Introduction of Medical Device Development

What Are Medical Devices and Regulations for Them?

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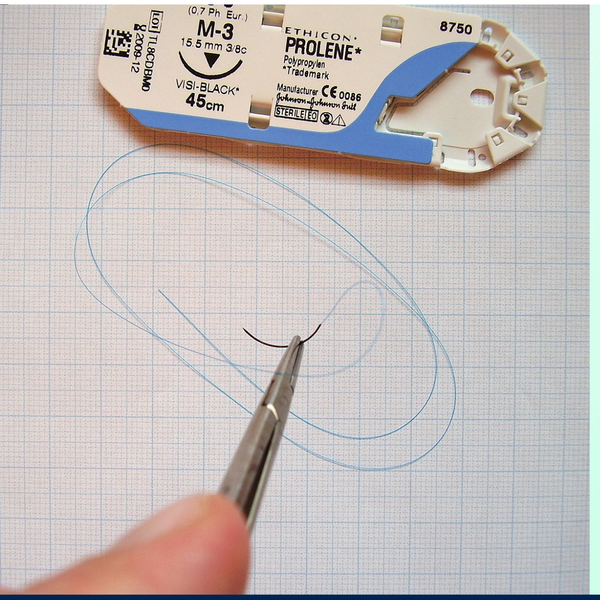
What Are Medical Devices?

Medical device is one of the broadest categories that include most of the items you can find in hospitals/clinics such as

- Sutures
- Catheters
- Dressings
- Implantable devices (pacemaker, stent, orthopedic implants, vascular grafts, etc)




What Are Medical Devices?

Exact definition of medical devices is dependent upon regulation as some medical device-like products can be in other regulatory categories (cosmetics, biologics, combination products).

FDA U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation & Research (CDER) - *Drugs*

Center for Biologics Evaluation & Research (CBER) - *Biologics*

Center for Devices & Radiological Health (CDRH) - *Devices*

Center for Food Safety & Applied Nutrition (CFSAN) - *Cosmetics*

Definition of Medical Devices

For US FDA, Section 201(h) of Federal Food, Drug, and Cosmetic Act (FD&C Act)

- Instrument, apparatus, machine, implant, in vitro reagent, including component, part, or accessory
- Diagnoses, cures, mitigates, treats, or prevents disease or condition
- Affects structure or function of body (key differentiating factor from cosmetics)
- Doesn't achieve purpose as a drug (key differentiating factor from drugs)
- Excludes certain software functions (data storage, administrative support, electronic patient records)

Combination Products - Device, Drug, Biologics?

Combination Products **involves at least *two* regulatory component types:**

Device + Drug + Biologics

Examples:

- Drug-eluting cardiovascular stent (drug + device)
- Fibrin-based hemostatic agent (biologics + device)

Regulatory responsibilities from involved component types. One Center usually takes the lead and the Office of Combination Products facilitates jurisdiction

- Drug-dominant combination products -> CDER leads
- Device-dominant combination products -> CDRH leads
- Biologics-dominant combination products -> CBER leads

www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm148279.htm

Medical Device Regulations (US FDA)

21 Code of Federal Regulations (CFR): Parts 800-1050

- 800-861: Cross-cutting device requirements
  - Example: 812 - Investigational Device Exemption (IDE)
  - Example: 820 - Quality System Regulation
- 862-1050: Device-specific requirements
  - Example: 876 - Gastroenterology and Urology Devices

21 CFR: Parts 1-99

- General medical requirements that also apply to medical devices

***Regulatory compliance* is one of the most critical components of medical device development in all stages**

Device Guidance Documents

For some medical devices, FDA provides Device Guidance Documents to aid the development

- Non-binding (following the guidance does not guarantee regulatory clearance or rejection)
- Elaborating on applicable laws & regulations
- Types of Device Guidance Documents:
  - Drafts: Agency's proposed thinking; public comment period
  - Final: Agency's thinking; may incorporate public comment gathered for Drafts
- Example Device Guidance Documents:
  - Recommendations for the Use of Clinical Data in Premarket Notification [510(k)] Submissions
  - Soft (Hydrophilic) Daily Wear Contact Lenses - Performance Criteria for Safety and Performance Based Pathway
  - Implanted Brain-Computer Interface (BCI) Devices for Patients with Paralysis or Amputation - Non-clinical Testing and Clinical Considerations

www.fda.gov/RegulatoryInformation/Guidances/default.htm

Device Classification

Medical devices are further classified into three categories that affects the applying regulatory requirements and development process significantly:

- Based on device description & intended use
- Determines extent of regulatory control
- Class I, II, or III (I is the lowest risk; III is the highest risk to patients)
- Product Codes: Three-letter coding to group similar devices and intended use (for example, FRO)

Class	Risk	Controls	Submission	Example
I	Lowest	General	Exempt* 510(k)	Surgical gauze
II	Moderate	General & Special	510(k)* Exempt	Catheter
III	Highest	General & PMA	PMA	Pacemaker

*More common submission requirement for this Class

Regulatory Controls for Medical Devices

- Requirements that apply to a product area (Product Code)
- Provide consistent requirements to foster predictable safe & effective medical devices
- With appropriate level of regulatory burden/oversight
- Generally broad but may be specific depending on product type/indication

Control	Regulation (21 CFR Part)	Brief Description
Labeling	801	Provide information for users
Medical Device Reporting	803	Report device-related injuries and deaths
Establishment Registration	807	Register business with FDA
Device Listing	807	Identify devices
Quality System	820	Ensure safe, effective finished devices
Adulteration	FD&C Act 501	Provide device not proper for use
Misbranding	FD&C Act 502	Provide false or misleading labeling

Special Controls?

- Specific for Class II medical devices
- Not common and only available for a limited number of Class II devices
- Usually for historically well-established device types
- Found in "(b) *Classifications*" of the regulation (such as 21 CFR 876.5860(b))
- Types of Special Controls:
  - Design, Characterizations or Specifications
  - Testing
  - Special Labeling
  - Guidance Documents
- Example Special Controls:
  - Tissue Adhesive for the Topical Approximation of Skin - Class II Special Controls Guidance for Industry and FDA Staff
  - Surgical Sutures - Class II Special Controls Guidance Document for Industry and FDA Staff
  - Dental Amalgam, Mercury, and Amalgam Alloy - Class II Special Controls Guidance for Industry and FDA Staff

Bringing New Medical Devices to Market

Medical device development can be largely divided into three stages:

Performers
Academia, industry

Milestones
Basic science establishment
Technology development
IP generation

Regulatory Requirements
Low

Performers
Mostly industry

Milestones
Productization
Regulatory clearance
Commercial launch

Regulatory Requirements
High/Mandatory

Performers
Industry

Milestones
Regulatory compliance
Commercial distribution
Revenue/profit generation

Regulatory Requirements
High/Mandatory

New Device to Market: R&D Stage

1. Product Establishment

- ☑ Establish product (medical device) description
- ☑ Identify purpose of the device
  - Intended use (more broad)
  - Indication for use (more specific)
  - Duration of use
  - Target patient population (age; disease; health condition)

2. Technology Development

- ☑ Establish the scientific basis of the product (more like academic research)
- ☑ Establish the commercial basis of the product
  - Patent filing
  - IP ownership/licensing

3. Verify that Product is Medical Device (not drug, biologics, or cosmetics)

New Device to Market: Pre-Market Stage

4. Identify Classification and Regulatory Pathway

- ☑ Identify regulatory classification (Class I, II, or III)
- ☑ Classification will generally indicate regulatory pathway (premarket submission type) required for device

5. Develop Regulatory-Complying Valid Scientific Evidence

- ☑ 21 CFR 860.7(c)(1) - Requires valid scientific evidence for safety and effectiveness
- ☑ 21 CFR 860.7(c)(2) - Provides definition of valid scientific evidence

6. Prepare Premarket Submission

- ☑ Each type has its own sets of (1) processes, (2) applicable laws & regulations, (3) review times, and (4) evidence burdens required:
  - Investigational Device Exemption (IDE)
  - Premarket Notifications (510(k))
  - Premarket Approval Application (PMA)
  - De Novo
  - Humanitarian Device Exemption (HDE)

New Device to Market: Post-Market Stage

7. FDA Clearance by Getting Approval for the Premarket Submission

8. Commercial Launch

- ☑ Some Class I or II devices are exempt from premarket submission and can be commercially launched without it.

9. Post-Market Activities

- ☑ Various activities are required by regulation once the product is on the market including (1) tracking systems, (2) reporting of device malfunctions, (3) serious injuries or deaths, and (4) registering the establishments where devices are produced or distributed.
- ☑ Violations or issues identified during the post-market activities can lead to Recalls & Alerts:
  - Recalls
  - Safety Communications
  - Medical Device Reporting (MDR)

Investigational Device Exemption (IDE)

- Required to perform clinical research (clinical trials) on investigational devices.
- Required for majority of Class III devices and some of Class II or I devices.
- Usually based on bench top and pre-clinical scientific evidence.
- Collect safety and effectiveness data for future marketing applications.
- Require approval by the Institutional Review Board (IRB).
- Protect human patients.

Premarket Notification - 510(k)

- 510(k) is for low and moderate-risk devices (Class I and II).
- Requires "**Substantial Equivalence**" between a new device and a legally marketed device (predicates).
- Substantial equivalence compares
  - Intended use
  - Device features
  - Performance testing
- Identification of appropriate predicate device(s) is critical for 510(k) submission. There can be more than one predicate device.

Premarket Approval Application (PMA)

- PMA is for the highest-risk devices.
- Requires reasonable assurance of safety and effectiveness including scientific evidence from human clinical trials.
- Due to the need for human clinical trials, typically prepared after getting IDE.
- Scientific evidence for PMA should stand on its own, so therefore, there are no predicate devices for equivalence.
- Most extensive, lengthy, and expensive type of pre-market submission for medical devices.

De Novo

- Latin word for ‘From the Beginning’.
- De Novo is for devices that have no existing classification regulation.
- Marketing process for **novel** devices.
- Create new classification regulations.
- Alternative to PMA.
- Reduced regulatory burden/controls based on the risk-benefit profile of the device.
- Human clinical trials may or may not be required.

Humanitarian Device Exemption (HDE)

- Premarket submission for Humanitarian Use Devices.
- No more than 8,000 individuals per year in the United States to be qualified for HDE.
- Exempt from effectiveness scientific evidence requirements.
- Reasonable assurance of safety and probable benefits are still required.
- Due to the limited volume of use, typically not pursued for commercial purposes (humanitarian purposes).

Clinical Trials for Medical Devices vs Drugs

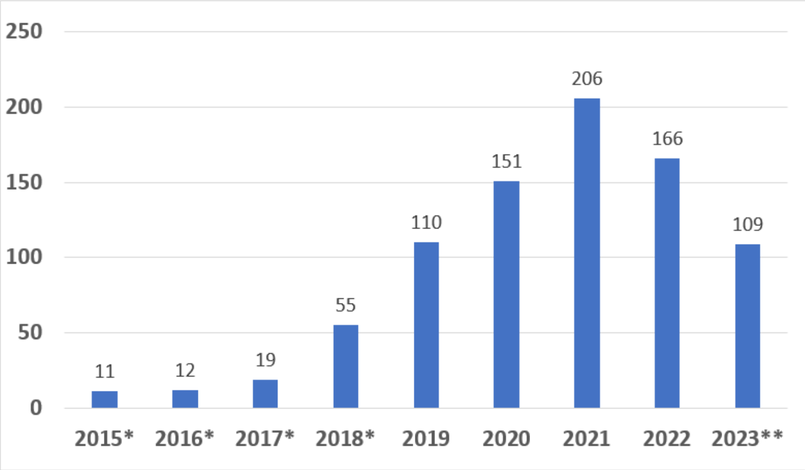
Medical devices may require human clinical trials for premarket submission like drugs. However, there are key differences in clinical trials for medical devices vs drugs:

- Unlike clinical trials for drugs, medical device only has one phase of clinical trial (pivotal) rather than Phase I, II, III, and IV.
- A simpler clinical trial requirement is one of the most critical reasons why medical device development is often much faster and/or cheaper than drug development.
- However, there are some exceptions where medical device development takes as long & expensive as drug development due to the inherent complexity of devices and nature of use:
  - Surgical robots ($100s million for 10+ years)
  - Combination products (drug/biologics + device)

Breakthrough Devices Program

Breakthrough Devices Program is a voluntary program for certain medical devices and device-led combination products that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions.

- Provides more support and potentially faster regulatory process once designated.
- Not very difficult to be granted but the actual benefits can vary.
- Popular when there were reimbursement benefits, but such privilege has been rescinded in 2021 (may change in the future).



Criteria	Description	Refer to Guidance
First Criterion	The device provides for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions	Section III.B.1
Second Criterion	The device also meets **at least one** of the following:	
	a. Represents Breakthrough Technology	Section III.B.2.a
	b. No Approved or Cleared Alternatives Exist	Section III.B.2.b
	c. Offers Significant Advantages over Existing Approved or Cleared Alternatives	Section III.B.2.c
	d. Device Availability is in the Best Interest of Patients	Section III.B.2.d

https://www.fda.gov/medical-devices/how-study-and-market-your-device/breakthrough-devices-program

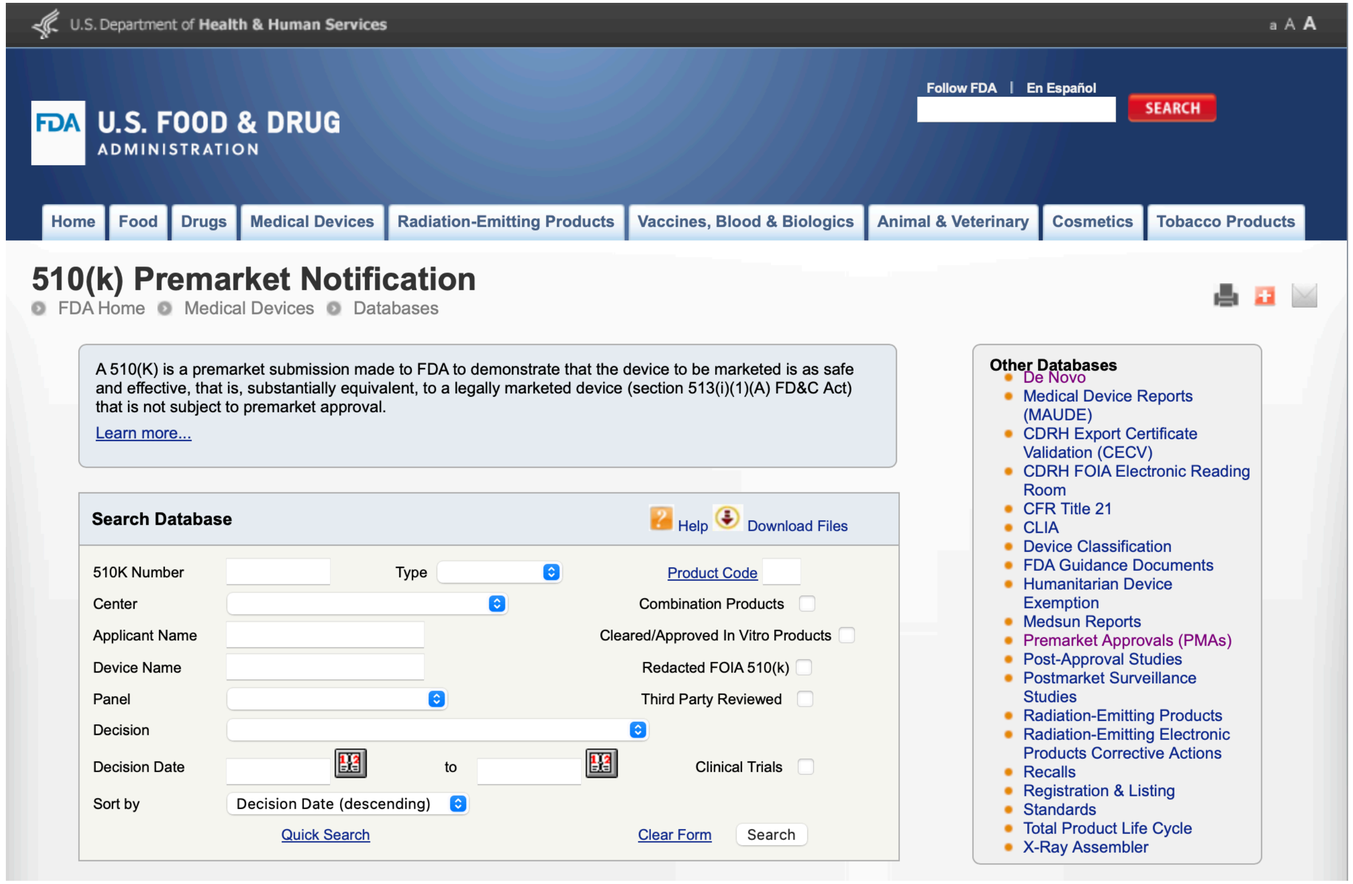
Other Regulatory Authorities than US FDA

Medical device regulations are specific to each jurisdiction/country. For example, medical devices marketed in Korea should follow KFDA (식약처) regulations; in Europe should obtain a CE Mark. There is no standard way to navigate, but several common considerations:

- US FDA regulations are typically considered as a golden standard.
- It is a lot easier/faster to get approval in other countries 'after' getting US FDA approval rather than the other way around.
- US is the biggest market for medical devices (40% of the global market), substantially bigger than any other country (for example, Korea accounts for less than 1% of the global market).
- Due to the above reasons, many companies (especially startups) aim to get US FDA approval first.
- However, there are significant level of regional division in medical device markets (for example, not all medical devices in US are available in Korea), making each case unique.

Other Resources: 510(k) Database

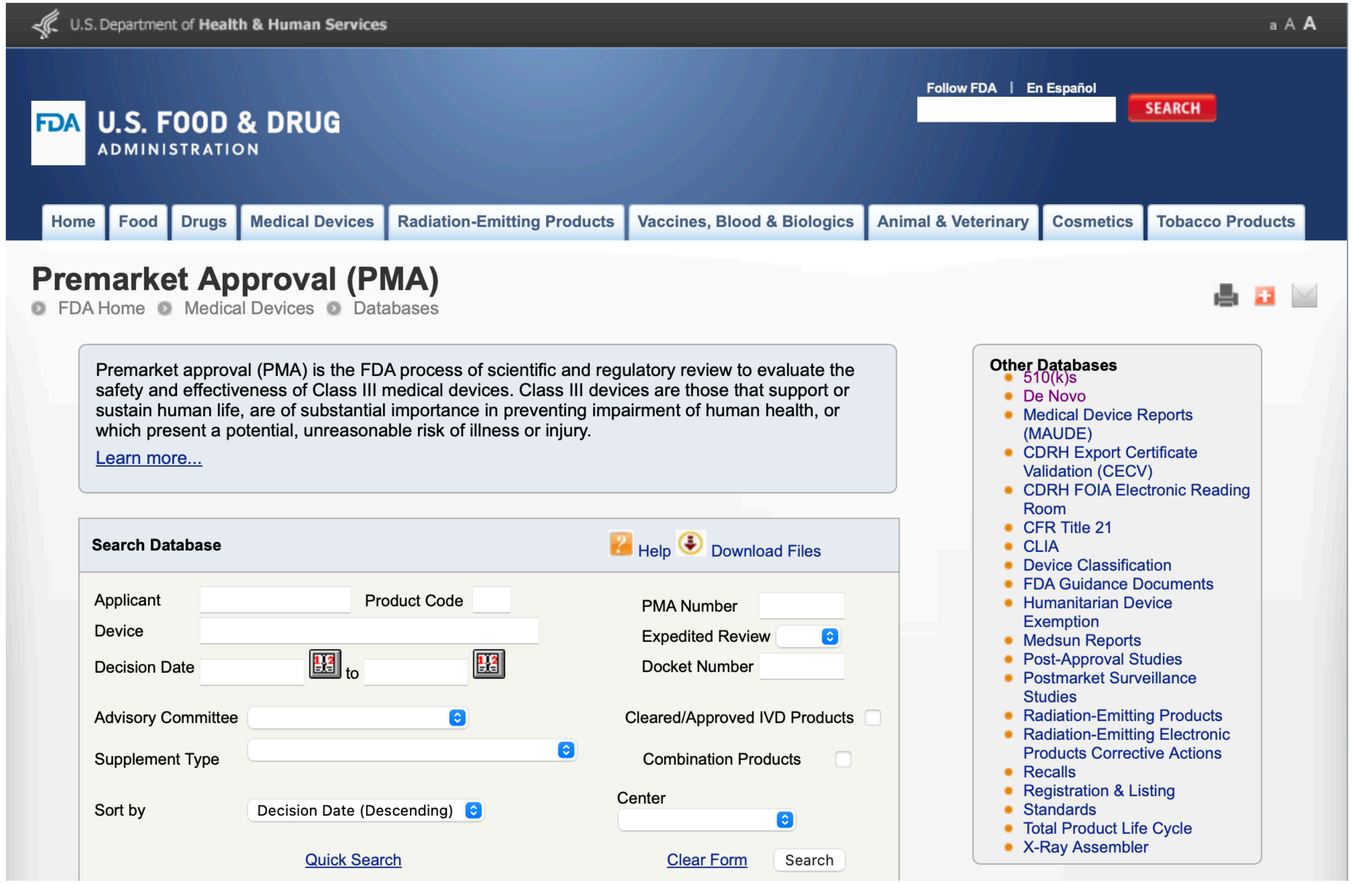
Previous 510(k) product's information and approval summary are publicly available in FDA's 510(k) Premarket Notification Database



https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm

Other Resources: PMA Database

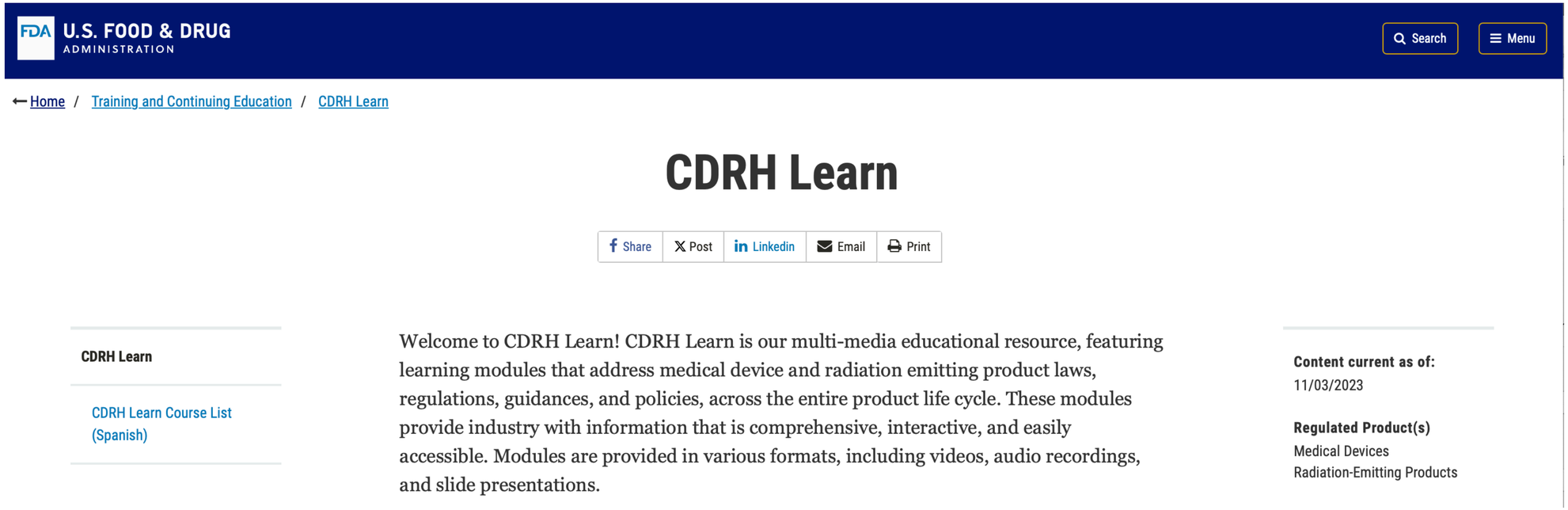
Previous PMA product's information and approval summary are publicly available in FDA's Premarket Approvals (PMA) Database



https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm

Other Resources: CDRH Learn

FDA CDRH provides various training modules on various topics on medical device regulations for self-learning online courses.



https://www.fda.gov/training-and-continuing-education/cdrh-learn

Questions?