Development and Regulation of Medical Devices

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OHSRP Education Series
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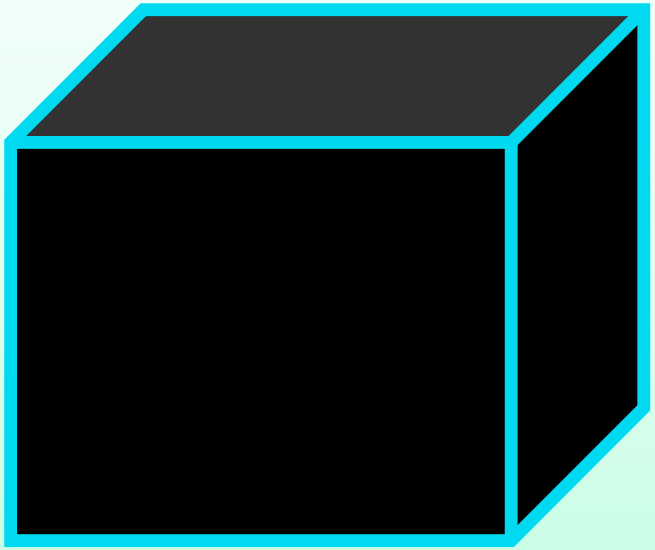
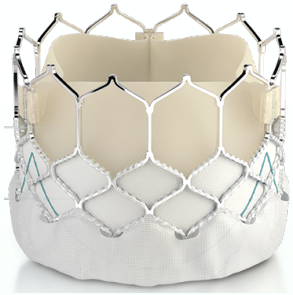
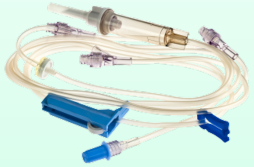


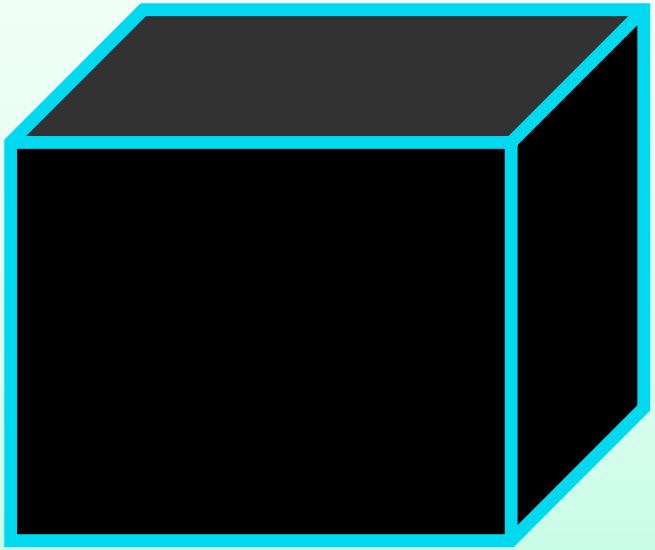
Stryker Patient Care



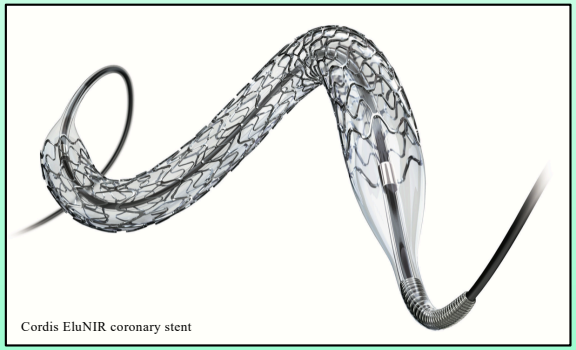
Edwards SAPIEN 3



Baxter



Canon Medical Systems



Cordis EluNIR coronary stent

Pew Charitable Trusts

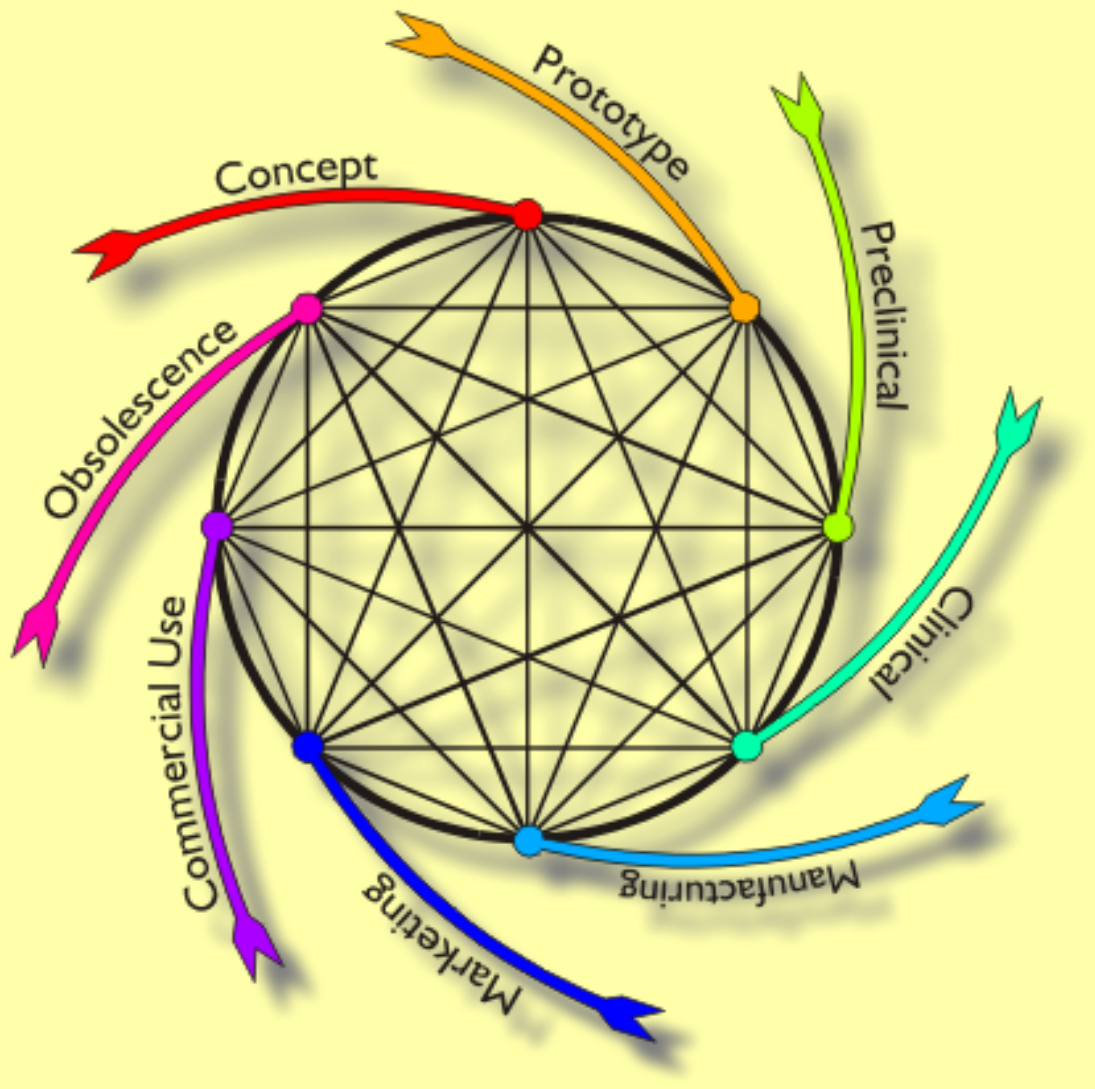
Safe Therapeutic Products

- Drugs
  - Pure molecules
  - Toxicology
  - Short half-life
  - Long market life
  - Drug interactions
  - Wrong Drug/Dose
  - Large clinical studies
  - Good Manufacturing Practices
- Devices
  - Complex components
  - Biocompatibility
  - Durable Equipment
  - Rapid product cycles
  - Malfunction
  - User Error
  - Bench/animal studies
  - Small to moderate size clinical studies
  - Quality Systems (ISO 9001)

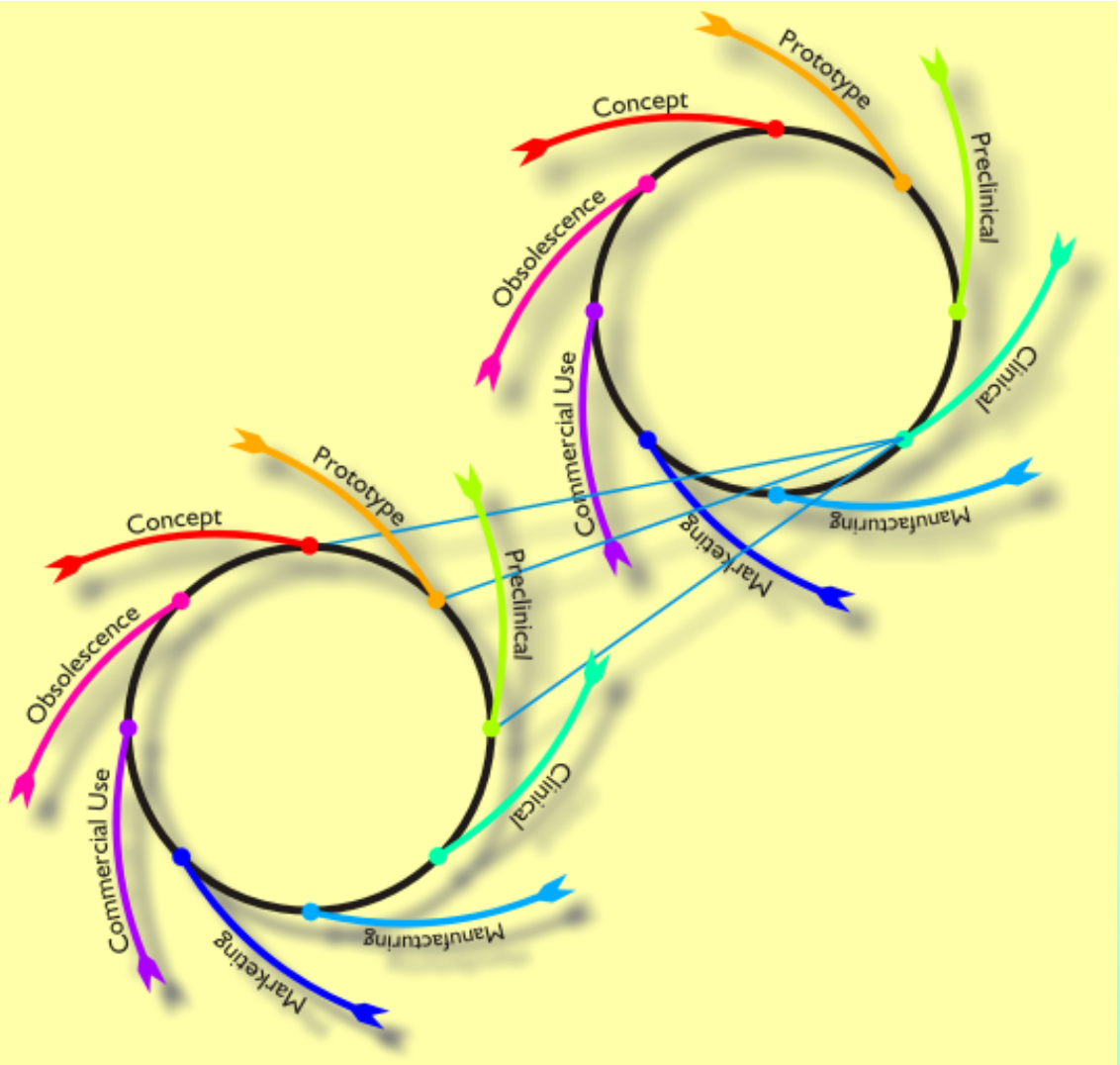
Outline

- Device development process
- Devices, drugs and combination products
- Safety, effectiveness and pathways to market
- Investigational Device Exemption (IDE) regulations
  - Application of the regulations
  - Exemption
  - Significant Risk vs Non-Significant Risk studies
  - Approval process for clinical research
  - Interacting with the FDA
- In Vitro Diagnostic devices (Jonathan Green)

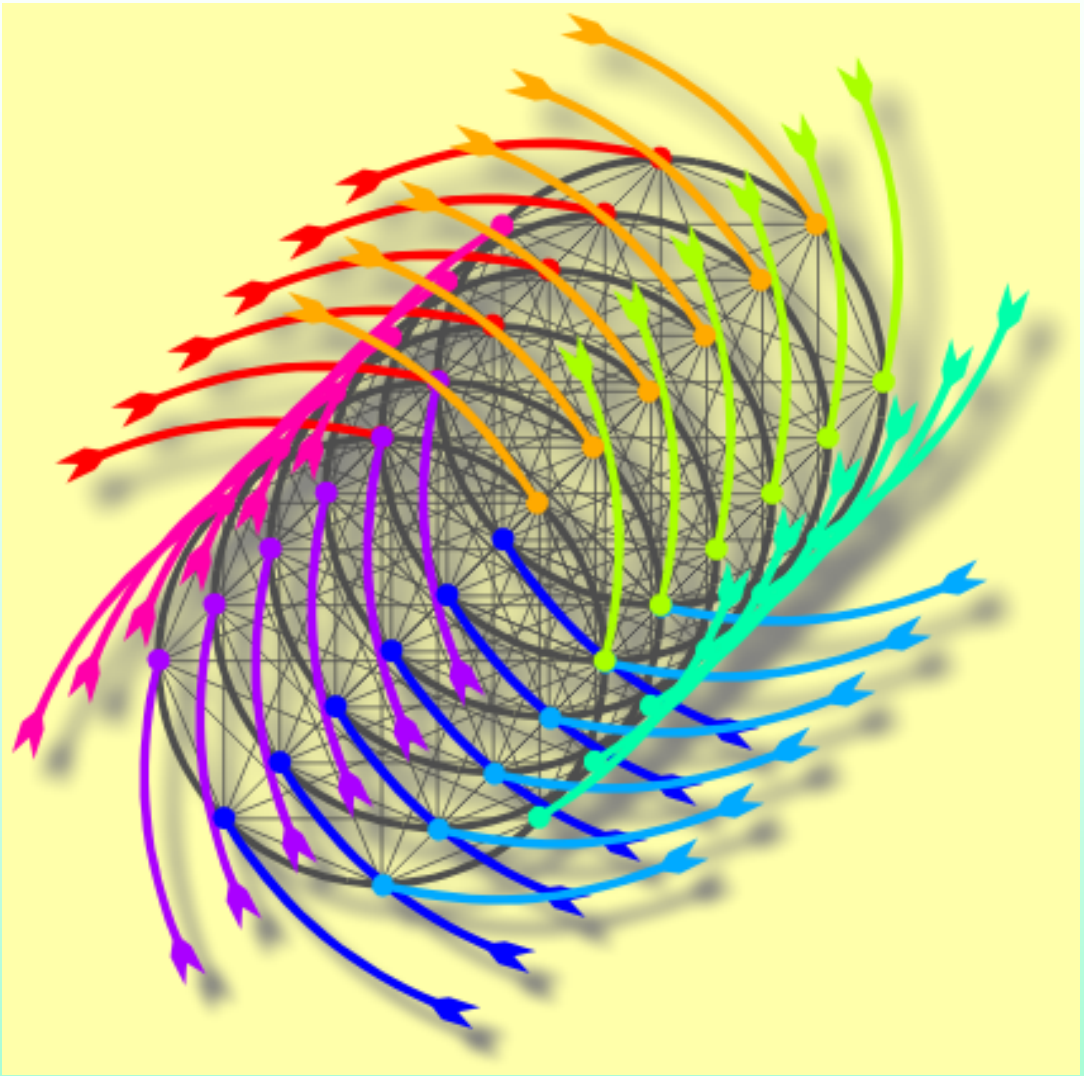
Total Product Life Cycle



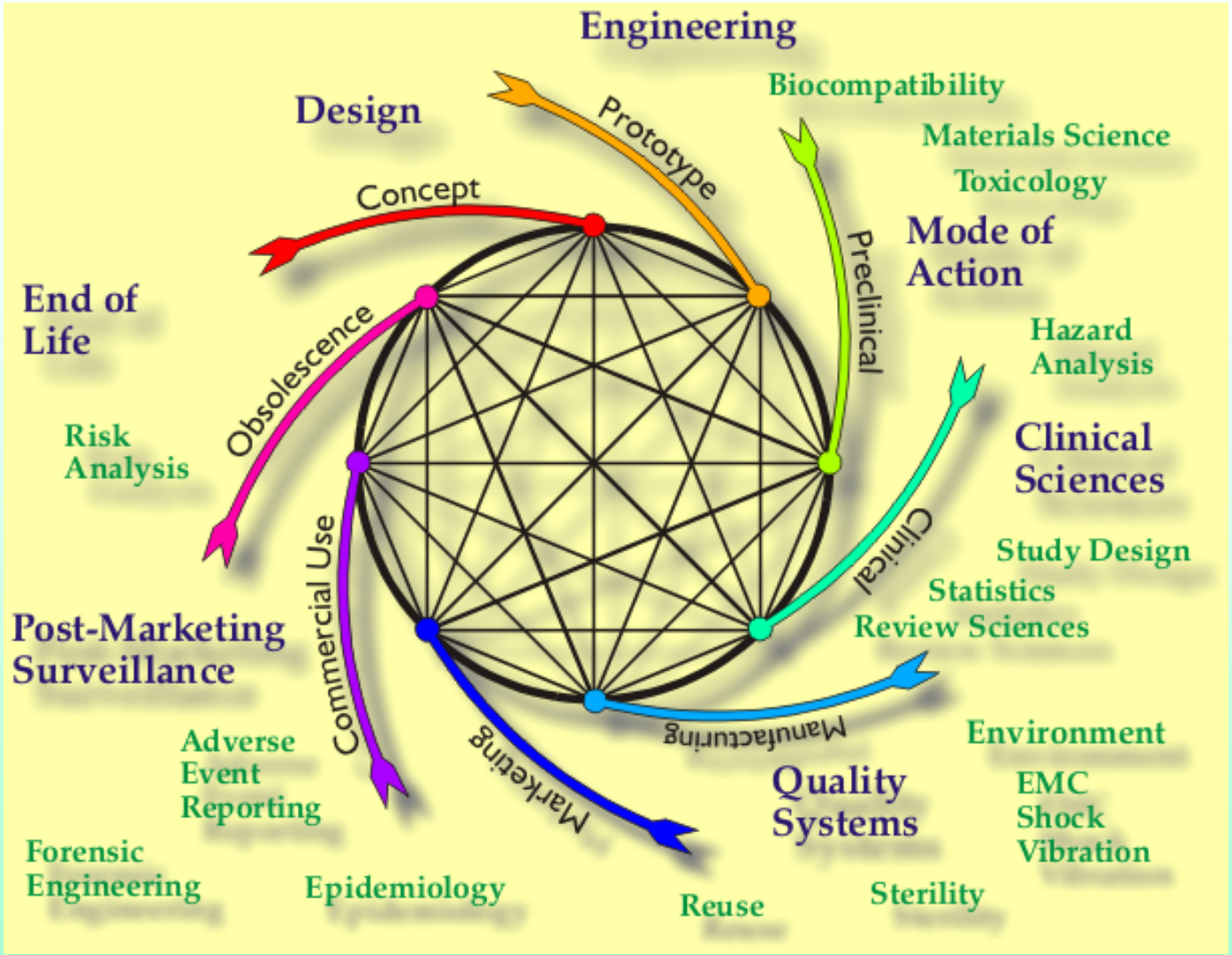
Cross-generations



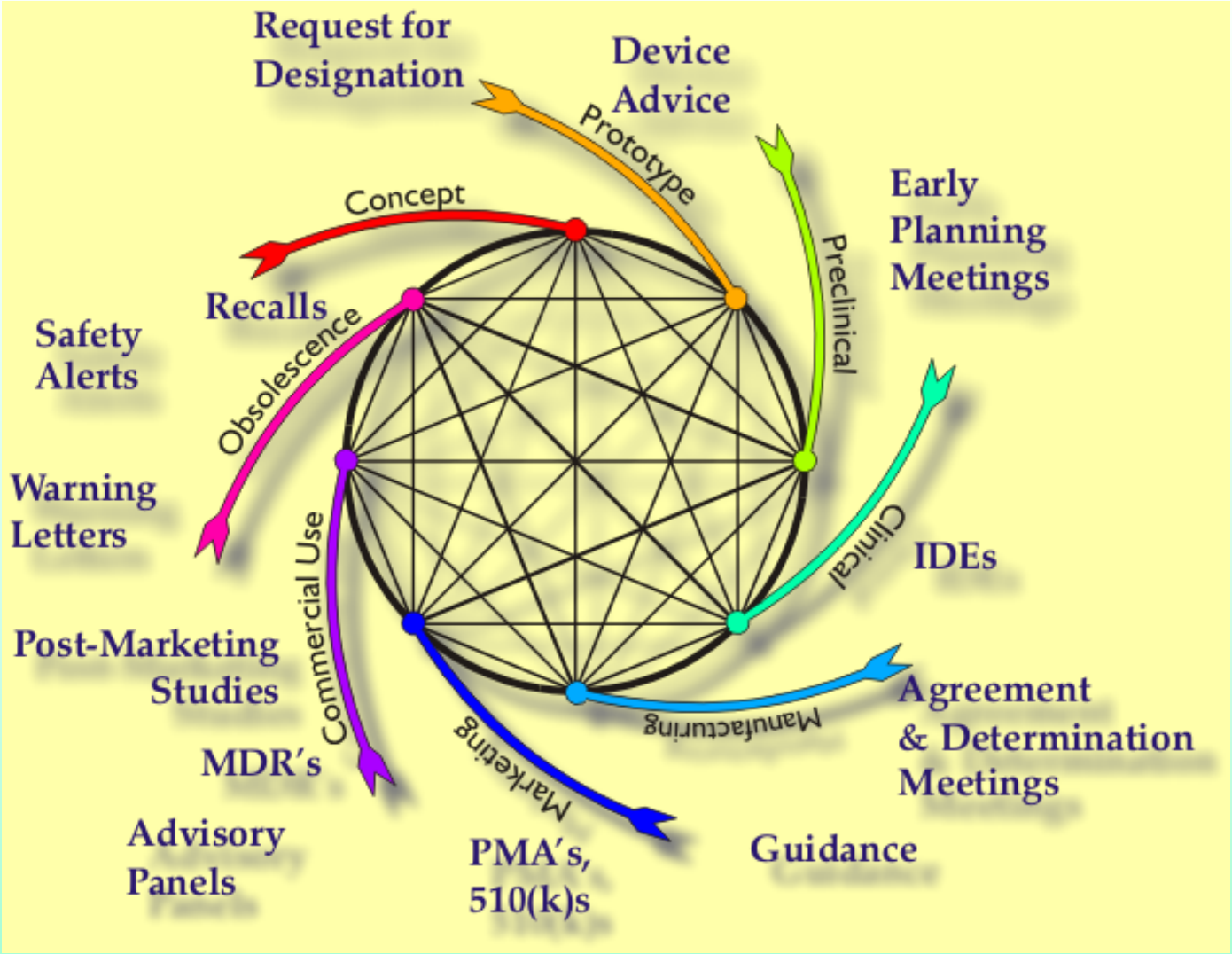
The Pipeline



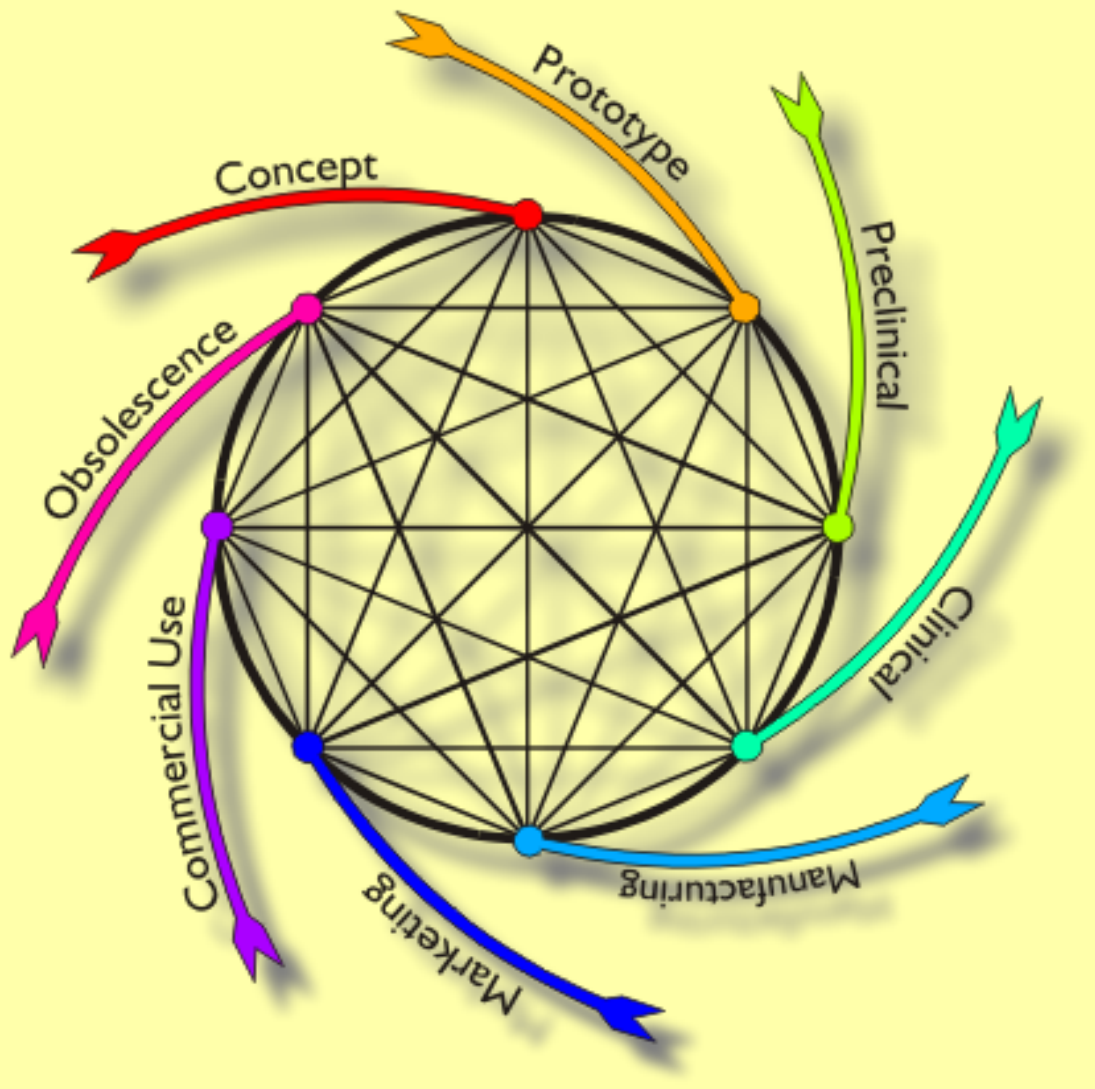
Science Cycle



Regulatory Cycle



Total Product Life Cycle



Device…

"means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar article, including any component, part, or accessory, which is

(1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,

(2) 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

(3) 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 its primary intended purposes"

Device…

- Classification as a device
  - Classified: FDA database
  - New device, unclassified

Product Classification

FDA Home › Medical Devices › Databases

This database includes:

- a list of all medical devices with their associated classifications, product codes, FDA Premarket Review organizations, and other regulatory information.

learn more...

Search Database

Help Download Files

Device: magnetic resonance

Product Code:

Review Panel:

Regulation Number:

Submission Type:

Third Party Elligible:

Implanted Device:

Life-Sustain/Support Device:

Device Class:

Summary Malfunction Reporting:

Go to Quick Search

Clear Form

search

Product Classification

FDA Home › Medical Devices › Databases

1 to 4 of 4 results
magnetic resonance

Results per page 5

New Search Export to Excel Help

Product Code	Device		Regulation Number	Device Class
MOS	Coil, Magnetic Resonance, Specialty	Magnetic Resonance Diagnostic Device	892.1000	2
LNH	System, Nuclear Magnetic Resonance Imaging	Magnetic Resonance Diagnostic Device	892.1000	2
LNI	System, Nuclear Magnetic Resonance Spectroscopic	Magnetic Resonance Diagnostic Device	892.1000	2
OUO	Tomographic Imager Combining Emission Computed Tom ...	Emission Computed Tomography System	892.1200	2

[Code of Federal Regulations]
[Title 21, Volume 8]
[Revised as of April 1, 2019]
[CITE: 21CFR892.1000]

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

PART 892 -- RADIOLOGY DEVICES

Subpart B--Diagnostic Devices

Sec. 892.1000 Magnetic resonance diagnostic device.

(a) *Identification.* A magnetic resonance diagnostic device is intended for general diagnostic use to present images which reflect the spatial distribution and/or magnetic resonance spectra which reflect frequency and distribution of nuclei exhibiting nuclear magnetic resonance. Other physical parameters derived from the images and/or spectra may also be produced. The device includes hydrogen-1 (proton) imaging, sodium-23 imaging, hydrogen-1 spectroscopy, phosphorus-31 spectroscopy, and chemical shift imaging (preserving simultaneous frequency and spatial information).

(b) *Classification.* Class II.

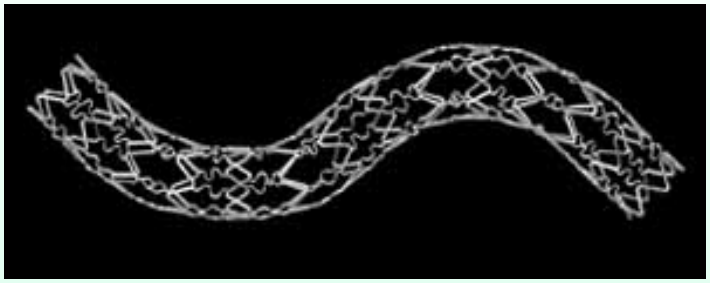
[53 FR 5078, Feb. 1, 1989]

Devices

- "Device" refers to
  - the physical device, and
  - its indication for use
- Example: Biliary stents
  - Indication for use: treatment of biliary strictures
  - Use for peripheral arterial disease represents a new device (same physical item, new indication for use)

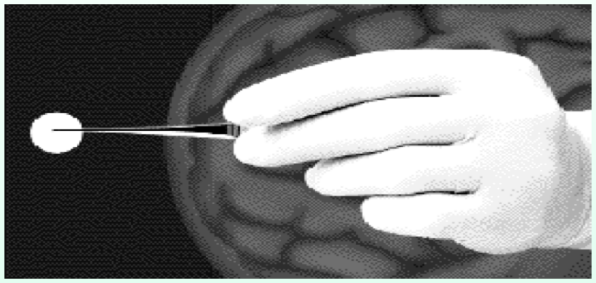
Combination Product Jurisdiction

Drug Eluting Stent



- Primary Mode of Action:
  - Stent opens artery
- Secondary Actions
  - Drug prevents inflammation and restenosis of artery
- Regulated as a Device (PMA)

Drug Eluting Disk



- Primary Mode of Action:
  - Cancer chemotherapy for brain tumor
- Secondary Actions
  - Device for local drug delivery
- Regulated as a Drug (NDA)

Safe and Effective

- FD&C Act grants explicit authority to ensure that devices are safe and effective before marketed rather than limited to reacting to hazardous devices after marketing

Safety

- ...that the probable benefits to health...for its intended use...when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks
- absence of unreasonable risk of illness or injury
- May require
  - in vitro studies
  - in vivo studies
  - clinical investigations

Effectiveness

- ...that in a significant portion of the target population, the use of the device for its intended uses and conditions of use...will provide clinically significant results
- shown principally through well-controlled investigations

Device Classification

- Medical devices vary widely in complexity and potential risk
- Classification determined on the basis of the nature of the device and the extent of FDA control to ensure safety and effectiveness
- Class I, II, and III in order of increasing risk

Class I: General Controls

- General Controls
  - Prohibit adulterated or misbranded devices
  - Good Manufacturing Practices
  - Registration by manufacturers
- Lead shields, operating room tables
- Most Class I devices are exempted from submission of a 510(k) prior to marketing

Class II: General and Special Controls

- General Controls as for Class I
- Special Controls-established by regulation
  - Performance standards, patient registries, post-market surveillance
  - Guidance documents outlining specific nonclinical and, potentially, clinical studies
- Substantial equivalence to a predicate device(s)
- 510(k) submission required for most, although not all, Class II devices
- Imaging systems (CT, US, MR), IVC filters

Class III: General Controls and Premarket Approval

- General and special controls cannot provide reasonable assurance of safety and effectiveness
- Typical characteristics
  - Implants
  - Support or sustain human life
  - Present a potentially unreasonable risk of illness or injury
- Ventricular assist devices, heart valves
- Require an approved premarket approval (PMA) application before commercial distribution

Approval for marketing: PMA Application

- Required of all new Class III devices
- PMA application: demonstrate safety and effectiveness through:
  - Design validation
  - Manufacturing control
  - Performance testing
  - Animal studies
  - Clinical trials

Humanitarian Device Exemption

- Humanitarian Use Device:
  - for treatment of a disease/condition that affects or manifests in not more than 8,000 individuals/yr in the US
- HDE Application
  - Similar in form and content to a PMA application
  - Demonstrate safety and probable benefit
  - Clinical investigations demonstrating effectiveness not required
- Restrictions: Use in facilities under IRB supervision
- Example: Therasphere (unresectable HCC)

Practice of Medicine

- FDA is prohibited by law from regulating practice of medicine
- Use of legally marketed device for “off-label” indication as part of practice of medicine for an individual patient
  - May require local IRB approval
  - Approved IDE not required
- Clinical investigation (even one patient) must be conducted in accordance with the IDE regulation

Unapproved/Uncleared Devices

- An unapproved/uncleared medical device may only be used on human subjects when the device is under clinical investigation and when used by investigators participating in a clinical trial.
- Must comply with all applicable requirements

Testing Strategy (simplified)

Intended use of the medical device including target population: identify appropriate tests

- Identify potential **safety** and effectiveness issues through an analysis of the potential **failure modes**
- Identify design specifications: characteristics of the device needed to maximize performance and minimize the potential problems, under the expected conditions of use
- Identify the tests that will demonstrate if the design requirements are met

Investigational Device Exemptions (IDE)

Decision tree

Questions, in order:

- Is it a device?
  - Legally marketed/in commercial distribution
  - Indications for use
  - Class I, II, III is irrelevant
- Applicability of IDE regulations?
- Is the study exempt?
- If not exempt and therefore subject to the IDE regulations, is the study (not the device) SR or NSR?

IDE: Purpose

- Discovery and development of new devices requires exemption from the requirements that apply to devices in commercial distribution
- IDE regulation:
  - Encourages discovery and development of devices consistent with protection of public health and safety and with ethical standards

IDE: Investigation

- Conduct of a clinical investigation of a medical device requires approval under the IDE regulation
- Investigation: a clinical investigation or research, which involves one or more subjects, to determine the safety or effectiveness of a device

IDE: Investigation

- Sponsor-investigator studies of unapproved devices or new intended use of approved device (even if no marketing application planned) are subject to the regulation

Exemptions

- An investigation is exempt from the IDE regulation if the device is used or investigated in accordance with the indications in the approved labeling
  - Comparative study of two stents approved for treatment of coronary artery stenosis

    vs.
  - Study of an approved coronary stent for treatment of intracranial arterial stenosis in the setting of acute stroke

Significant Risk (SR)/Non-Significant Risk (NSR) studies

- Significant risk study: one which "presents a potential for serious risk to the health, safety, or welfare of a subject."
- Risk includes risk of any ancillary procedures
- Degree of risk of STUDY, not the device, determines level of regulatory control

https://www.fda.gov/media/75459/download

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) studies

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Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors

Significant Risk and Nonsignificant Risk Medical Device Studies

Additional copies are available from:

Office of Good Clinical Practice
Office of Special Medical Programs, Office of the Commissioner
Food and Drug Administration
10903 New Hampshire Ave., WO32-5129
Silver Spring, MD 20993-5129
(Tel) (301)-796-8340
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf

or

Division of Small Manufacturers, International, and Consumer Assistance
Office of Communication, Education and Radiation Programs
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Ave., WO66-4521
Silver Spring, MD 20993
Tel: 1-800-638-2041 or 301-796-7100
dsmica@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health (CDRH)

January 2006

Protocol Review/Approval Process

- Sponsor: provides initial assessment of risk
- IRB: responsible for determination of SR/NSR
- Non-Significant Risk study: IRB approval
  - IRB acts as a surrogate for the FDA
- Significant Risk study in the US:
  - Both IRB approval and an approved or conditionally approved IDE application are required before the study may begin
- If FDA determines a study is SR, decision is binding

Required Elements of an IDE

- US sponsor (manufacturer or investigator)
- Report of prior investigations
- Investigational plan
- Manufacturing information
- Investigator and IRB information
- Sales information
- Labeling
- Informed consent

21 CFR 812

Basic Physiological Research

- Investigating a physiological principle
- Only using the device to address the research question
- Not evaluating the safety/effectiveness of the device

- No IDE needed; IRB approval and informed consent should be obtained

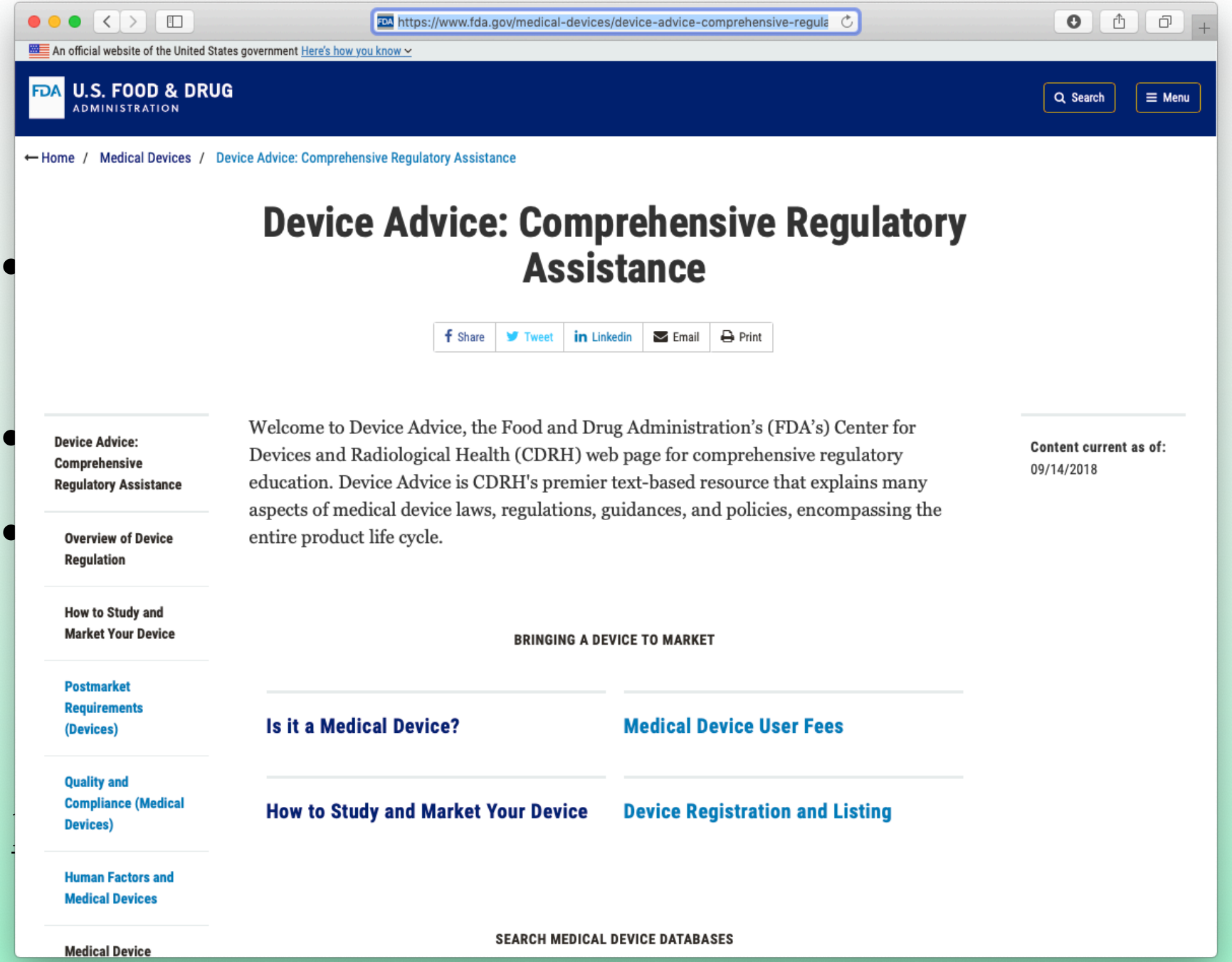
Basic Physiological Research

- NO FDA guidance
- NO defined regulation by the FDA
- Sometimes the use of device is intrinsic and central to the effect that is being investigated and may be inseparable from testing the safety and effectiveness of the device or delivered treatment procedures that are being investigated
- Recommended contacting FDA's IDE staff through Q-submission program

CDRH

- Device Advice: Comprehensive Regulatory Assistance
- How to Study and Market Your Device
- Device Advice: Investigational Device Exemption (IDE)

https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance


https://www.fda.gov/medical-devices/device-advice-comprehensive-regula
An official website of the United States government Here's how you know
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Menu
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Device Advice: Comprehensive Regulatory Assistance
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Email
Print
Device Advice: Comprehensive Regulatory Assistance
Overview of Device Regulation
How to Study and Market Your Device
Postmarket Requirements (Devices)
Quality and Compliance (Medical Devices)
Human Factors and Medical Devices
Medical Device
Welcome to Device Advice, the Food and Drug Administration's (FDA's) Center for Devices and Radiological Health (CDRH) web page for comprehensive regulatory education. Device Advice is CDRH's premier text-based resource that explains many aspects of medical device laws, regulations, guidances, and policies, encompassing the entire product life cycle.
Content current as of:
09/14/2018
BRINGING A DEVICE TO MARKET
Is it a Medical Device?
Medical Device User Fees
How to Study and Market Your Device
Device Registration and Listing
SEARCH MEDICAL DEVICE DATABASES

Pre-Submission Program (Q-subm.)

- Informal, confidential feedback
- Generally 60 day review (not statutory)
- Letter, phone, fax, email, meeting
- Not required; provides an opportunity for informal FDA feedback to help guide device development
- Appropriate during testing or protocol development
  - Pre-clinical
  - Clinical

https://www.fda.gov/media/114034/download

Pre-Su subm.)

- Informa
- General
- Letter, p
- Not req formal FDA fe ment
- Appropr opment
  - Pre-cl
  - Clinic

34/download

Contains Nonbinding Recommendations

Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program

Guidance for Industry and Food and Drug Administration Staff

Document issued on May 7, 2019.

This guidance supersedes "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff," dated September 29, 2017.

For questions about this document regarding CDRH-regulated devices, contact ORP: Office of Regulatory Programs/DRP1: Division of Submission Support at 301-796-5640. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently OMB control number. The OMB control number for this collection is 0910-0756 (expires January 31, 2020).

See additional PRA statement in Section V of the guidance.

FDA U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

Recurring Myths

- Don’t talk to the FDA until you submit you application because <?>
  - FDA encourages dialogue early in device development to facilitate entry into clinical trials and marketing
  - Better to find out sooner than later about concerns
  - For IDE’s, improved likelihood of approval on 1st or 2nd submission

Recurring Myths

- The FDA would never approve a study of <fill in the blank>
  - FDA submissions are usually something new
  - Transcatheter heart valves
  - Surgically implanted retinal grids for blindness

Let the science guide you,
not your guess as to what the
Agency will approve

Recurring Myths

- I cannot do this study because the FDA's Guidance Document prohibits it.
  - Guidance is just "guidance"
  - Presents FDA views on regulatory requirements
  - Not binding on FDA or sponsor
  - Does not prescribe fixed study design

Let the science guide you.

From Bench to Bedside

- Develop and test your device
  - Iterative design
  - Identify and address failure modes
  - Test to show design requirements are met
- Develop the clinical research protocol
  - Is it a device?
  - Do the IDE regulations apply?
  - Is the study exempt?
  - If not exempt is the study (not the device) SR or NSR?
    - IRB alone or IRB + FDA

From Bench to Bedside

- Use all the resources available to you
  - NIH/IRB documents
  - Protocol management teams
  - IRB
  - FDA
    - Website
    - Online training, education, webinars
  - Publications on regulatory matters
  - Direct FDA interactions, as required