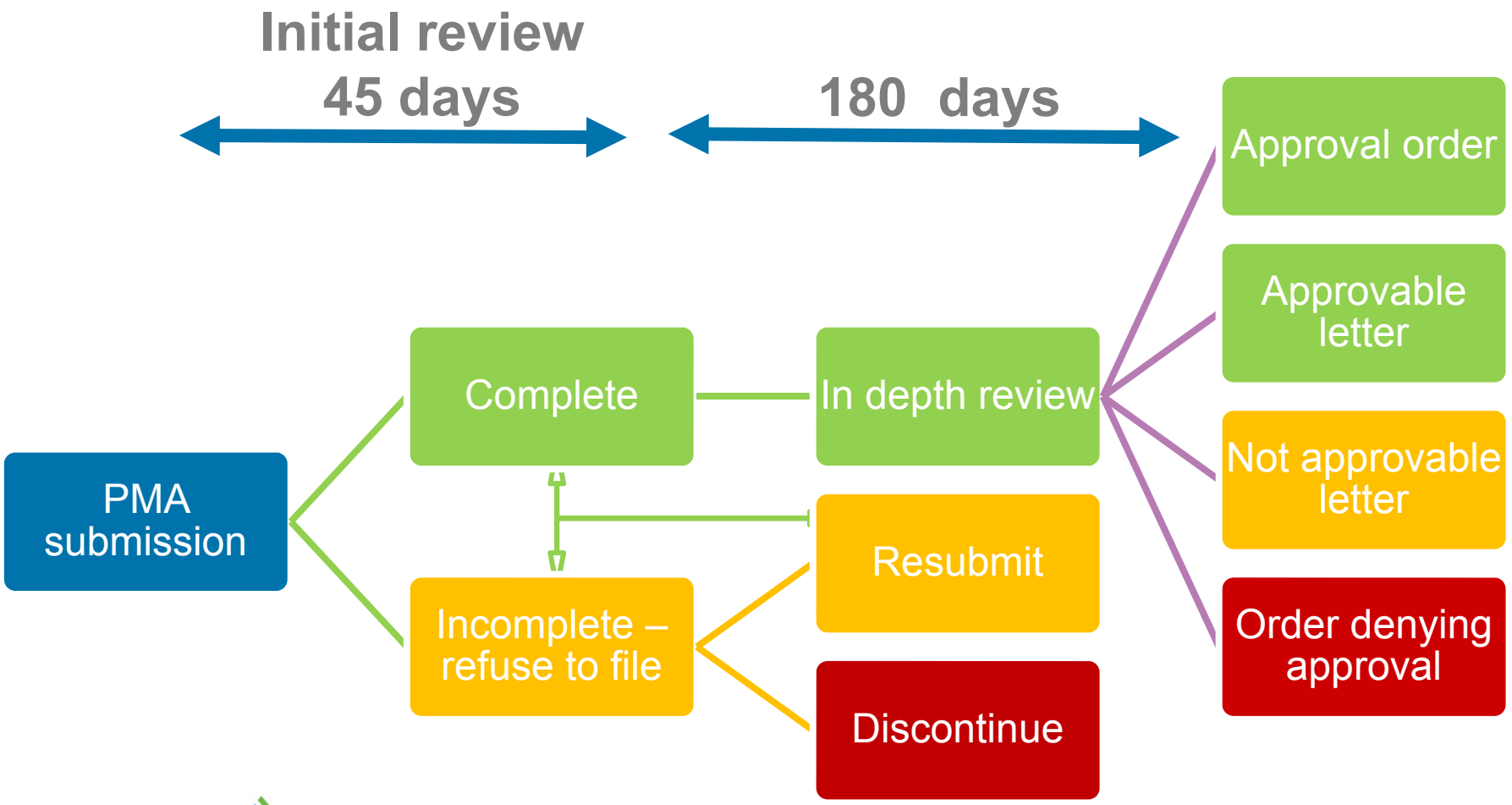
PMA Application

- Includes reports of investigations to show device is safe and effective (including clinical studies)
- Statement of the components, ingredients, and properties and of the principle or principles of operation, of the device
- Description of the methods, facilities, and control for the manufacture, processing, packing, and installation of the device
- Reference to any relevant performance standards and the device ability to meet the performance standard
- Sample of the device and components
- Proposed labeling
- Certification related to clinical trials
- Other relevant information the FDA may require

BIOCATALYST DEVELOPMENT

PMA Review process



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Summary: 510(k) vs PMA

510(k) Premarket Notifiction	PMA Premarket Approval
Class II (most Class I devices and a few Class II are 510(k) exempt)	Class III devices
Approx. 5000 per year	Approx. 50 per year
~50 to 100 pages	~1000 pages
~10% need clinical studies	All need clinical studies
90-day review period (target)	180-day review period (target)
Substantially equivalent to legally marketed predicate device	No Class I or Class II predicate available
$5,170 (application fee)*	$258,520*

*fee reductions for small businesses (<$100M in sales)

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Clinical trials of a device

- Requires an approved Investigational Device Exemption (IDE) before study is initiated (unless non-significant risk)
  - an investigational plan approved by an institutional review board (IRB)
  - complete report of prior investigations if no IRB has approved them
  - description of the methods, facilities, and controls
  - sample investigator agreements, names & addresses
  - labeling stating that the device is for investigational use only
- Study must follow GCP (Good Clinical Practices
  - informed consent from all patients
  - monitoring of the study
  - required records and reports

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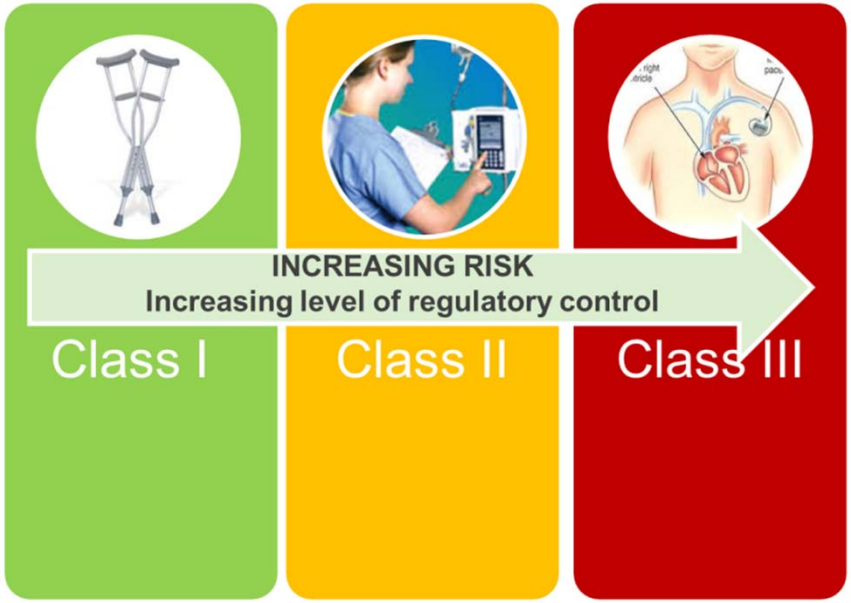
Some examples

- Crutch
- Infusion pump
- Implantable cardiac pacemaker



BIOCATALYST DEVELOPMENT

Crutch

- Device Crutch
- Regulation Description Crutch.
- Regulation Medical Specialty Physical Medicine
- Review Panel Physical Medicine
- Product Code IPR
- Premarket Review Office of Device Evaluation (ODE)
- Division of Neurological and Physical Medicine Devices (DNPMD)
- Physical Medicine and Neurotherapueutic Devices Branch (PNDB)
- Submission Type **510(K) Exempt**
- Regulation Number 890.3150
- **Device Class 1**
- Total Product Life Cycle (TPLC) TPLC Product Code Report
- GMP Exempt? Yes

BIOCATALYST DEVELOPMENT 4

Infusion pump

- Device Pump, Infusion
- Regulation Description Infusion pump.
- Regulation Medical Specialty General Hospital
- Review Panel General Hospital
- Product Code FRN
- Premarket Review (ODE) Office of Device Evaluation
- Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices (DAGRID)
- General Hospital Devices Branch (GHDB)
- **Submission Type** **510(k)**
- Regulation Number 880.5725
- **Device Class** **2**
- Total Product Life Cycle (TPLC) TPLC Product Code Report
- GMP Exempt? No

BIOCATALYST DEVELOPMENT 4

- Recognized Consensus Standards
  - ISO 7886-2 First edition 1996-05-15 Sterile hypodermic syringes for single use - Part 2: Syringes for use with power-driven syringe pumps
  - ISO 26825 First edition 2008-08-15 Anaesthetic and respiratory equipment - User-applied labels for syringes containing drugs used during anaesthesia - Colours, design and performance
  - ISO 23908 First edition 2011-06-11 Sharps injury protection - Requirements and test methods - Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling
  - ISO 9626 First edition 1991-09-01 Stainless steel needle tubing for the manufacture of medical devices [Including: Amendment 1 (2001)]
- Guidance Documents
  - Guidance for Industry and FDA Staff - Total Product Life Cycle: Infusion Pump - Premarket Notification [510(k)] Submissions [http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm206153.htm]
  - Guidance on the Content of Premarket Notification [510(k)] Submissions for External Infusion Pumps
- Third Party Review
- Eligible for Accredited Persons Program

Cardiac pacemaker

- Device Pulse-Generator, Single Chamber, Sensor Driven, Implantable
- Review Panel Cardiovascular
- Product Code LWO
- Premarket Review Office of Device Evaluation (ODE)
- Division of Cardiovascular Devices (DCD)
- Implantable Electrophysical Devices Branch (IEDB)
- Submission Type PMA
- **Device Class 3**
- Total Product Life Cycle (TPLC) Product Code Report TPLC
- GMP Exempt? No

- Recognized Consensus Standards
  - AAMI/ANSI/ISO 27185:2012 Cardiac Rhythm Management Devices -- Symbols to be Used With Cardiac Rhythm Managment Device Labels, and Information to be Supplied -- General Requirements
  - ISO 27185 First edition 2012-02-15 Cardiac Rhythm Management Devices - Symbols to be Used With Cardiac Rhythm Management Device Labels, and Information to be Supplied - General Requirements
  - AAMI TIR41:2011 Technical Information Report Active implantable medical devices - Guidance for designation of left ventricle and implantable cardioverter defibrillator lead connectors and pulse generator connector cavities for implantable pacemakers and implantable cardioverter defibrillators
  - ISO 5841-3 Third edition 2013-04-15 Implants for Surgery - Cardiac Pacemakers - Part 3: Low-Profile Connectors (IS-1) for Implantable Pacemakers
- Third Party Review: Not Third Party Eligible

BIOCATALYST 4 DEVELOPMENT

Comparison of device approvals in Canada and Europe *vs* US

	US	Canada	Europe
Regulatory authority	FDA:	Heath Canada TPD, Medical Devices Bureau	Competent authority of the country where your company or authorized representative is located:
Regulation	Food and Drug & Cosmetic Act, 21 CFR 814 & 807	Medical Devices Regulation, SOR/98-282	Medical Device Directive (MDD) 93/42EEC Active Implantable Medical Device Directive (AIMDD) 90/385/EEC IVDD 98/79/EC
Classifications (risk-based plus)	I, II, III (predicates found in database)	I, II, III, IV (flowcharts, rule-based)	I, IIa, IIb, III (flowcharts, rule based)
Submission type	PMA (Class III) /510(k) (Class II)	Device license application (except Class I)	Product technical dossier/file – obtain CE mark (except Class I, non-sterile, non-measuring)

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Comparison of device approvals in Canada and Europe *vs* US

	US	Canada	Europe
Quality management system	21CFR 820; random inspections for compliance; inspections prior to approval of PMA for Class III devices (pilot program to submit third-party ISO 13485 audits)	For all except Class I ISO 13488 (Class II) or 13485 (Class III & IV - deals with both design and manufacturing standards)	ISO 13485
Third party audits/reviews of submission	Sometimes	ISO audit is performed by accredited 3rd party (registrars) – guidance document available	Yes –Notified Body, a third party accredited by European authorities to audit medical device companies and products
Clinical trials	IDE	Investigational testing authorization (ITA) for all but Class I	Statement to competent authority

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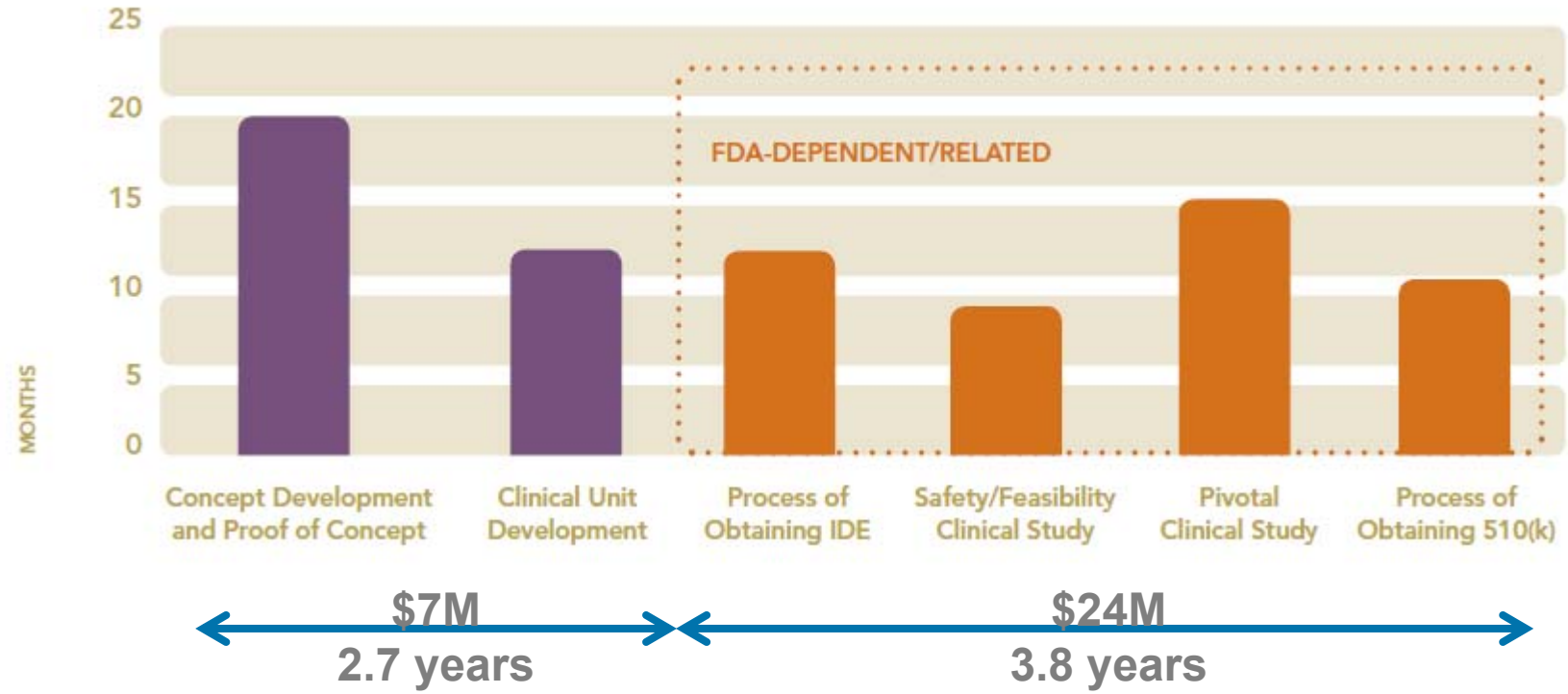
Time/costs for 510(k) device



Source: Josh Makower, FDA Impact on U.S. Medical Technology Innovation:A Survey of Over 200 Medical Technology Companies • November 2010

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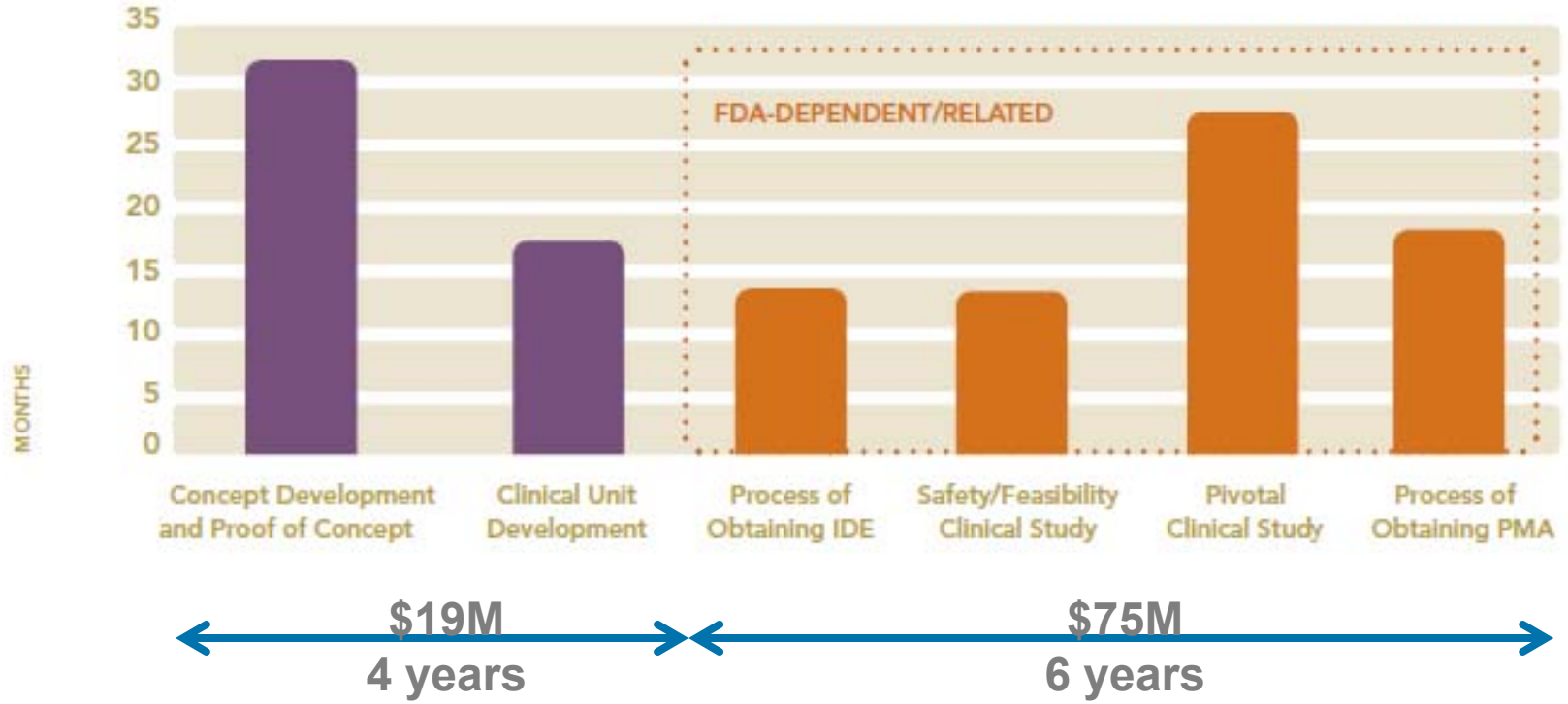
Time/costs for a PMA device



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