FDA Regulation of Image Modalities

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2023 RSNA CLINICAL TRIALS METHODOLOGY WORKSHOP

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FINANCIAL DISCLOSURES

NO DISCLOSURES

(But many thanks to Dr. Daniel Sullivan, MD…)

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LEARNING OBJECTIVES

- **Understand** the **general approach FDA uses to classify and evaluate** the **safety** and **efficacy** of **medical products** (drugs, biologics, and devices).
- **Understand** the **pathways to market** for FDA-regulated products
- **Identify** the **resources available to help sponsors and investigators** understand what they need to do to apply for medical product approval

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AGENDA

- FDA 101: Mission, Legislative History, Definitions and other bits of alphabet soup
- Pathways to Market
- Resources for Sponsors and Investigators

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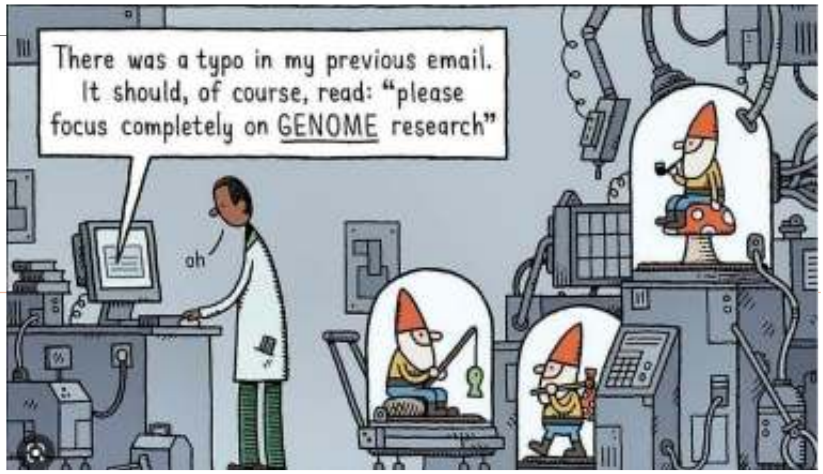
FDA 101



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FDA 101:

Mission

The **Food and Drug Administration (FDA)** is responsible for **protecting the public health** by **ensuring the safety, efficacy, and security of human and veterinary drugs, biological products,** and **medical devices**; and by ensuring the safety of our nation's **food supply**, **cosmetics**, and **products that emit radiation**.

- **Mission of OHRP** "The Office for Human Research Protections (OHRP) provides leadership in the protection of the rights, welfare, and wellbeing of subjects involved in research conducted or supported by the U.S. Department of Health and Human Services. OHRP helps ensure this by providing clarification and guidance, developing educational programs and materials, maintaining regulatory oversight, and providing advice on ethical and regulatory issues in biomedical and social-behavioral research."

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FDA 101:
Key Legislation

- **Food and Drugs Act of 1906** was the first of more than 200 laws … [governing] public health and consumer protections (initially did not include devices)
- **Federal Food, Drug, and Cosmetic (FD&C) Act of 1938** was passed after a legally marketed toxic elixir killed 107 people, including many children. The law authorized the FDA to demand evidence of safety for new drugs, issue standards for food, and conduct factory inspections (still no devices).
- **Kefauver-Harris Amendments of 1962** were inspired by the thalidomide tragedy in Europe, strengthened the rules for drug safety and required manufacturers to prove their drugs' effectiveness (still no device regulation).
- **Medical Device Amendments of 1976** followed a U.S. Senate finding that faulty medical devices had caused 10,000 injuries, including 731 deaths. The law applied safety and effectiveness "safeguards" to new devices.
- **FDA Revised Regulations adopted 1981** incorporating protections for human subjects

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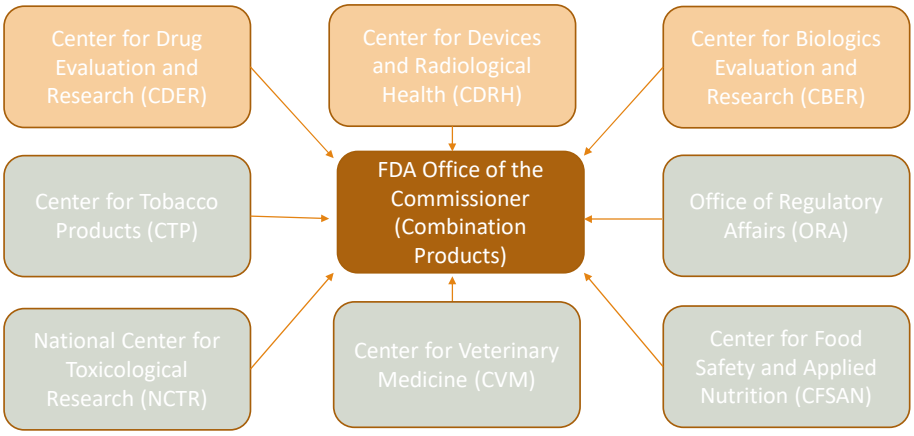
FDA 101:
Organizational Chart



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FDA 101:
Centers and Divisions

CDRH – Ensures the availability, safety, and effectiveness of **medical devices and radiological products**

CDER – Assures that all prescription and over-the-counter **drugs** are safe and effective

CBER – Ensures the safety, purity, potency, and effectiveness of **biological products** including vaccines, blood and blood products, and cells, tissues, and gene therapies

OCP – broad responsibilities covering the regulatory life cycle of **drug-device, drug-biologic, and device-biologic combination products**

FDA 101:
Definitions

CLINICAL INVESTIGATION: means **any experiment that involves a test article and one or more human subjects** and that either is **subject to requirements for prior submission to the Food and Drug Administration** under section 505(i) or 520(g) of the act, **or is not subject to requirements for prior submission** to the Food and Drug Administration under these sections of the act, **but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit**. (21 CFR 50.3(c))

APPLICATION FOR RESEARCH OR MARKETING PERMIT: 25 separate regulatory submissions are considered to be or be in support of an application for research of marketing permit. The list of regulatory submission types includes new drug applications, information on food and color additives, bioavailability and bioequivalence data, clinical trial data from studies of infant formula, and information on OTC and prescription drugs, biologics, in vitro diagnostic devices, medical devices, electronic products, etc. (21 CFR 50.3(b))

FDA 101:
Definitions

INTENDED USE: The objective intent of the persons legally responsible for the labeling of [the pharmaceutical product or medical device].

21 CFR 801.4 and 21 CFR 201.128

ASSESSING INTENDED USE

- Any relevant source of information may be used to determine intended use, including:
- The product's labeling,
- Promotional claims
- Advertising
- Any other relevant source

United States v. Travia, 180 F. Supp. 2d 115, 119 (D.D.C. 2001) *"Labeling is not exclusive evidence of the sellers' intent. Rather, as the very language quoted by the defendants themselves states, `it is well established "that the intended use of a product, within the meaning of the [FD&C Act], is determined from its label, accompanying labeling, promotional claims, advertising, and any other relevant source"' . . . even consumer intent could be relevant, so long as it was pertinent to demonstrating the seller's intent . . .*

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FDA 101:
Definitions

APPROVED OR CLEARED MEDICAL PRODUCT: a medical product that may be legally introduced into interstate commerce for at least one use under the FD&C Act or the PHS Act as a result of having satisfied applicable premarket statutory and regulatory requirements (including devices that are granted marketing authorization or are exempt from premarket notification).

APPROVED OR CLEARED MEDICAL USE: an intended use included in the required labeling for an FDA-approved medical product, an intended use included in the indications for use statement for a device cleared or granted marketing authorization by FDA, or an intended use of a device that falls within an exemption from premarket notification.

UNAPPROVED USE OF AN APPROVED PRODUCT: an intended use that is not included in the required labeling of an FDA-approved medical product, an intended use that is not included in the indications for use statement for a device cleared or granted marketing authorization by FDA, or an intended use of a device that does not fall within an exemption from premarket notification.

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FDA 101:
Definitions

MEDICAL DEVICE: An **instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent**, or other similar or related article:

- recognized in the official National Formulary, or the United States Pharmacopeia,
- **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 of any function of the body** of man or other animals,

Which does not achieve any of **its** principal intended **purposes through chemical action** within the body or by being metabolized (Section 201(h) of the FFDCA).

ITEMS REGULATED BY FDA AS MEDICAL DEVICES: software*, in vitro diagnostic tests, some mobile apps and digital health products…

- That said, specific software functions including data storage, administrative support, and electronic patient records were excluded from the definition of medical device as a result of the 21st Century Cures Act.

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FDA 101:
Definitions

SAFETY: There is reasonable assurance that **a device is safe when it can be determined, based upon valid scientific evidence, that the probable 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**. 21 CFR 860.7(d)(1)

EFFECTIVENESS: There is reasonable assurance **that a device is effective when it can be determined, based upon valid scientific evidence, that in a 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.** 21 CFR 860.7(e)(1)

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FDA 101:
Definitions

VALID SCIENTIFIC EVIDENCE: (Varies from device to device)

- Well-controlled investigations,
- Partially controlled studies,
- Studies and objective trials without matched controls,
- Well-documented case histories conducted by qualified experts, and
- Reports of significant human experience [qualified experts] with a marketed device

The following are not ignored, but are not considered valid scientific evidence:

- Isolated case reports
- Random experience
- Reports lacking sufficient details to permit scientific evaluation
- Unsubstantiated opinions

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FDA 101:
Definitions

DRUG: An article

- **Recognized in the** official **US Pharmacopeia** (or equivalent)
- **Intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease** in man or other animals
- (other than food) **intended to affect the structure or any function** of the body of man or other animals via chemical interaction
- Article **intended for use as a component of any** article **specified above**

(Section 201(g)(1) of the FFDCA)

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FDA 101:
Definitions

INVESTIGATIONAL NEW DRUG: A drug that is not FDA approved *for the indication being studied*

- Contrast agents and radiopharmaceuticals are drugs
- Image-guided delivery of drugs may be a drug or a device-drug combination

FDA 101:
Definitions

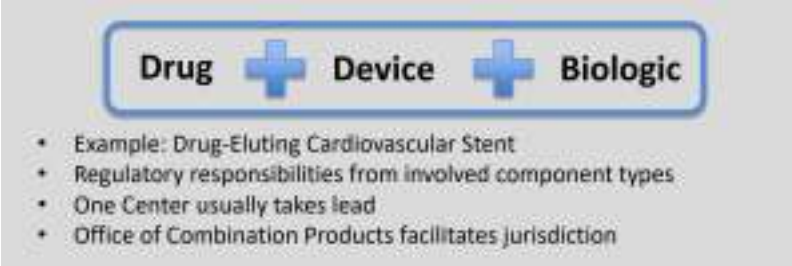
BIOLOGIC: **Biological products are regulated by the Food and Drug Administration (FDA)** and are **used to diagnose, prevent, treat, and cure diseases and medical conditions**. Biological products are a **diverse category of products** and are **generally large, complex molecules**.

These products may be produced through biotechnology in a living system, such as a microorganism, plant cell, or animal cell, and are often more difficult to characterize than small molecule drugs. There are many types of biological products approved for use in the United States, including **therapeutic proteins** (such as filgrastim), **monoclonal antibodies** (such as adalimumab), and **vaccines** (such as those for influenza and tetanus). (https://www.fda.gov/files/drugs/published/Biological-Product-Definitions.pdf)

FDA 101:
Definitions

COMBINATION PRODUCT:

- Comprised of two or more regulated components
- Any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product.



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FDA 101:
Definitions

RADIOACTIVE DRUG RESEARCH COMMITTEE (RDRC) PROGRAM: (21 CFR 361.1)

"Permits **basic research** using radioactive drugs in humans **without** an IND when the drug is administered under the following conditions:

- The research is considered basic science research and is done for the purpose of advancing scientific knowledge – intended to obtain basic information regarding the **metabolism** (including kinetics, distribution, dosimetry, and localization) of a radioactive drug or regarding **human physiology, pathophysiology, or biochemistry**
  - **not** intended for immediate therapeutic, diagnostic or similar purposes (e.g. preventive benefit to the study subject from the research), and
  - **not** intended to determine the safety and effectiveness of a radioactive drug in humans."

PATHWAYS TO MARKET

PATHWAYS TO MARKET

Device Classifications

- Medical devices, “based on device description and intended use,” are divided into three classes
  - Class I, II, and III
  - Increasing in risk from Class I to Class III
- Devices are also assigned a three-letter code. Like devices and devices with similar intended use are coded for purposes of identification and consistent regulation
- Device classifications will drive the nature and extent of the regulatory controls imposed upon the device pre and post market

PATHWAYS TO MARKET

MEDICAL DEVICES

EXAMPLES OF DEVICES BY CLASS

Class I: elastic bandages, non-sterile examination gloves, crutches, splints, tongue depressor, oxygen mask

Class II: powered wheelchairs, infusion pumps, CT, MRI, and most diagnostic ultrasound, CR/DR (except digital mammography), catheters, contact lenses

Class III: Digital mammography, coronary stent, defibrillator orthopedic implant

PATHWAYS TO MARKET

MEDICAL DEVICES

CONTROLS: Regulatory requirements, **assigned to devices** based on device class and product code, in order **to ensure consistent requirements** across devices **and "foster predictably safe medical devices."**

- **General Controls**: apply to all medical devices
- **Specific Controls**: apply only to class II devices and are relatively uncommon.
  - Examples include: design requirements, characteristics or specifications, testing, special labeling, guidance documents
- **Pre-Market Approval Application**: required for class III devices

PATHWAYS TO MARKET

MEDICAL DEVICES

General Controls: Examples

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

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PATHWAYS TO MARKET

MEDICAL DEVICES

Classes of Medical Devices

Class	Risk	Controls	Submission
I	Lowest	General	• Exempt* • 510(k)
II	Moderate	General and Special (if available)	• 510(k)* • Exempt
III	Highest	General and PMA	• PMA

* More common submission requirement of this Class

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PATHWAYS TO MARKET

MEDICAL DEVICES

1. ESTABLISH YOUR DEVICE
- Intended use, indications for use, duration of use, target population

2. CONFIRM THAT YOUR DEVICE IS A MEDICAL DEVICE
- See definition slide

3. IDENTIFY CLASS AND REGULATORY PATHWAY
- See prior slide

4. AMASS VALID SCIENTIFIC EVIDENCE
- Well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience [qualified experts] with a marketed device

5. COMPLETE YOUR PRE-MARKET SUBMISSION (unless the device is class I)

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PATHWAYS TO MARKET

MEDICAL DEVICES

PREMARKET SUBMISSIONS:

1. INVESTIGATIONAL DEVICE EXEMPTION (IDE)
2. PREMARKET NOTIFICATION (510K)
3. PREMARKET APPROVAL (PMA)
4. DE NOVO
5. HUMANITARIAN DEVICE EXEMPTION

PATHWAYS TO MARKET

MEDICAL DEVICES

INVESTIGATIONAL DEVICE EXEMPTION (IDE):

Allows an investigational device to be shipped (placed into interstate commerce) for purposes of investigation – aka, collecting safety and efficacy data about the device

- **Studies of investigational devices** subject to the IDE regulations (21 CF part 812) require IRB review
- **Significant Risk Devices** require an approved IDE from FDA and IRB approval prior to testing in humans
  - Devices that are intended as an implant, purported or represented to be for a use in supporting or sustaining human life, is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease; or oherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
- **Nonsignificant Risk Devices** are considered to have an approved IDE once the IRB has approved the study protocol and make the NSR determination
  - A device not meeting the definition of a significant risk device

PATHWAYS TO MARKET

MEDICAL DEVICES

INVESTIGATIONAL DEVICE EXEMPTION (IDE):

IDE Exempt Device Studies: Exempt from an Exemption – and not eligible for an exempt determination – but may be reviewed via the expedited via the expedited pathway (one reviewer)

- On label investigation of a cleared or approved drug, biologic, or medical device
- Investigations of a diagnostic device, if the sponsor complies with applicable [labeling] requirements in § 809.10(c) and if the testing:
  - (i) Is noninvasive,
  - (ii) Does not require an invasive sampling procedure that presents significant risk,
  - (iii) Does not by design or intention introduce energy into a subject, and
  - (iv) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

PATHWAYS TO MARKET

MEDICAL DEVICES

PREMARKET NOTIFICATION (510K):

- Class II devices, mostly
- Intent is to demonstrate "substantial equivalence" to a predicate (legally marketed) device with the same intended use.
  - 510k process will compare intended uses, device specifications, and results of performance testing
- When FDA finds a device substantially equivalent, it is "cleared"/receives "510k clearance"

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PATHWAYS TO MARKET

MEDICAL DEVICES

PRE-MARKET APPROVAL (PMA): An

- Class III devices, mostly.
- Demonstrate reasonable assurance of safety and effectiveness (i.e., usually need clinical trial data)
  - Very device and indication specific
- When FDA finds a device safe and effective for its intended use, it is "approved".

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PATHWAYS TO MARKET:

REGULATORY SUBMISSIONS DRUGS AND BIOLOGICS

- **INVESTIGATIONAL NEW DRUG (EXEMPTION) (IND)**
  - Allows a new drug (or biologic) to be shipped for investigational
- **NEW DRUG APPLICATION (NDA)**
  - Needs pre-clinical and clinical data
- **ABBREVIATED NEW DRUG APPLICATION (ANDA)**
  - For generic versions of approved drugs
  - No safety and effectiveness clinical trials required (only need to demonstrate equivalence)
- **BLA: BIOLOGIC LICENSE APPLICATION**

For New Drugs and Biologics:

An IND will required for testing in human subjects and (for the most part) and an NDA will be required as part of the premarket approval process

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PATHWAYS TO MARKET: New Drugs and Biologics

https://www.fda.gov/media/82381/download

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PATHWAYS TO MARKET: New Drugs and Biologics

https://www.fda.gov/media/82381/download

PATHWAYS TO MARKET:
DRUGS AND BIOLOGICS

TYPES OF INVESTIGATIONAL NEW DRUG (EXEMPTION) (IND):

Four types of **traditional INDs**:

- An investigator-initiated IND
- Exploratory ("phase 0", x-IND)
- Treatment (Compassionate-Use) IND
- Emergency use IND (E-IND)

Exploratory IND

PATHWAYS TO MARKET:
DRUGS AND BIOLOGICS

Traditional IND
- Single agent
- Plans for Phase 1, 2, 3 trials and NDA
- Extensive pre-clinical data needed to begin
- Dose escalation, therapeutic evaluation

Exploratory IND
- Multiple agents under one IND,
- Microdosing, first-in-man studies
- No therapeutic intent
- Biodistribution, pharmacokinetics, safety
- Less pre-clinical data required

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PATHWAYS TO MARKET:
DRUGS AND BIOLOGICS

IND APPLICATION: REQUIRED CONTENT

Pharmacology/toxicology in animals

Dosimetry for radiopharmaceuticals

CMC: Chemistry, Manufacturing and Controls

Some of these data may be referenced from existing INDs or the literature

Clinical Information

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PATHWAYS TO MARKET:

DRUGS AND BIOLOGICS

RDRC V. IND: WHEN DO I NEED EACH?

- **RDRC: for basic research only**
  - e.g., kinetics, distribution, dosimetry
  - NOT for safety or efficacy, or for FDA submission
  - Pediatric studies restricted
  - Only small doses and few patients (usually <30)
  - Drug must have been in humans before
- **IND: not restricted to basic research**
  - Can study safety and efficacy (i.e., clinical trials)
  - Can support FDA submission
  - Can do basic research
  - Pediatric studies less restricted

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PATHWAYS TO MARKET:

DRUGS AND BIOLOGICS

OFF-LABEL USE OF AN FDA-APPROVED DRUG IN A CLINICAL TRIAL: DO YOU NEED AN IND?

- Defined in FDA regulations (21 CFR 312.2(b))
- Exempt if:
  - Investigation not being done to "change the label"
  - Investigation does not involve dosage, route of administration, or use in a patient population that significantly increases risks
- Some IRBs will make the determination; others require that you ask FDA

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SPECIAL TOPICS

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SPECIAL TOPICS:
SOFTWARE AS A MEDICAL DEVICE (SAMD)

Almost all commercially-intended software related to medical imaging must be FDA-approved.

"Depending on intended use of a device, assessment of technical performance alone may not be sufficient and clinical validation may be necessary."

Semi-automated QI Function: Clinical validation will probably be needed.

Fully Automated QI Function: "Tested on clinical data that represent the variety of expected use cases, including cases expected to challenge the algorithm".

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SPEICAL TOPICS:

AI AND MACHINE LEARNING

Agency proposing framework to give manufacturers option to submit a plan for AI/ML-based modifications during initial premarket review

Initial premarket phase would include

- Review initial SaMD performance
- Review plan for modifications
- Review ability to manage/control resultant risks of modifications

RESOURCES FOR SPONSORS AND INVESTIGATORS

ADDITIONAL RESOURCES FOR INVESTIGATORS:

FDA GUIDANCE

- **Device Advice: Comprehensive Regulatory Assistance:**
  - Overview of Device Regulation
  - How to Study and Market your Device
  - Postmarket Requirements
  - Quality Control, Compliance
- **Search for FDA Guidance Documents: Searchable database of official FDA Guidance Documents and other regulatory guidance.**
  - Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors, Significant Risk and Nonsignificant Risk Medical Device Studies 01/2006
  - Software as a Medical Device (SAMD): Clinical Evaluation, Guidance for Industry and FDA Staff, 12/2017
  - Clinical Decision Support Software Guidance for Industry and FDA and Drug Administration Staff, 09/ 2022
  - Content of Premarket Submissions for Device Software Functions, Draft Guidance for Industry and FDA Staff, 11/2021
  - Deciding When to Submit a 510(k) for a Software Change to an Existing Device Guidance for Industry and FDA Staff, 10/2017
- FDA **Medical Device Databases: accessible here**

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RESOURCES FOR SPONSORS AND INVESTIGATORS:

DRUGS AND BIOLOGICS

FDA Guidance on the IND process with multiple links to other documentation:

- http://www.fda.gov/cder/regulatory/applications/ind_page_1.htm

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