FDA Regulation of Medical Devices Premarket Requirements

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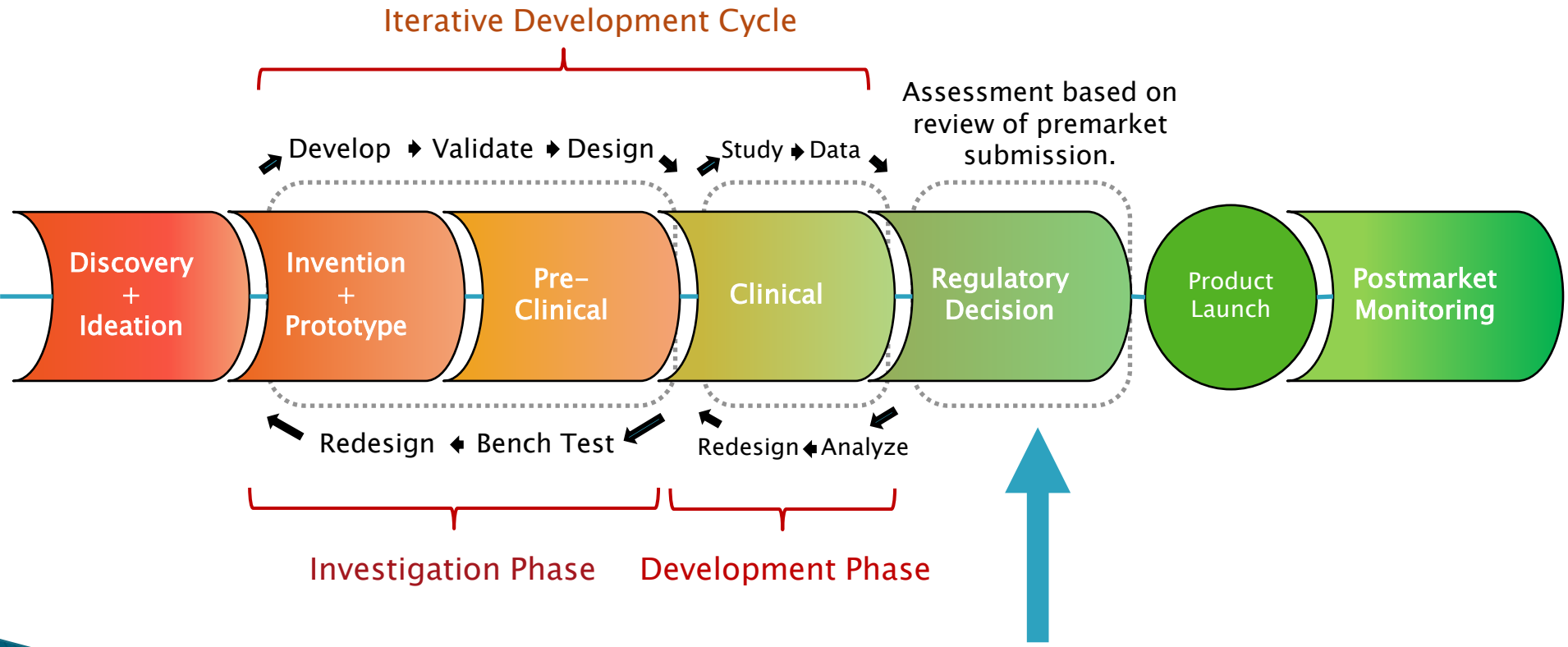
Medical Device Development Pathway



Adopted from CDRH *Innovation Initiative*, February 2011.

Landscape

- FDA Authority
  - Medical Device Act of 1976
  - FDA Modernization Act of 1997
  - Federal Food, Drug and Cosmetic Act (FFDCA)
  - Medical Device User Fee Act (MDUFA)
- Premarket Requirements
  - A Premarket Approval (PMA) application or 510(k) must be submitted. Approval or clearance depends on risk!

Federal Food, Drug and Cosmetic Act 1997…

- Generally speaking, under the Federal Food, Drug and Cosmetic Act (FFDCA), manufacturers:
  - Are prohibited from selling an adulterated product;
  - Are prohibited from misbranding a product;
  - Must register their facility with FDA and list all of the medical devices that they produce or process;
  - Must file the appropriate premarket submission with the agency at least 90 days before introducing a *nonexempt* device onto the market; and
  - Must report to FDA any incident that they are aware of that suggests that their device may have caused or contributed to a death or serious injury.

Johnson, J. A., *FDA Regulation of Medical Devices*, 2016

Products Regulated by the FDA…

Table 5.2 Products regulated by the FDA

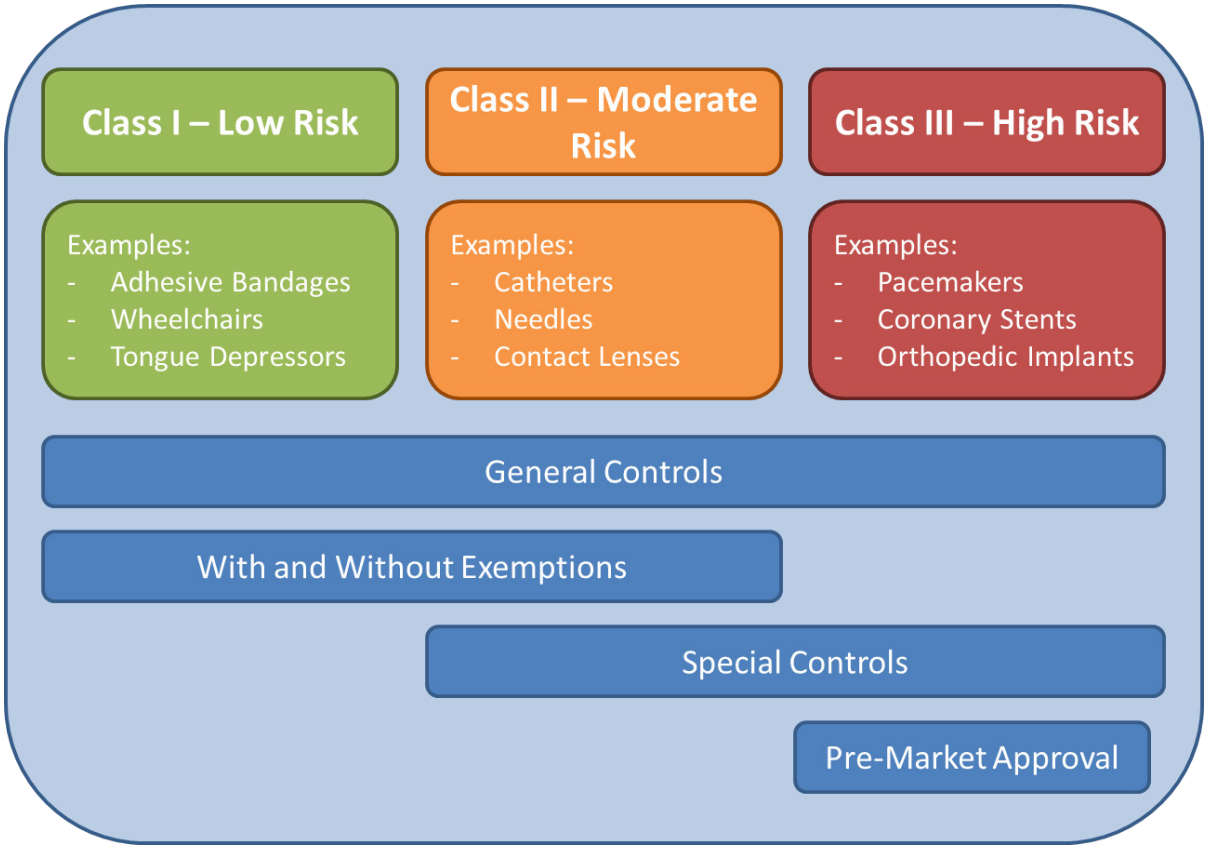
Blood-related biologics; blood substitutes, etc.	Product and manufacturing establishment licensing; safety of the nation's blood supply; research to establish product standards and develop improved testing methods
Cosmetics	Safety and labeling
Drugs (including biological large molecule drugs)	Product approvals; over the counter (OTC) and prescription drug labeling; drug manufacturing standards
Foods	Labeling; safety of all food products (except meat and poultry); bottled water
Medical devices	Pre-market approval of new devices; manufacturing and performance standards; tracking reports of device malfunctioning and serious adverse reactions
Radiation-emitting electronic products	Radiation safety performance standards for microwave ovens, television receivers, diagnostic X-ray equipment, cabinet X-ray systems (such as baggage X rays at airports), laser products; ultrasonic therapy equipment, mercury vapor lamps, and sunlamps; accrediting and inspecting mammography facilities
Veterinary products	Livestock feeds; pet foods; veterinary drugs and devices

Mehta, Shreefal S. *Commercializing Successful Biomedical Technologies : Basic Principles for the Development of Drugs, Diagnostics, and Devices.* Cambridge ; New York: Cambridge ; New York : Cambridge University Press, 2008.

Premarket Requirements

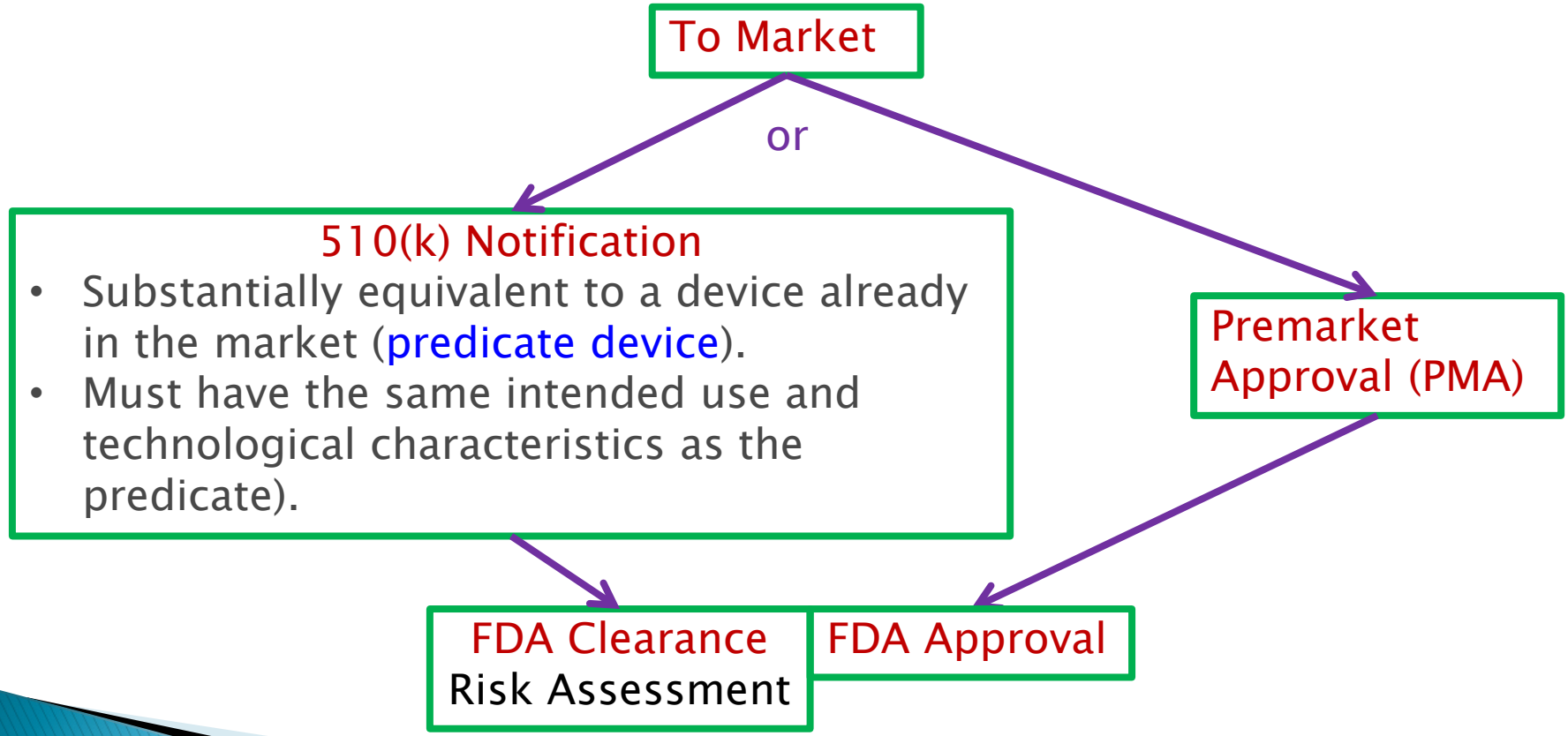
- Device Classification
- Medical Device Marketing Application Types:
  - Premarket Approval (PMA)
    - PMA Supplements
    - Evaluations of the PMA and PMA Supplement Process
    - Humanitarian Device Exemption (HDE)
  - 510(k) Notification – Substantially Equivalent Device
    - Traditional 510k
    - Abbreviated 510k
    - Special 510k
    - De Novo 510k

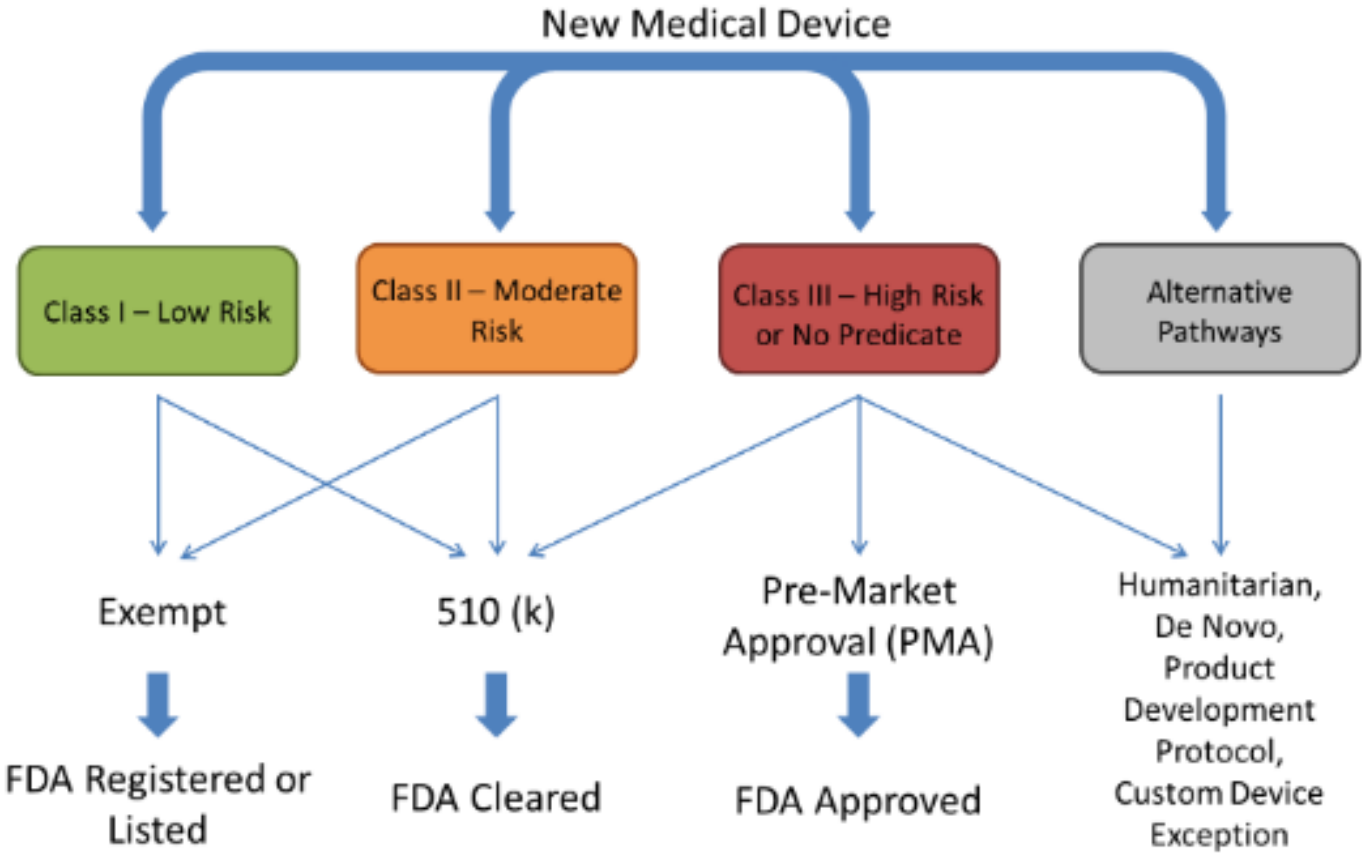
Device Classification…



Wickert, L Medical device classification in the United States 2019.

Premarket Review Path





Wickert, L Exploring FDA approval pathways for medical devices 2019.

Premarket Approval (PMA)

- FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices.
  - Summaries of nonclinical and clinical data supporting the application and conclusions drawn from the studies.
  - Device description including significant physical and performance characteristics.
  - Indications for use, description of the patient population and disease or condition that the device will diagnose, treat, prevent, cure, or mitigate.
  - *A Investigational Device Exemption is* required before the clinical study (unless exempt). Must have *Institutional Review Board (IRB)* approval.

Johnson, J. A., *FDA Regulation of Medical Devices*, 2016

- Description of the foreign and U.S. marketing history, including if the device has been withdrawn from marketing for any reason related to the safety or effectiveness of the device.
- Proposed labeling.
- Description of the manufacturing process.
- FDA may order a post-approval study .
- *PMA Supplements* are required to make a change to an approved PMA device.
- FDA approval does not imply Medicare coverage.

Clinical Studies…

- Required:
  - Randomized Controlled Trial (RCT).
  - Blinded Clinical Trial.
  - *Crossover trials are now recommended by FDA.*
- Issues:
  - Use of surrogate end point (e.g. low cholesterol lab) value vs direct patient benefit (less death from heart disease).
  - Reporting bias.
  - Failure to timely publish clinical results (or substantially different than was submitted).
  - Accessibility to patients of data the FDA used in the PMA.
  - Lack of clinical data in the *PMA Supplement*.

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journal homepage: www.elsevier.com/locate/conctc

Design and analysis of crossover trials for investigating high-risk medical devices: A review

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During evaluation of new investigational medical devices, the FDA recommends that investigators design a crossover clinical trial, in which the patients are arranged to cross over from one treatment arm to another. The FDA annually receives the premarket applications of investigational medical devices, in which sponsors design and conduct crossover trials as their confirmatory clinical trials for evaluating safety and effectiveness of the devices.

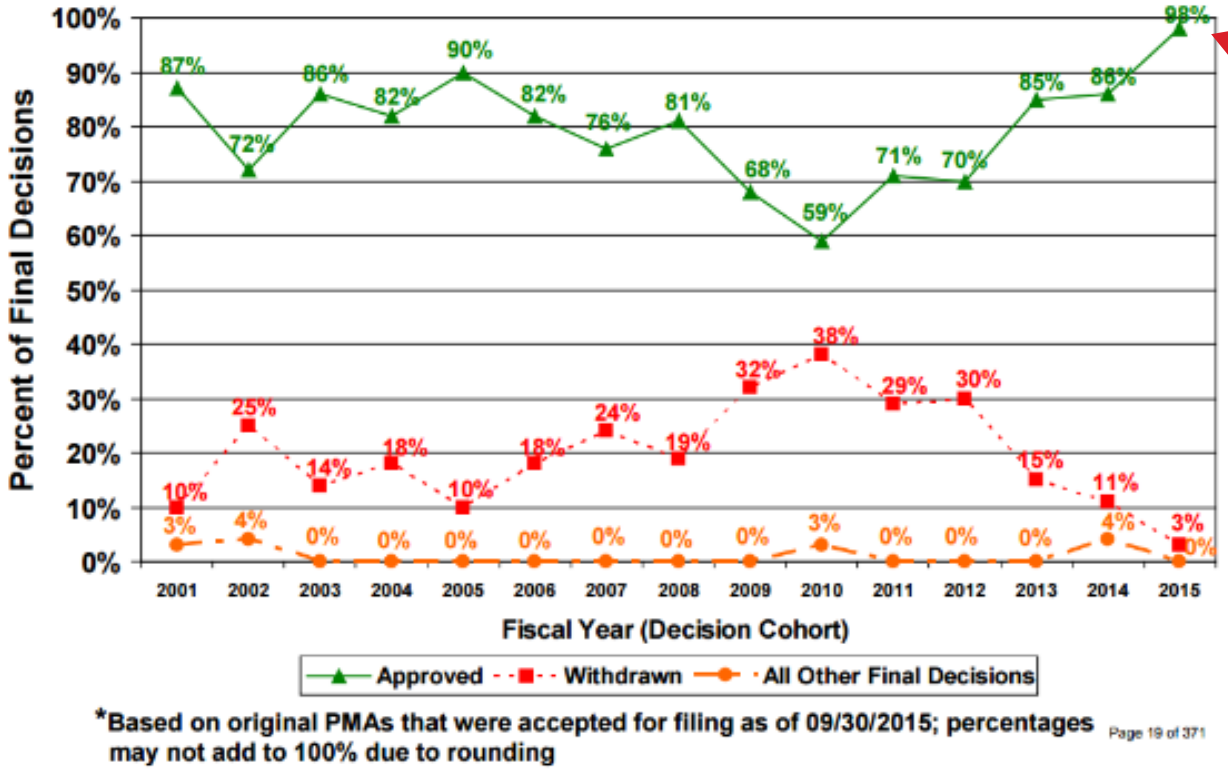
Prof. Steven S. Saliterman

Good Clinical Practices (21 CFR)

- Investigational Device Exemptions (812)
  - Covers the procedures for the conduct of clinical studies with medical devices including application, responsibilities of sponsors and investigators, labeling, records, and reports.
- Protection of Human Subjects (50)
  - Provides the requirements and general elements of informed consent;
- Institutional Review Boards (56)
  - Covers the procedures and responsibilities for institutional review boards (IRBs) that approve clinical investigations protocols;

- Financial Disclosure by Clinical Investigators (54)
  - Covers the disclosure of financial compensation to clinical investigators which is part of FDA's assessment of the reliability of the clinical data.
- Design Controls of the Quality System Regulation (820 Subpart C)
  - Provides the requirement for procedures to control the design of the device in order to ensure that the specified design requirements are met.

PMAs (%) Approved 2001-2015



98%

Brennam , Z. FDA Sees Record-High PMA Approval Rate for 2015, Regulatory Affairs Professional Society, November 2015.

Investigational Device Exemption (IDE)

- Allows the device to be used in an a clinical study in order to collect safety and effectiveness data.
  - Usually in support of the PMA.
  - An investigational plan approved by an institutional review board (IRB). If the study involves a significant risk device, the IDE must also be approved by FDA;
  - Informed consent from all patients;
  - Labeling stating that the device is for investigational use only;
  - Monitoring of the study and;
  - Required records and reports
- Do not require PMA, 510(k), establishment registration or listing. Exempt from *Quality System*.

Humanitarian Device Exemption (HDE)

- Diseases or conditions that affect fewer than 4,000 individuals in the United States per year.
- Exempt from the effectiveness requirements to encourage manufacturers to develop devices for these small markets.
- IRB approval required.
- Potential insurers may not cover the device.
- Cannot be another similar legally marketed device.

510(k) Notification

- A premarket submission made to FDA to demonstrate that the device to be marketed is as safe and effective, that is, substantially equivalent, to a legally marketed device.
  - Required for a moderate-risk medical device that is not exempt from premarket review.
  - Typically Class II, rarely Class III.
  - Must be *substantial equivalence* with a *predicate* device.
    - Previously cleared Class I or II device that does not require a PMA.
  - Three types: *Traditional*, *Special* and *Abbreviated*.
  - *De Novo* – novel devices without a predicate.

- Substantial Equivalence Defined:
  - A device is substantially equivalent if, in comparison to a predicate it:
    - has the same intended use as the predicate; **and**
    - has the same technological characteristics as the predicate; **or**
    - has the same intended use as the predicate; **and**
    - has different technological characteristics and does not raise different questions of safety and effectiveness; **and**
    - the information submitted to FDA demonstrates that the device is at least as safe and effective as the legally marketed device.

- Traditional 510(k)
  - Name of the device, a description of the device, a comparison with a predicate device, the intended use of the device, and the proposed label, labeling, and advertisements for the device and directions for use.
  - Generally do not require premarket inspection and post market studies.

Johnson, J. A., *FDA Regulation of Medical Devices*, 2016

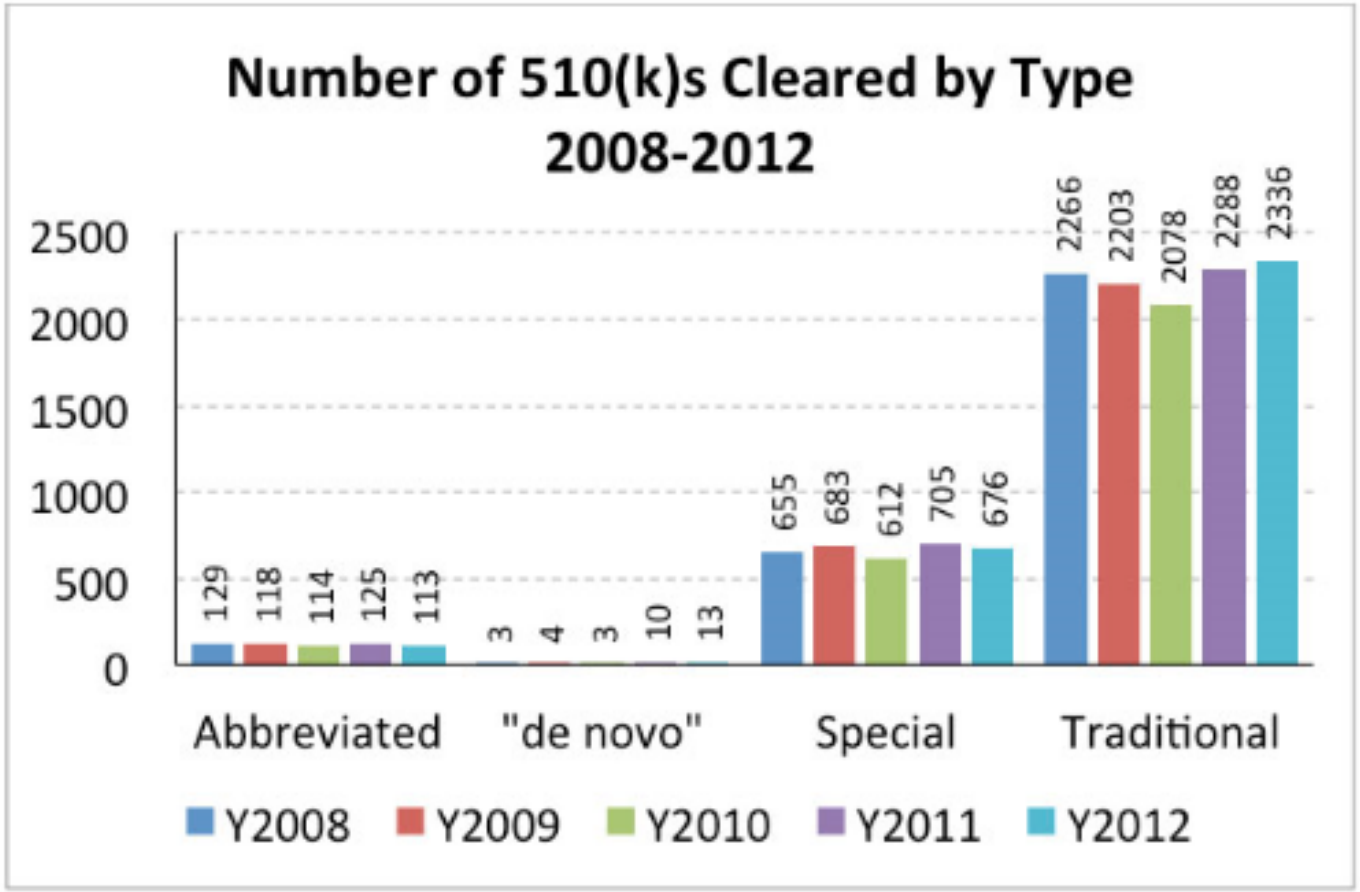
- Abbreviated 510(k)
  - Uses guidance documents developed by FDA to communicate regulatory and scientific expectations to industry.
  - FDA can either develop performance or consensus standards or 'recognize' those developed by outside parties.
  - The manufacturer describes what guidance document, special control, or performance standard was used, and how it was used to assess performance of their device.
  - Requires a product description, representative labeling, and a summary of the performance characteristics.

Johnson, J. A., *FDA Regulation of Medical Devices*, 2016

- Special 510(k)
  - Used for a modification to a device that has already been cleared under the 510(k) process.
  - Typically uses the design control requirement of the Quality System (QS) regulation.
    - The QS regulation describes the good manufacturing practice (GMP) requirements for medical devices.

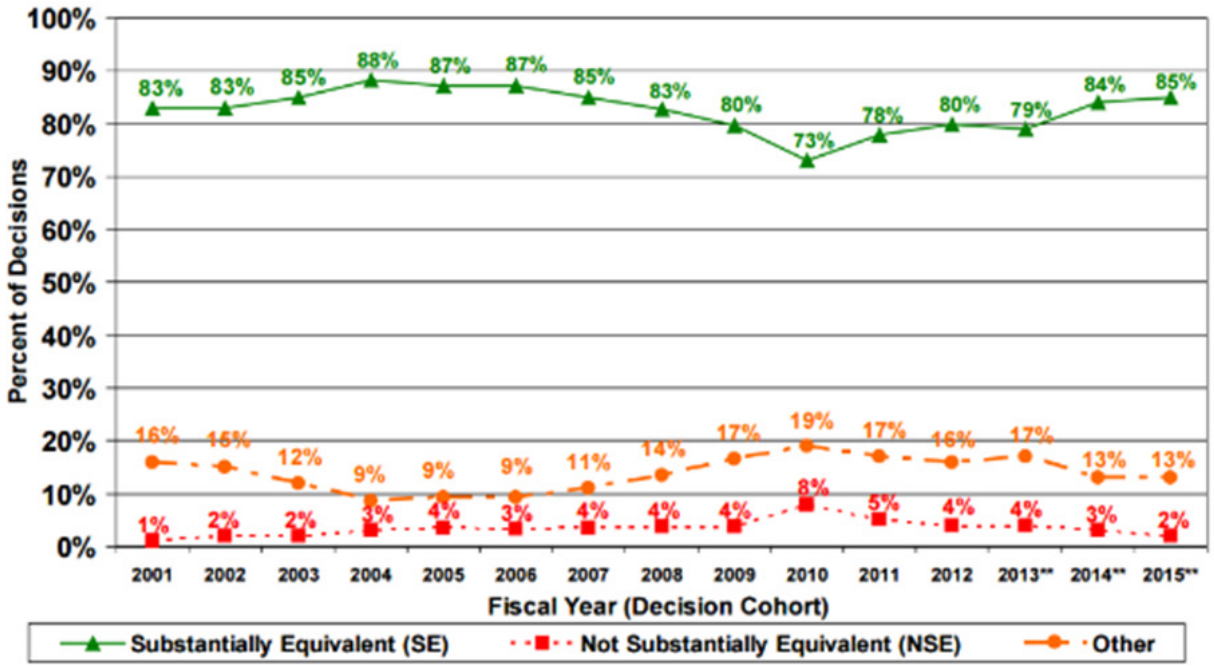
- De NOVO 510(k)
  - Under the FFDCA, novel devices lacking a legally marketed predicate are automatically designated Class III.
  - FDAMA amended FFDCA Section 513(f) to allow FDA to establish a new, expedited mechanism for reclassifying these devices based on risk, thus reducing the regulatory burden on manufacturers.
  - The de novo 510(k), though requiring more data than a traditional 510(k), often requires less information than a premarket approval (PMA) application.

Johnson, J. A., *FDA Regulation of Medical Devices*, 2016



Medical Device and Diagnostic Industry Qmed, 510(k) Statistical Patterns, December 2012.

Percent of 510(k)s Determined to be Substantially Equivalent (SE)*



*Percentages may not add to 100% due to rounding

**Excludes final decisions made on FY 2013 - FY 2015 receipts that were not accepted for review as of 09/30/2015

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Brennam , Z. FDA Sees Record-High PMA Approval Rate for 2015, Regulatory Affairs Professional Society, November 2015.

Comparison PMA and 510(k) Process

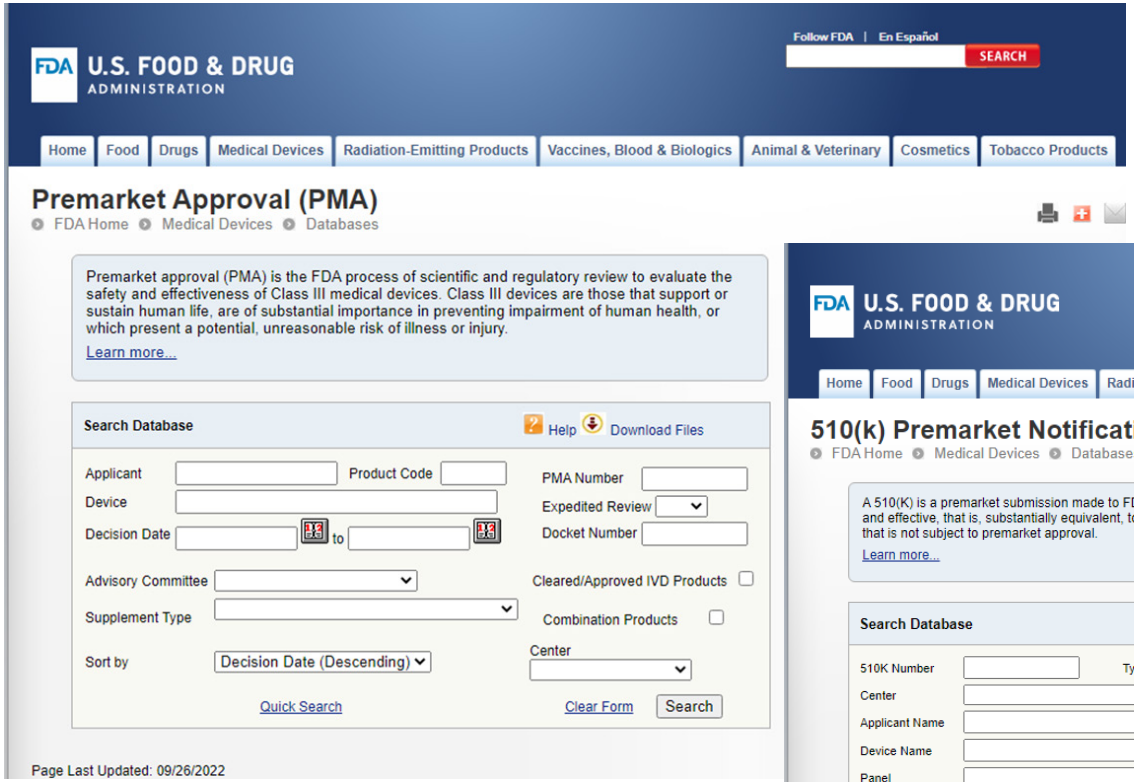
Table 5.4 Comparison of the PMA and 510(k) processes

Characteristic	PMA submission	510(k) submission
Time to collect data	Several years	Several months
Submission size	Several thousand pages	Much less
Manufacturing details	Process, methods, details required	Typically not required
Pre-approval inspection of device manufacturing facility	Required	Not required
Clinical trial site review	Often required	Not required
Review time	1 year	90 days
Post-approval annual reports	Required	Not required
Submission availability through Freedom of information (FOI) Act	Not available	Available
Scientific advisory panels convened to assist FDA in review	Sometimes	Rarely

Mehta, Shreefal S. *Commercializing Successful Biomedical Technologies : Basic Principles for the Development of Drugs, Diagnostics, and Devices.* Cambridge ; New York: Cambridge ; New York : Cambridge University Press, 2008.

Medical Device User Fees ($)

Year	Review Path	Large Business (>100m Revenue)	Small Business
2016	510(k)	5,228	2,614
	513g	3,529	1,765
	PMA	261,388	65,347
2017	510(k)	4,690	2,345
	513g	3,166	1,583
	PMA	234,495	58,624
2018	510(k)	10,566	2,642
	513g	4,195	2,098
	PMA	310,764	77,691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Premarket Approval (PMA)
FDA Home Medical Devices Databases
Premarket approval (PMA) is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. Class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury.
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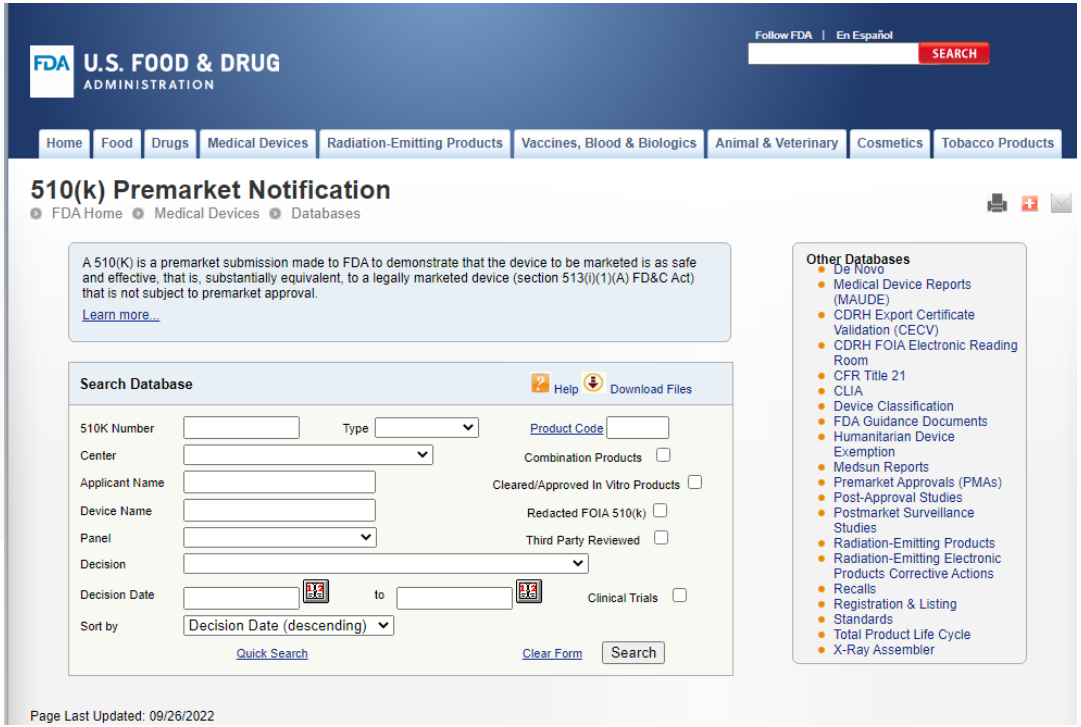
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A 510(K) is a premarket submission made to FDA to demonstrate that the device to be marketed is as safe and effective, that is, substantially equivalent, to a legally marketed device (section 513(i)(1)(A) FD&C Act) that is not subject to premarket approval.
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De Novo
Medical Device Reports (MAUDE)
CDRH Export Certificate Validation (CECV)
CDRH FOIA Electronic Reading Room
CFR Title 21
CLIA
Device Classification
FDA Guidance Documents
Humanitarian Device Exemption
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Postmarket Surveillance Studies
Radiation-Emitting Products
Radiation-Emitting Electronic Products Corrective Actions
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Standards
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Summary – Authorization Pathways