# FDA Session

AI Forum
February 9, 2024

https://www.mcra.com/

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# Hi, My Name is…

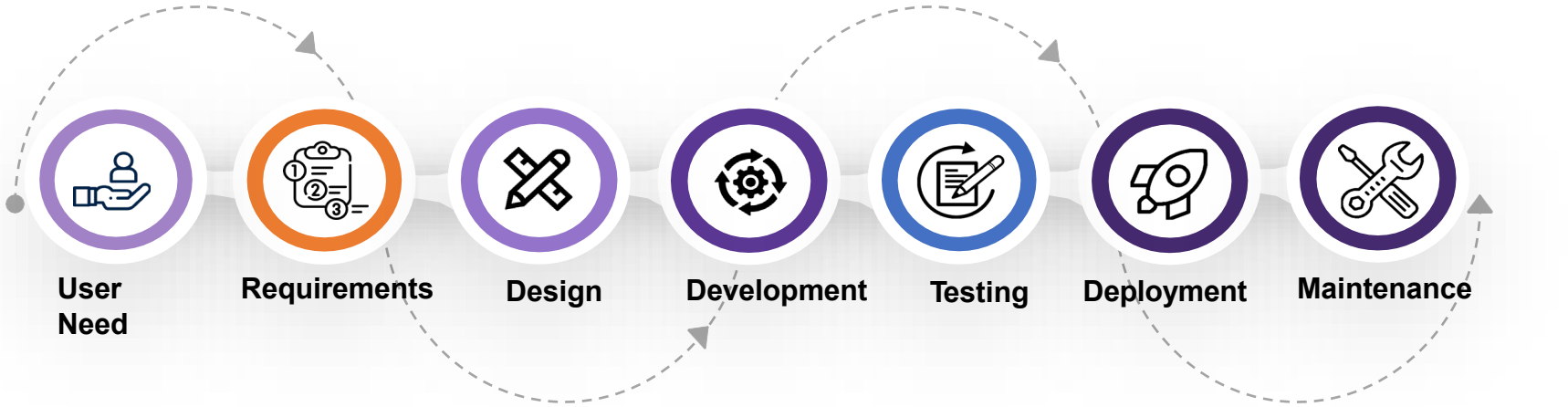

**Alex Cadotte**

***Sr. Director, Digital Health & Radiology Regulatory Affairs***

Previously employed by FDA as Lead Reviewer and Team Lead.

acadotte@mcra.com


# MCRA's Integrated Advisory Service Lines




- Initial Hazard Analysis
- Cybersecurity Policies
- Initial QMS Procedures
- Market Opp + Value Proposition
- Regulatory Strategy

- Quality Manual and QMS SOPs
- HIPAA + GDPR Compliance
- Training and Validation Plans
- Clinical Protocol Development
- Threat Modeling
- Use Related Risk Analysis

- Clinical Study Execution
- Usability Testing
- Cybersecurity Testing
- Reimbursement Assessment
- 2° Market Reg Strategy

- QMS SOPs for Distribution
- Cybersecurity Maintenance
- Use Related Risk Analysis
- Evidence Generation Plan

- Health Economics Data
- Post-Market Changes
- Patient Access

# Today's Objectives

- Answer the following questions:
  - Is your technology regulated by FDA?
  - What testing will you need to perform to gain FDA clearance or approval?
  - How is the testing done? Nima - MCRA's AI & Imaging Center
  - What pathways are available to you?
  - What should you plan to do next?

# Regulatory 101

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# Statutory Definition of Medical Device

*Per Section 201(h) of the Food, Drug, and Cosmetic Act, a device is:*

*An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:*

- *recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,*
- *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 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 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. The term "device" does not include software functions excluded pursuant to section 520(o).*

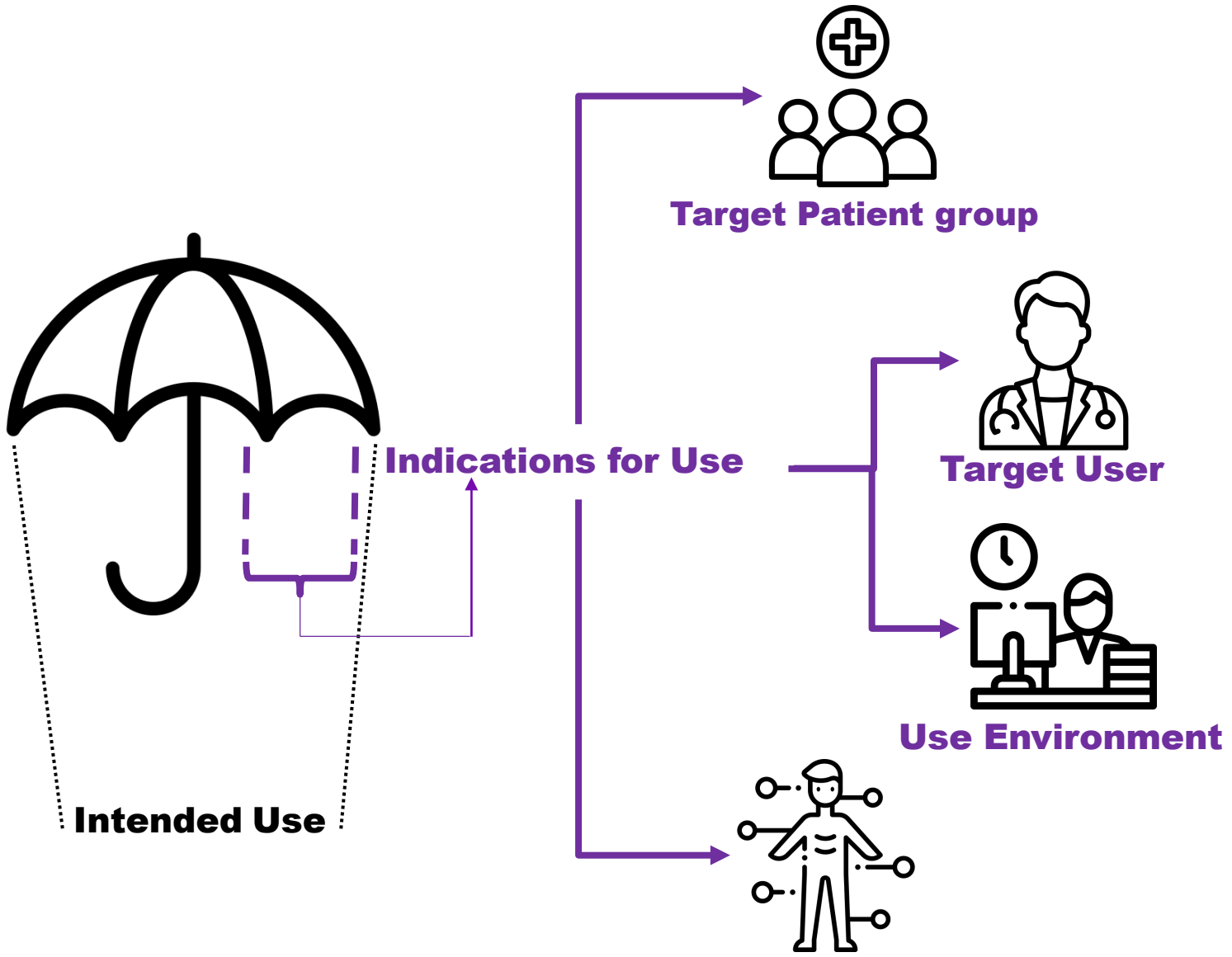
# Intended Use vs. Indications for Use

**Intended Use**

refers to objective intent which can be shown by:

- Labeling
- Advertising materials
- Oral/written statements
- Implied or expressed claims

21 CFR 801.4

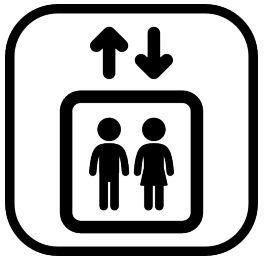


# Use Case and Labeling Claims

- Let's craft an indications for use statement:
  - Who are your Target User(s)?
  - What disease or population are look targeting?
  - Where do you intend/expect your product to be used?
  - How do you want your device or device outputs to be used?
  - Do you expect to sell your product direct to patient/consumer or through a physician?

The indications for use statement is the foundation for all activities that involve the FDA

# Classify Your Device



## Class I

Generals Controls (with and without exemptions)

Most Class I devices are exempt from premarket notification process (510(k))

## Class II

General and Special Controls (with and without exemptions)

Most Class II devices are without exemptions and require either a De Novo or 510(k) submission.

## Class III

General Controls and Premarket Approval

All Class III devices are required to submit a premarket approval (PMA) application

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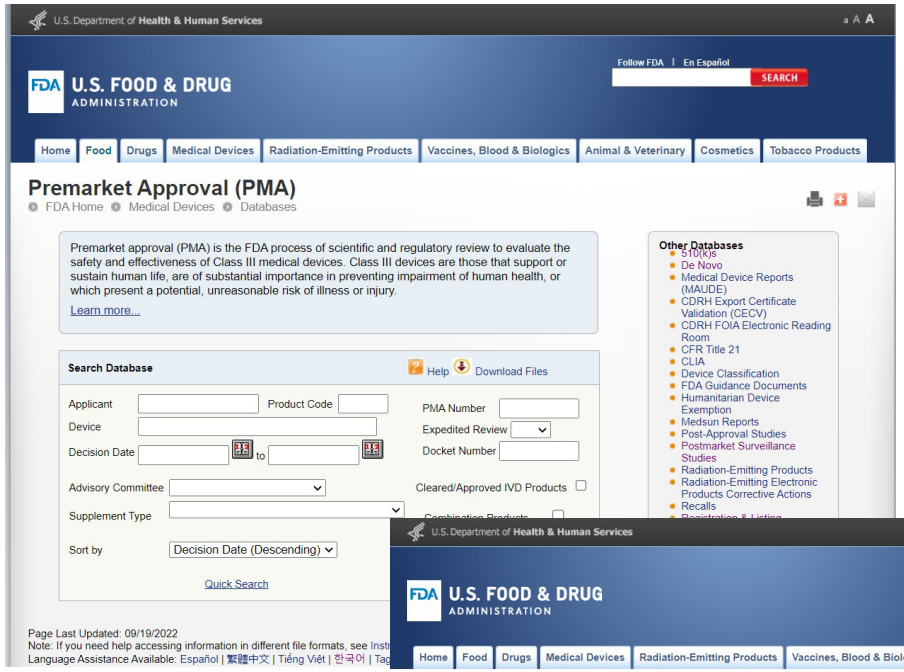
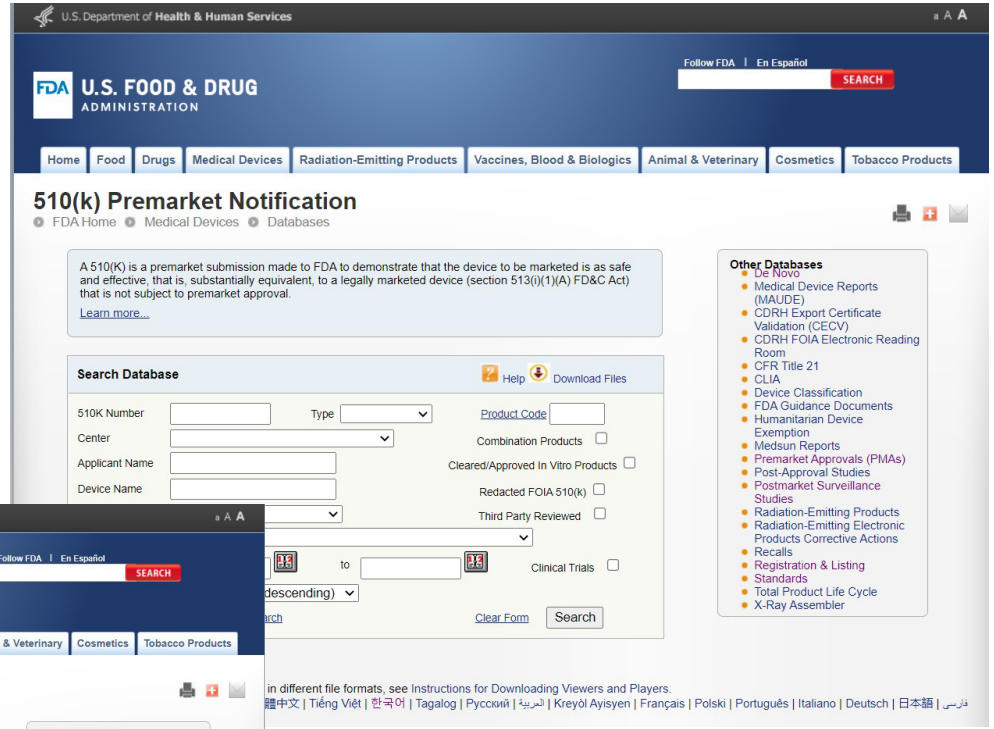
# Does Your Product Include Software?

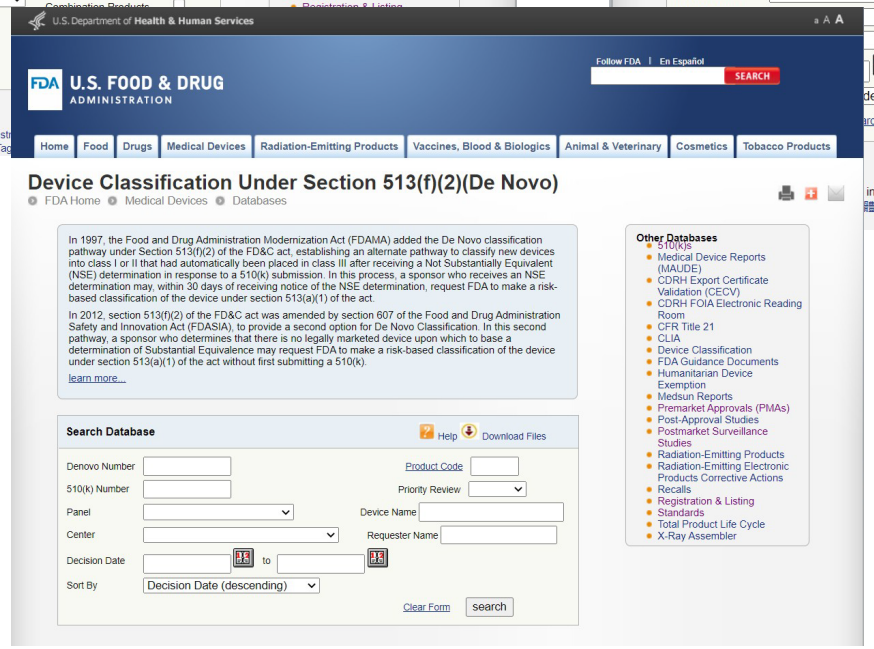
21st Century Cures Act established exclusions for certain software functions from the definition of a device, as defined in section 201(h) of the FD&C Act.

- Administrative functions
- Low-risk general wellness
- Electronic patient records
- Medical device data systems
- Clinical decision support software

# Identify Applicable Regulation and Procode



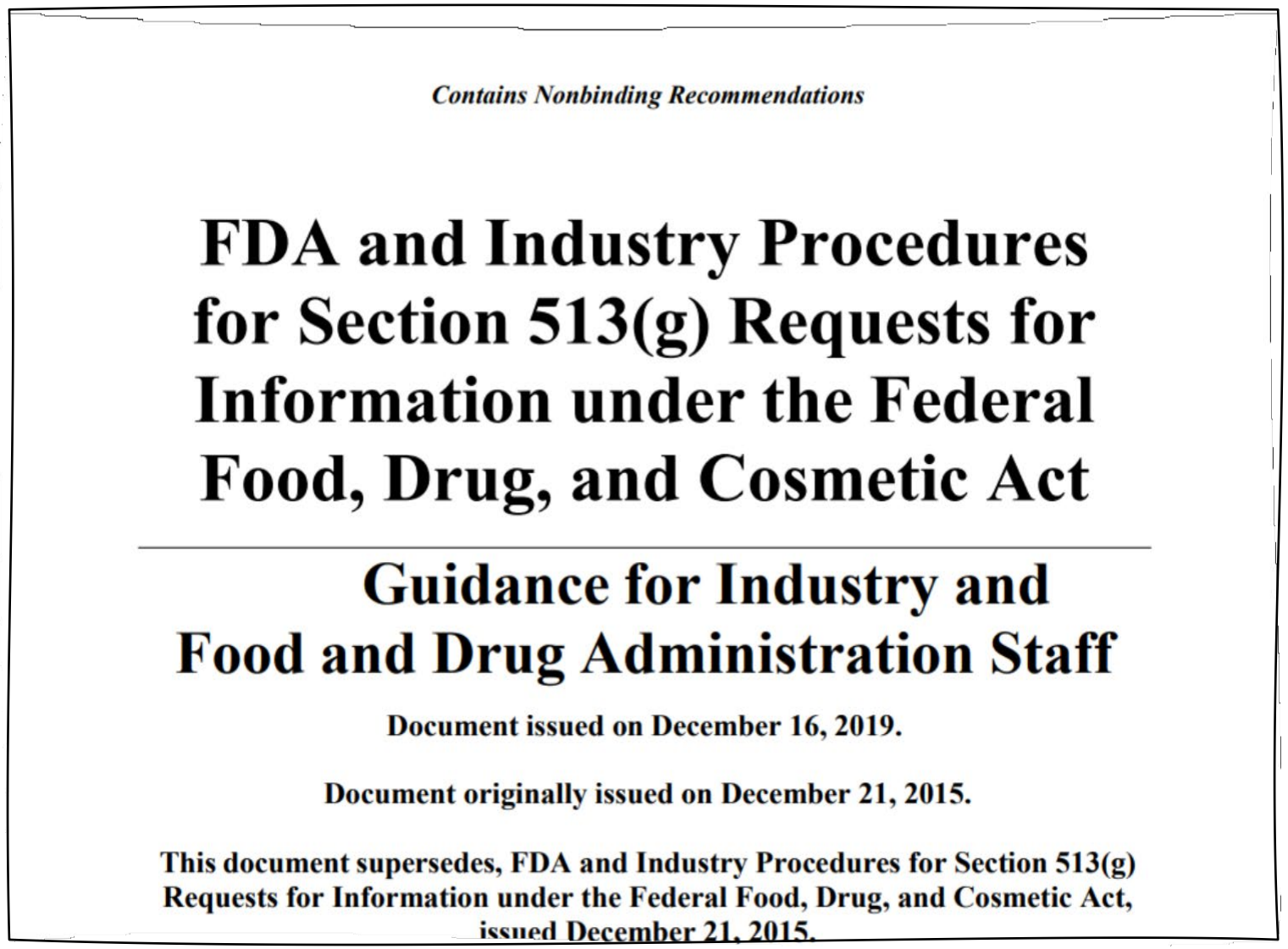




## Where to start

1. Do you have any competitor products?
2. Search for product classification with general device types

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

# Still Unsure? Submit a 513(g)



*Contains Nonbinding Recommendations*

**FDA and Industry Procedures for Section 513(g) Requests for Information under the Federal Food, Drug, and Cosmetic Act**

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**Guidance for Industry and Food and Drug Administration Staff**

**Document issued on December 16, 2019.**

**Document originally issued on December 21, 2015.**

**This document supersedes, FDA and Industry Procedures for Section 513(g) Requests for Information under the Federal Food, Drug, and Cosmetic Act, issued December 21, 2015.**

# Let's Pause to Ask Ourselves…

Is your technology or feature(s) regulated by FDA?

If yes, is it Class I, II, or III?

# Pre-Market Requirements

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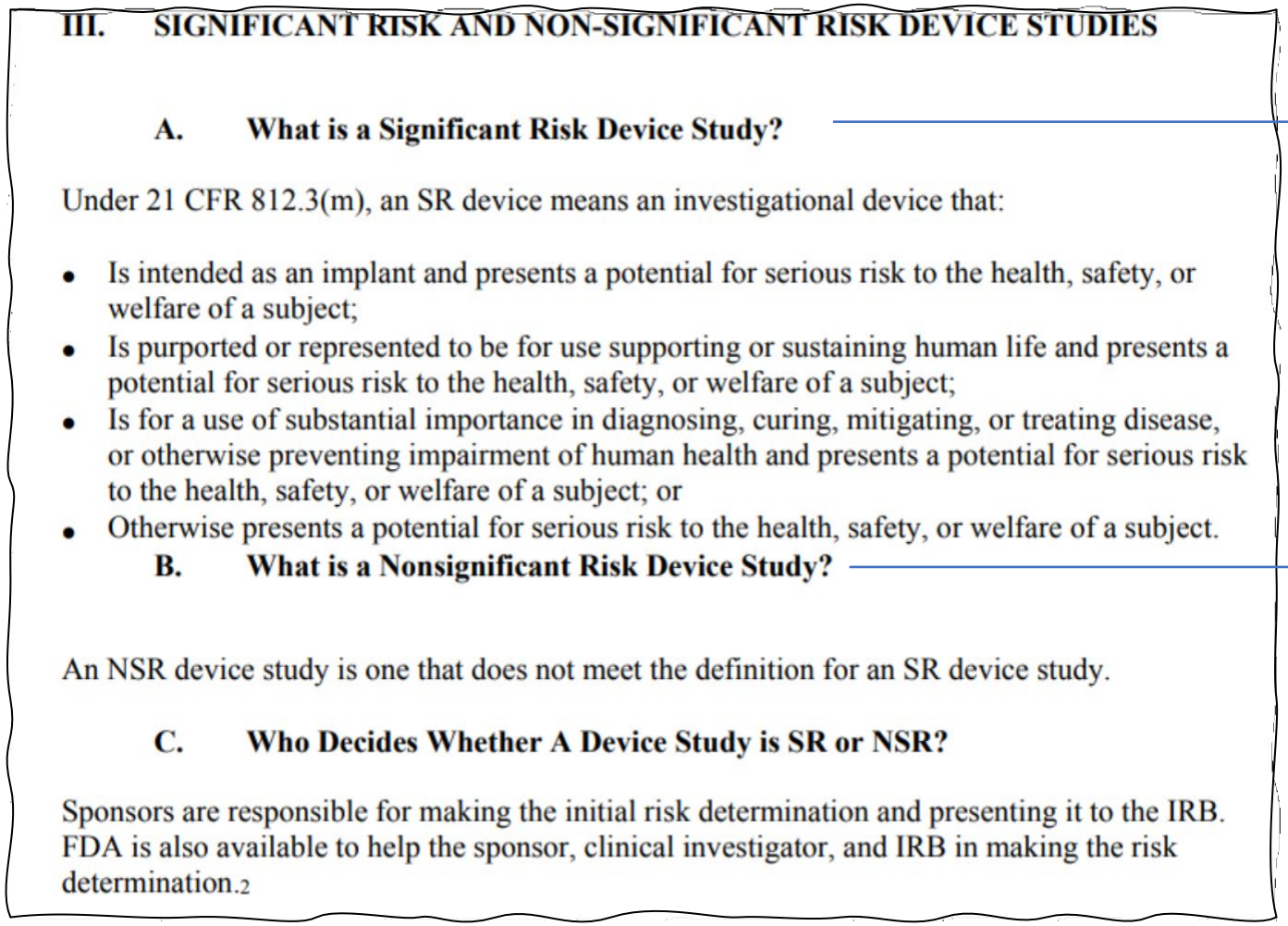
# Valid Scientific Evidence

- Where do I go to identify what I need to do:
  - Previously cleared and approved decisions summaries
  - FDA Guidance Documents
  - FDA Recognized Consensus Standards
- Evidence to be Considered:
  - Bench Top V&V
  - Software Validation
  - Cybersecurity Testing
  - Biocompatibility
  - Sterilization and Packaging Testing
  - Electrical Safety
  - Electromagnetic Compatibility
  - Wireless Performance
  - Human Factors & Usability Testing
  - Clinical Validation

# Determining the Evidence Needed

- Critical questions to ask that may eliminate evidence needed:
  - Does my product include hardware?
  - Does my product include AI/ML algorithms?
  - Does my product use off-the-shelf components/devices?
  - Does my product include in-house developed software?
  - Does my product make physical contact with a patient/user?
  - Does my product enter a sterile environment?
  - Does my product share information/data wirelessly?
  - Does my product connect to another device?

# Clinical Validation Testing



**III. SIGNIFICANT RISK AND NON-SIGNIFICANT RISK DEVICE STUDIES**

**A. What is a Significant Risk Device Study?**

Under 21 CFR 812.3(m), an SR device means an investigational device that:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

**B. What is a Nonsignificant Risk Device Study?**

An NSR device study is one that does not meet the definition for an SR device study.

**C. Who Decides Whether A Device Study is SR or NSR?**

Sponsors are responsible for making the initial risk determination and presenting it to the IRB. FDA is also available to help the sponsor, clinical investigator, and IRB in making the risk determination.[2]

Investigational Device Exemption (IDE) is required. Full compliance with 21 CFR 812 is required.

Investigational Device Exemption (IDE) is **NOT** required. Partial compliance with 21 CFR 812 is required.

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

# 10 Guiding Principles for AI/ML Devices

- Does your product include AI/ML-based software?

| |
|---|
| **1. Multi-Disciplinary Expertise Is Leveraged Throughout the Total Product Life Cycle** |
| **2. Good Software Engineering and Security Practices are Implemented** |
| **3. Clinical Study Participants and Data Sets Are Representative of the Intended Patient Population** |
| **4. Training Data Sets are Independent of Test Sets** |
| **5. Selected Reference Data Sets are Based Upon Best Available Methods** |
| **6. Model Design is Tailored to the Available Data and Reflects the Intended Use of the Device** |
| **7. Focus is Placed on the Performance of Human-AI Team** |
| **8. Testing Demonstrates Device Performance During Clinically Relevant Conditions** |
| **9. Users are Provided Clear, Essential Information** |
| **10. Deployed Models are Monitored for Performance and Retraining Risks are Managed** |

# Class III PMA Pre-Approval Inspection

- Class II FDAs and De Novos are not subject to pre-authorization inspection by FDA but are subject to post-market inspection.

- ALL Class III require onsite inspection BEFORE PMA can be approved, called the QSIT (or quality system inspection technique):
  - Management controls
  - Design Controls
  - Corrective and Preventative Actions
  - Production and Process Controls
  - Sampling Plans

    https://www.fda.gov/files/Guide-to-Inspections-of-Quality-Systems.pdf

# Let's Pause to Ask Ourselves…

What testing do you think you need to support a marketing application?

# FDA Submission Types and Timelines

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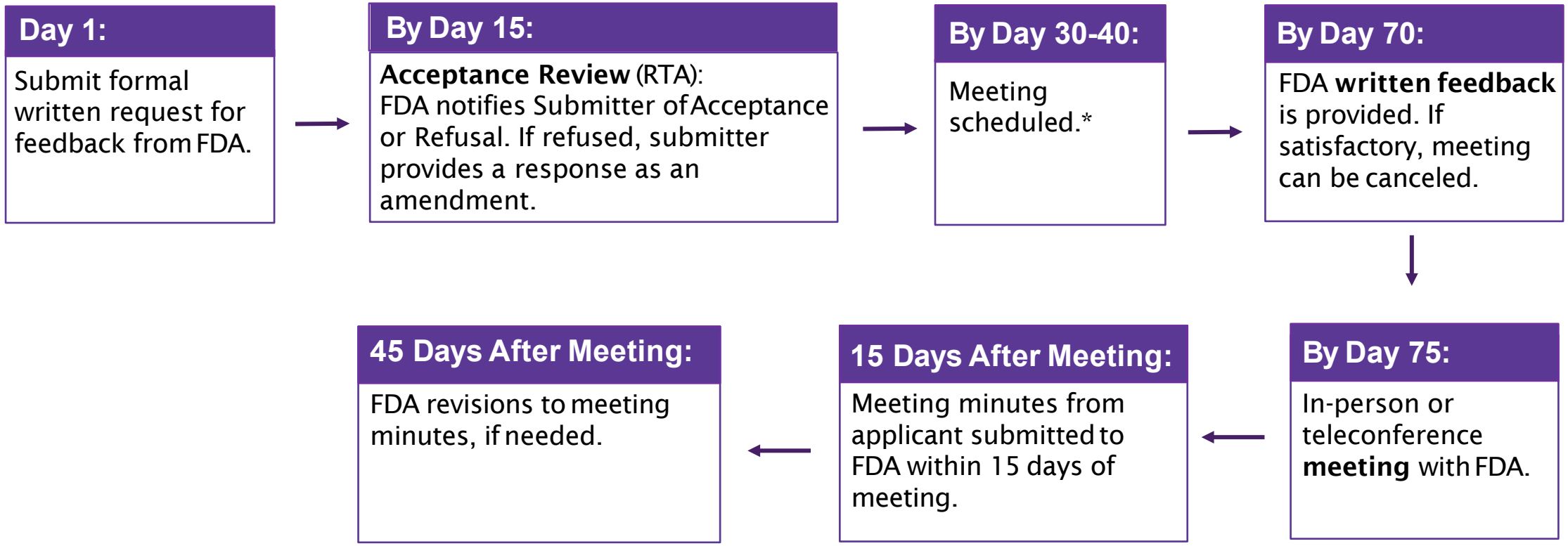
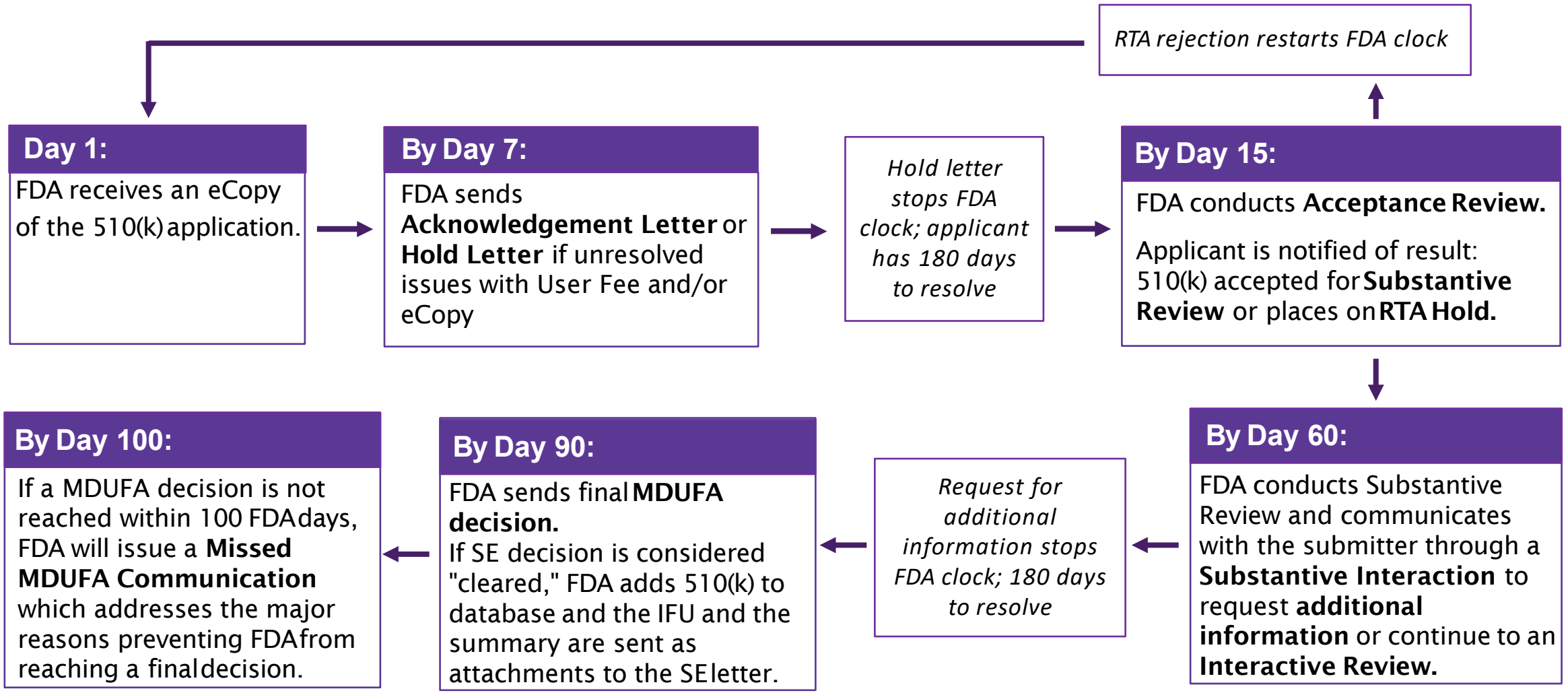
# Pre-Submission Timeline at FDA

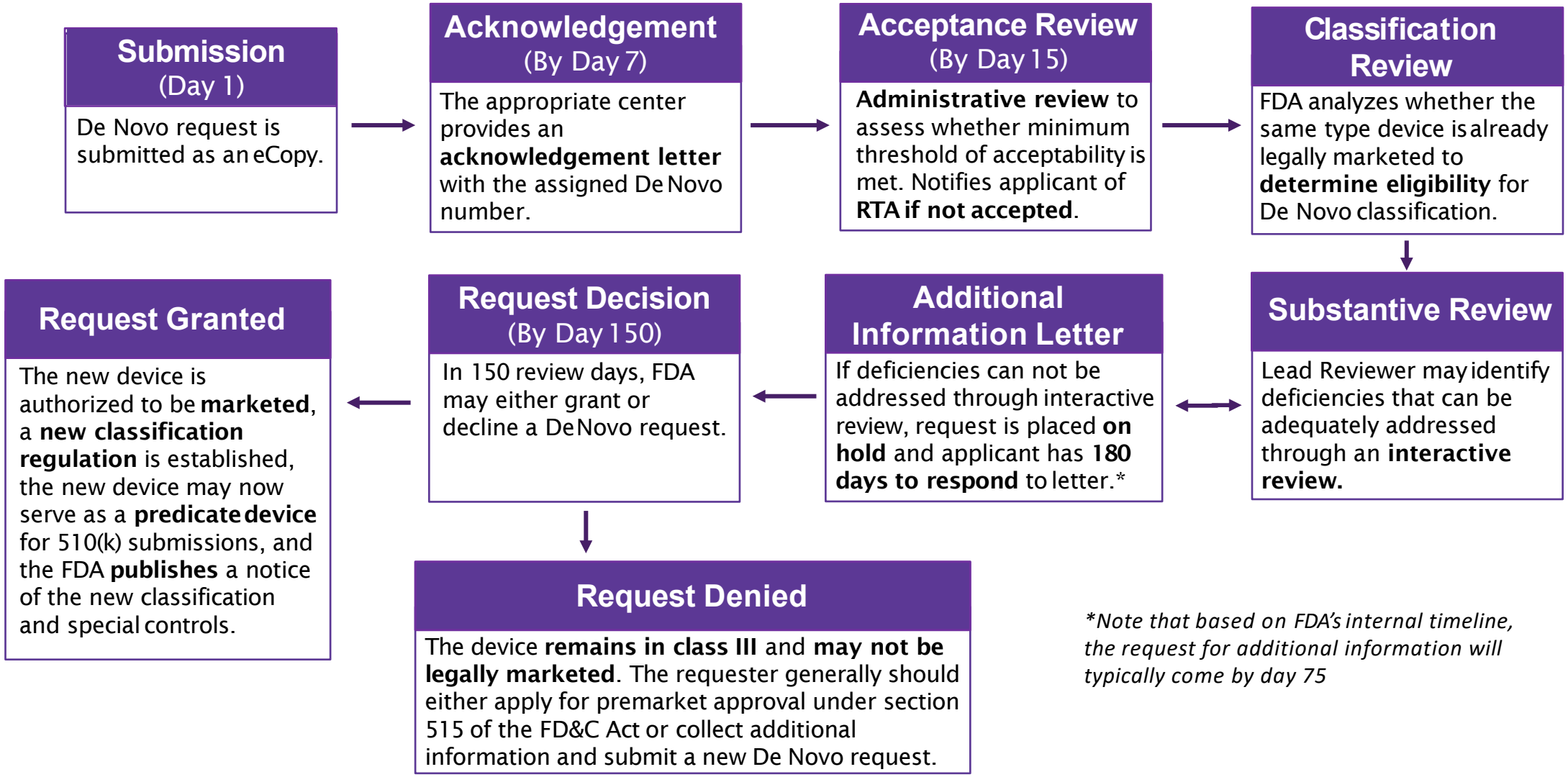



**If meeting is scheduled before day 75, written feedback must be given 5 days prior to meeting*

# Traditional 510(k) Timeline at FDA



# De Novo Timeline at FDA




**Note that based on FDA's internal timeline, the request for additional information will typically come by day 75*

# IDE Timeline at FDA

**Day 1:**
FDA notifies the sponsor via email of the date it receives the application.

**By Day 30***

**If Approved:**
Often, if FDA identifies concerns unrelated to subject safety, a **study design consideration** is issued with recommendations on how to improve the study. Suggested modifications may be necessary to enable the study to support a future marketing application.

**If Approved with Conditions:**
The sponsor may **begin subject enrollment** in clinical investigation in accordance **with limits**.

**If Disapproved:**
The sponsor **may not initiate enrollment** in the clinical investigation until **submission of an amendment** to the IDE to respond to the deficiencies identified in FDA's letter and notice of **new letter** from FDA granting approval or approval with conditions.

**Within 45 Days:**
The sponsor must **submit an amendment** addressing the issues identified as conditions of approval in FDA's letter.

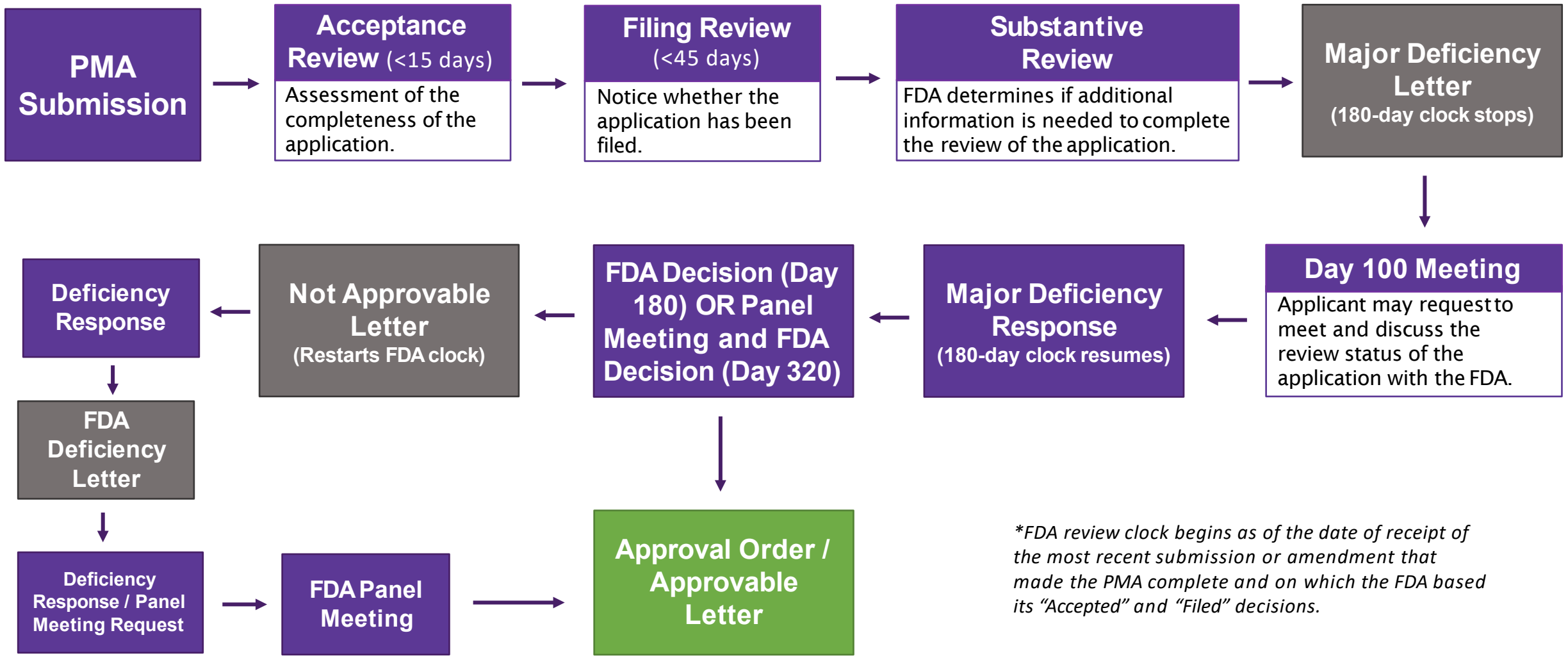
**Within 75 Days:**
FDA **informs of decision** regarding the amendment within 30 days after amendment submission.

**Amendment Disapproved:**
If concerns remain, FDA may place study **on hold** or issue another **approval with conditions** (sponsor must submit amendment in 45 days).

**Approved:**
If issues are resolved, the investigation may continue with **no limits**.

**If FDA has not otherwise informed the sponsor, the IDE application is **considered approved** 30 days after it has been received. Sponsor may **begin clinical investigation**.*

# Traditional PMA Timeline at FDA




**FDA review clock begins as of the date of receipt of the most recent submission or amendment that made the PMA complete and on which the FDA based its "Accepted" and "Filed" decisions.*

# Quality Management Considerations

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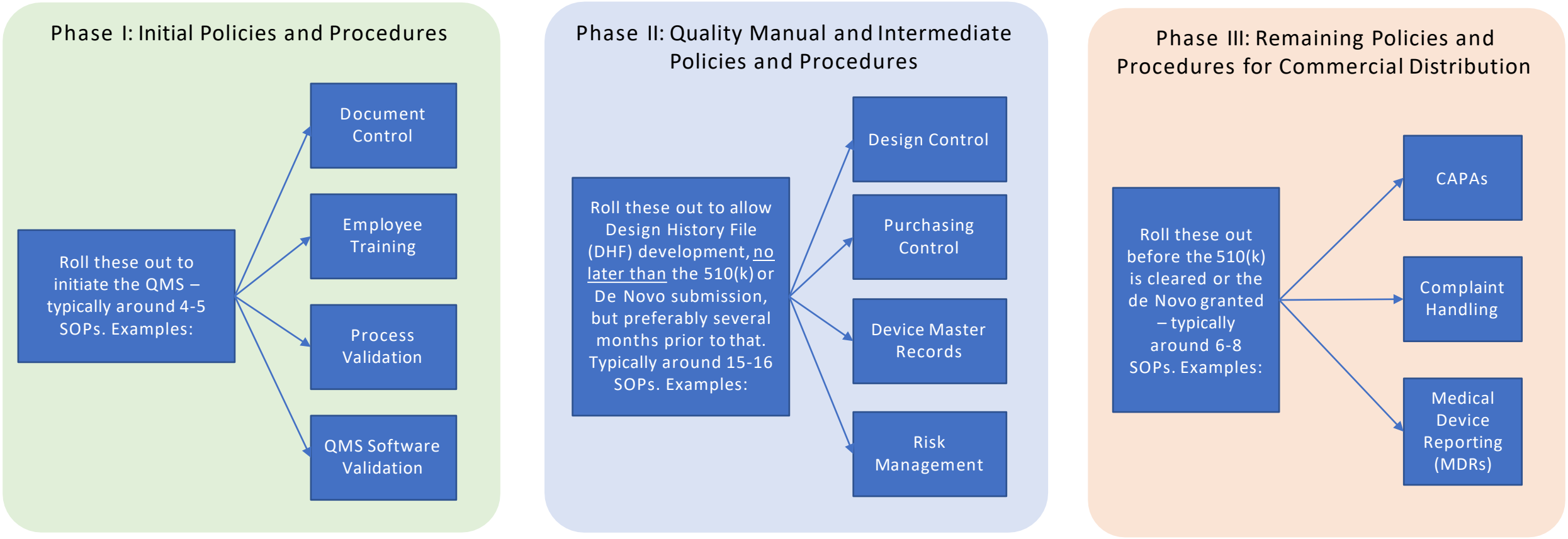
# Quality System Regulations

- All manufacturers of medical devices for distribution in the US have a Quality Management System, or QMS (often called a "Quality System" by FDA).
  - The QMS complies with Part 820 Quality System Regulation (QSR), which is similar to ISO 13485.
  - The QSR gives requirements for a range of quality activities – receiving goods, training personnel, handling complaints, etc.
  - Typically, each quality activity has a separate Standard Operating Procedure (SOP) in the manufacturer's QMS.

- Besides complying with the QSR (Part 820), the QMS also complies with:
  - Part 7 Subpart C (Recalls)
  - Part 801 Labeling
  - Part 803 Medical Device Reporting
  - Part 806 Medical Devices, Reports of Corrections and Removals
  - Part 830 Unique Device Identification

# Phased Implementation of QMS




The number of SOPs isn't dictated by FDA. It depends in part on the manufacturer's preferences, and on the type of device. For example, SaMDs require fewer SOPs than SiMDs.

# Expedited Pathways

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# Breakthrough Device Designation

- FDA Goal: Encourage medical technology development and patient access under current pre-market review pathway
- Benefits:
  - Increased FDA interaction to facilitate development - “Sprint Discussion”
  - Expedited review of pre-market submission (510(k), De Novo, PMA)
  - Possible commercial/marketing benefit with FDA recognition of technology
- NOT:
  - Marketing authorization (still need to submit 510(k), De Novo, or PMA)
  - No finalized and implemented reimbursement benefit
- Requirements:
  - Criteria 1: provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions
    - Demonstrate technical AND clinical success of device performance
  - Criteria 2: one or more of the following
    A. represent breakthrough technologies
    B. no approved or cleared alternatives exist
    C. offer significant advantages over existing approved or cleared alternatives, including the potential, compared to existing approved alternatives, to reduce or eliminate the need for hospitalization, improve patient quality of life, facilitate patients’ ability to manage their own care (such as through self-directed personal assistance), or establish long-term clinical efficiencies; or
    D. availability of which is in the best interest of patients

# Safer Technologies Program (STeP)

- FDA Goal: Encourage medical technology development and patient access under current pre-market review pathway (like Breakthrough Device Program)
- Benefits:
  - Increased FDA interaction to facilitate development - “Sprint Discussion”
  - Expedited review of pre-market submission (510(k), De Novo, PMA)
- NOT:
  - Marketing authorization (still need to submit 510(k), De Novo, or PMA)
- Requirements:
  - Criteria 1: should not be eligible for the Breakthrough Devices Program due to the less serious nature of the disease or condition treated, diagnosed, or prevented by the device
    - Demonstrate technical AND clinical success of device performance
  - Criteria 2: should be reasonably expected to significantly improve the benefit-risk profile of a treatment or diagnostic through substantial safety innovations that provide for one or more of the following:
    A. a reduction in the occurrence of a known serious adverse event,
    B. a reduction in the occurrence of a known device failure mode,
    C. a reduction in the occurrence of a known use-related hazard or use error, or
    D. an improvement in the safety of another device or intervention.

# Let's Pause to Ask Ourselves…

What pathway(s) should I be considering?

# Filing Logistics

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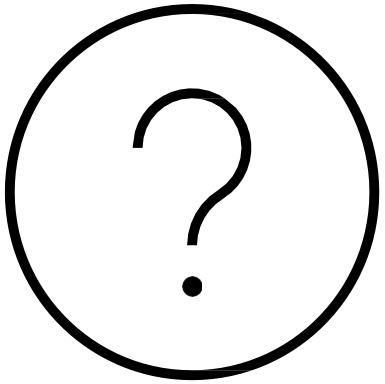
# MDUFA IV User Fees as of Oct 1, 2022

| Application Type | Standard Fee | Small Business Fee† |
|---|---|---|
| 510(k) | $19,870 | $4,967 |
| 513(g) | $5,961 | $2,980 |
| PMA, PDP, PMR, BLA | $441,547 | $110,387 |
| De Novo Classification Request | $132,464 | $33,116 |
| Panel-track Supplement | $353,238 | $88,309 |
| 180-Day Supplement | $66,232 | $16,558 |
| Real-Time Supplement | $30,908 | $7,727 |
| BLA Efficacy Supplement | $441,547 | $110,387 |
| 30-Day Notice | $7,065 | $3,532 |
| Annual Fee for Periodic Reporting on a Class III device (PMAs,PDPs) | $15,454 | $3,864 |

# Small Business Application

- A small business is defined as a business, including its affiliates, whose gross receipts and sales are less than $100 million for the most recent tax year.
- To apply, you must gather your tax documentation, obtain an organization ID, submit the application to FDA (Form 3602).
- This process could take several months, therefore, we recommend starting this now if you are interested in pursuing.
- Reduced Medical Device User Fees: Small Business Determination (SBD) Program | FDA

# Q&A



Thank you for your time and attention!

acadotte@mcra.com

MCRA Digital Health

# Northwestern Medicine Healthcare AI Forum

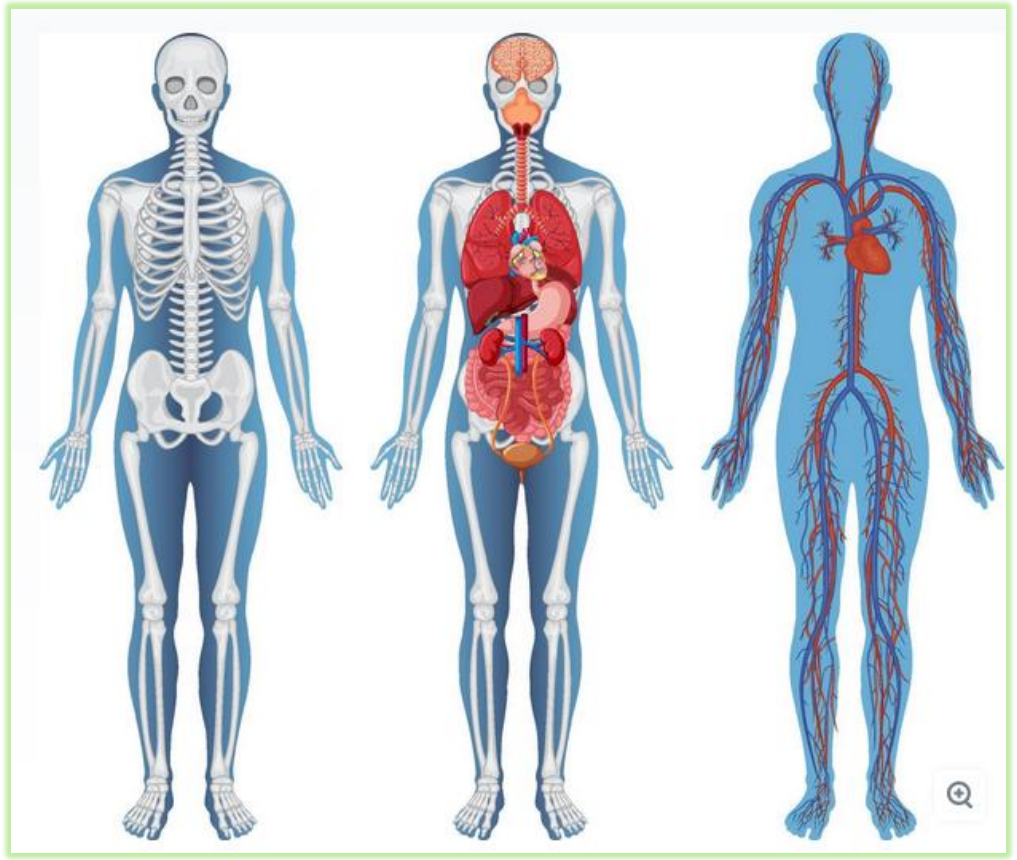
## MCRA AI & Imaging Center

**Nima Akhlaghi, PhD.**

**February 9, 2024**

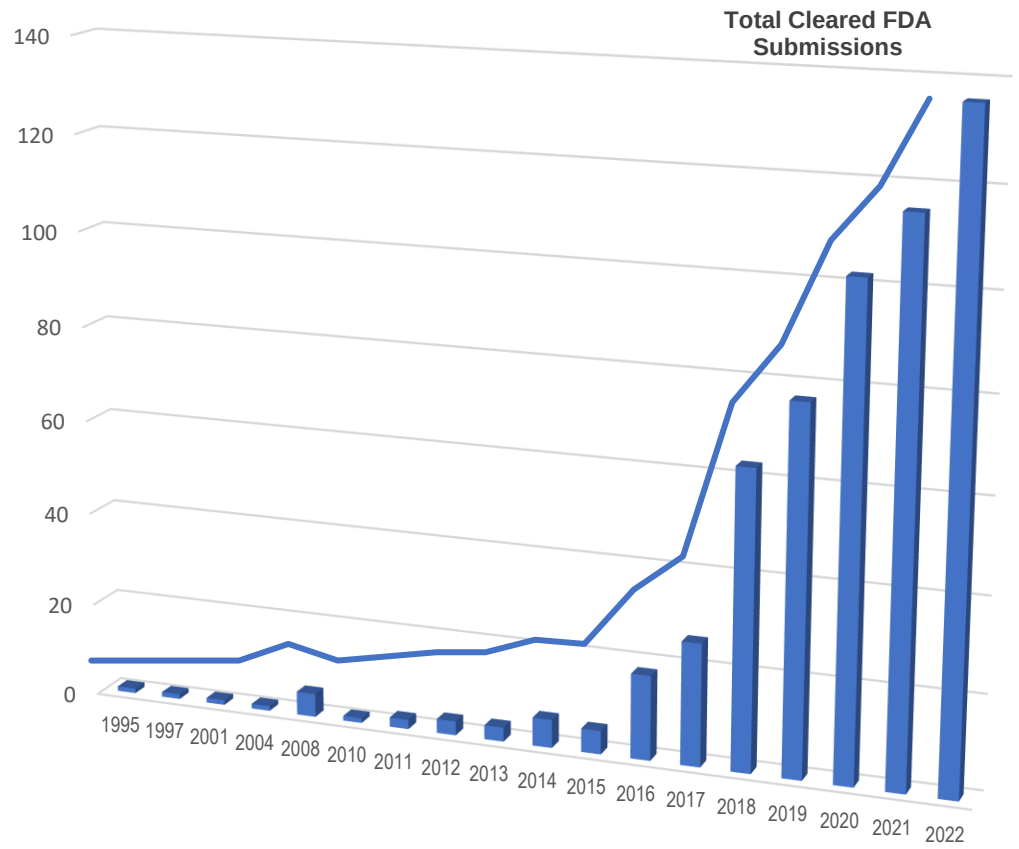
MCRA Digital Health

## Human Conditions



**>10,000 Conditions Needing AI Software**

## # FDA Software Approvals Since 1995




**>600 over 25 Years**
**2022/2023 over >160 Approvals**

## Assessment by American College of Radiology:

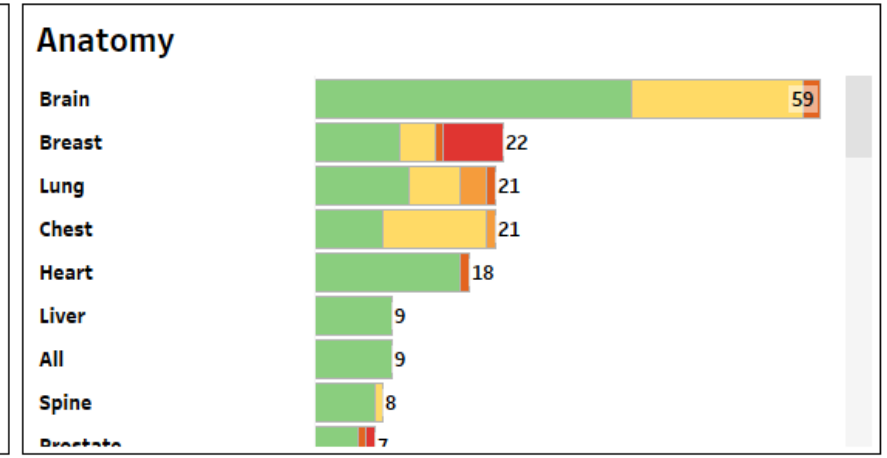
**TOTAL FDA CLEARED SAaMD PRODUCTS: 221**

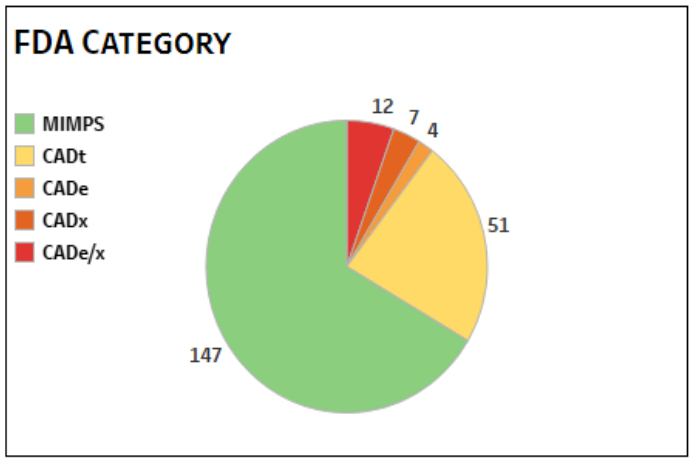
☑ Pediatric
☑ Adult

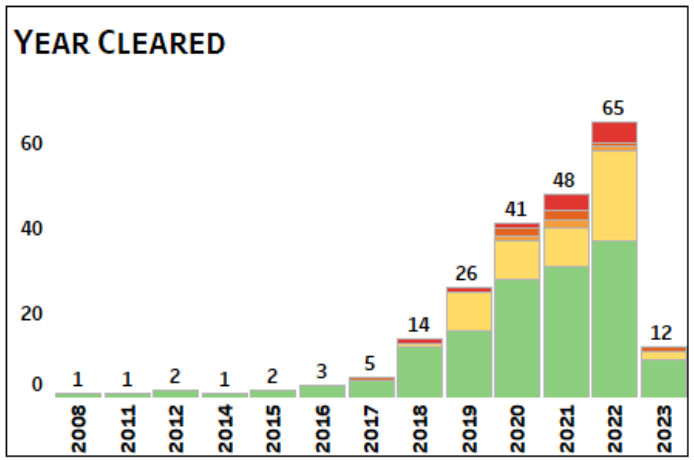
Company: (All)

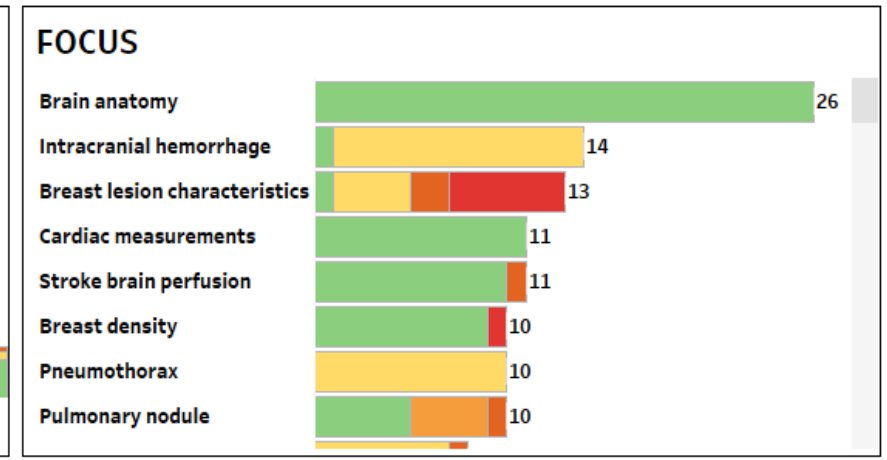
Date Cleared: 5/15/2008 – 2/24/2023

| Subspecialty | CT | MR | PET | US | XRAY/MAM |
|---|---|---|---|---|---|
| Abdominal | 13 | 19 | | 2 | 3 |
| Cardiac | 23 | 10 | 1 | 9 | 3 |
| Chest | 36 | 5 | | 2 | 19 |
| Musculoskeletal | 11 | 6 | | 2 | 12 |
| Neuroradiology | 53 | 31 | 2 | | 4 |
| Breast Imaging | 5 | 3 | | 4 | 21 |



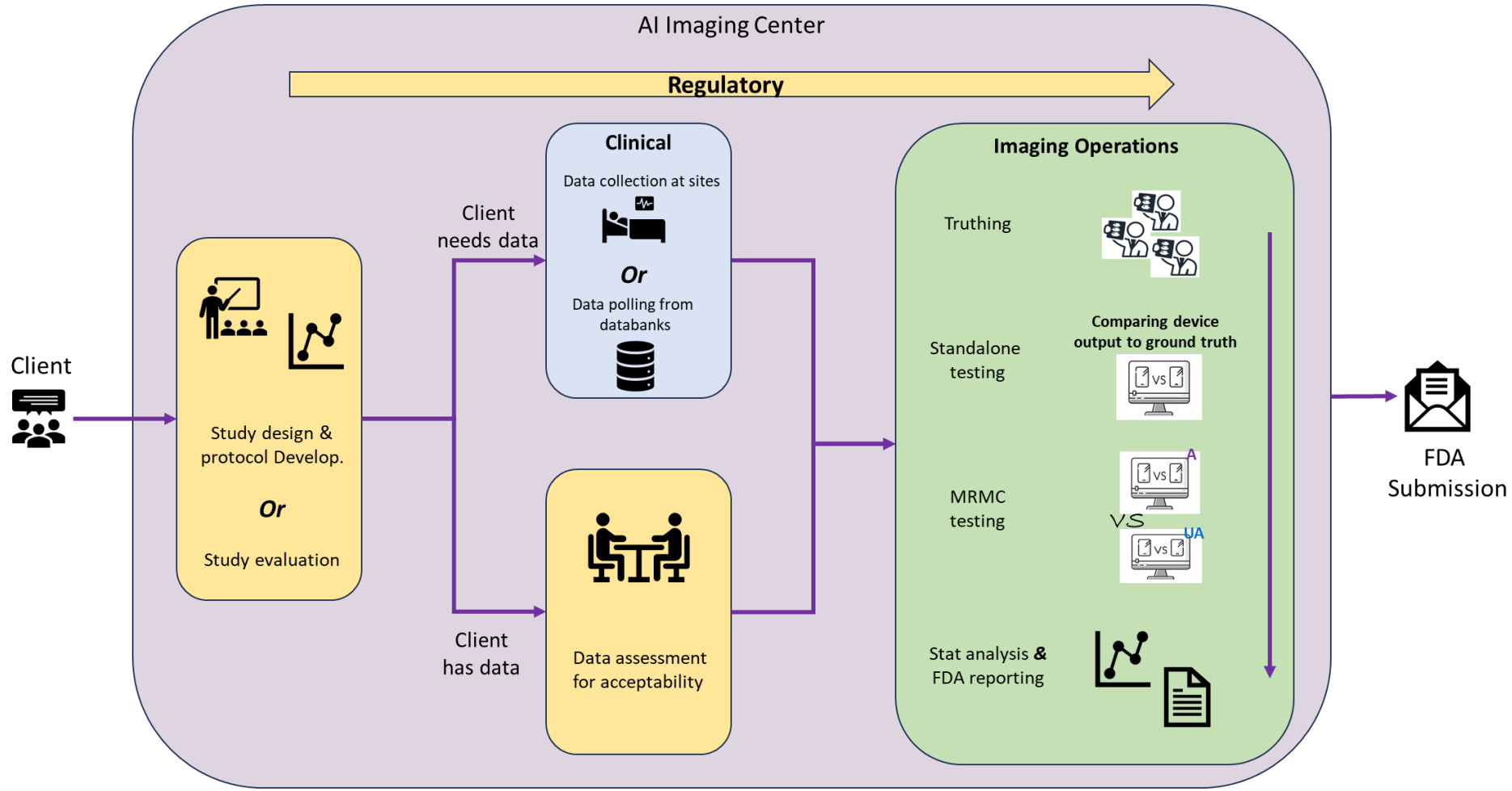




**Majority of FDA approvals are in therapeutic areas such Brain, Breast, Lung and Chest.**

# AI & Imaging Center - Workflow (Integrated solution for Study Lifecycle)



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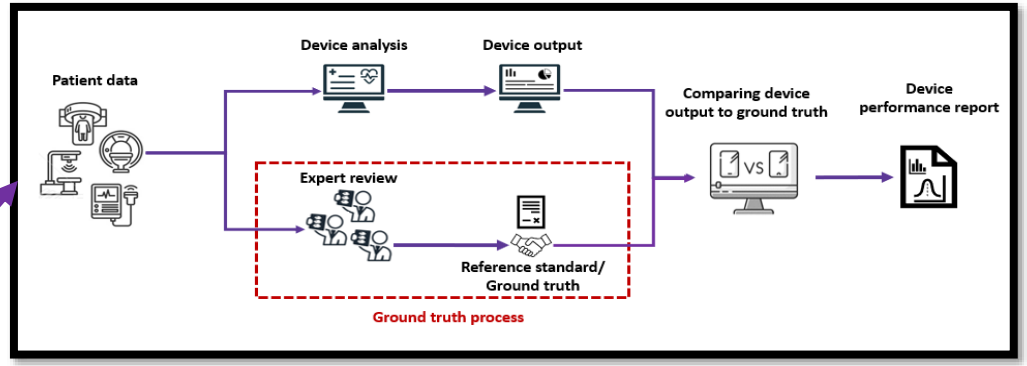
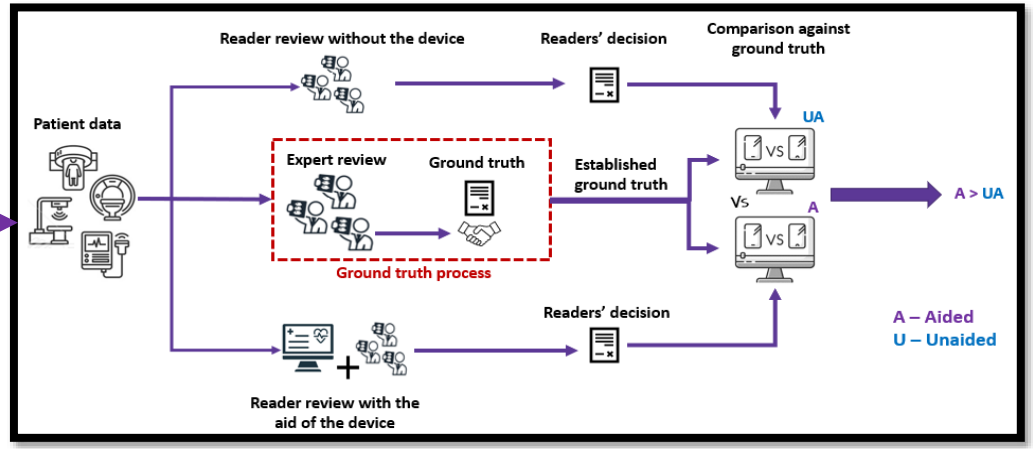
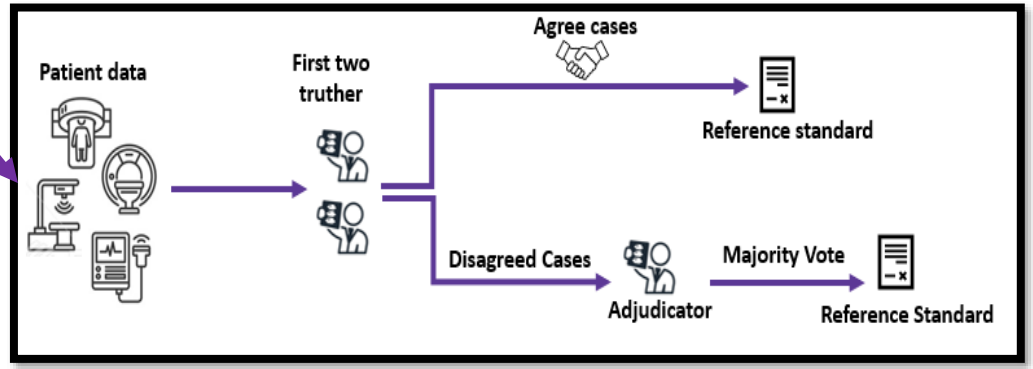
## Retrospective Studies

**Read by experts <u>without impact</u> on patient care**

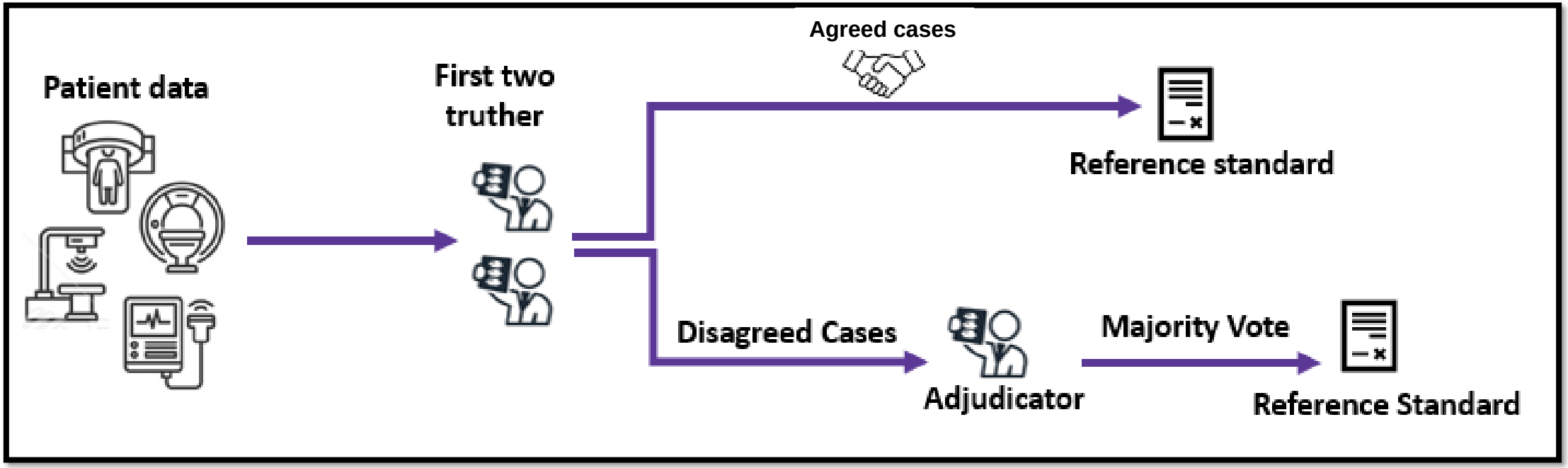


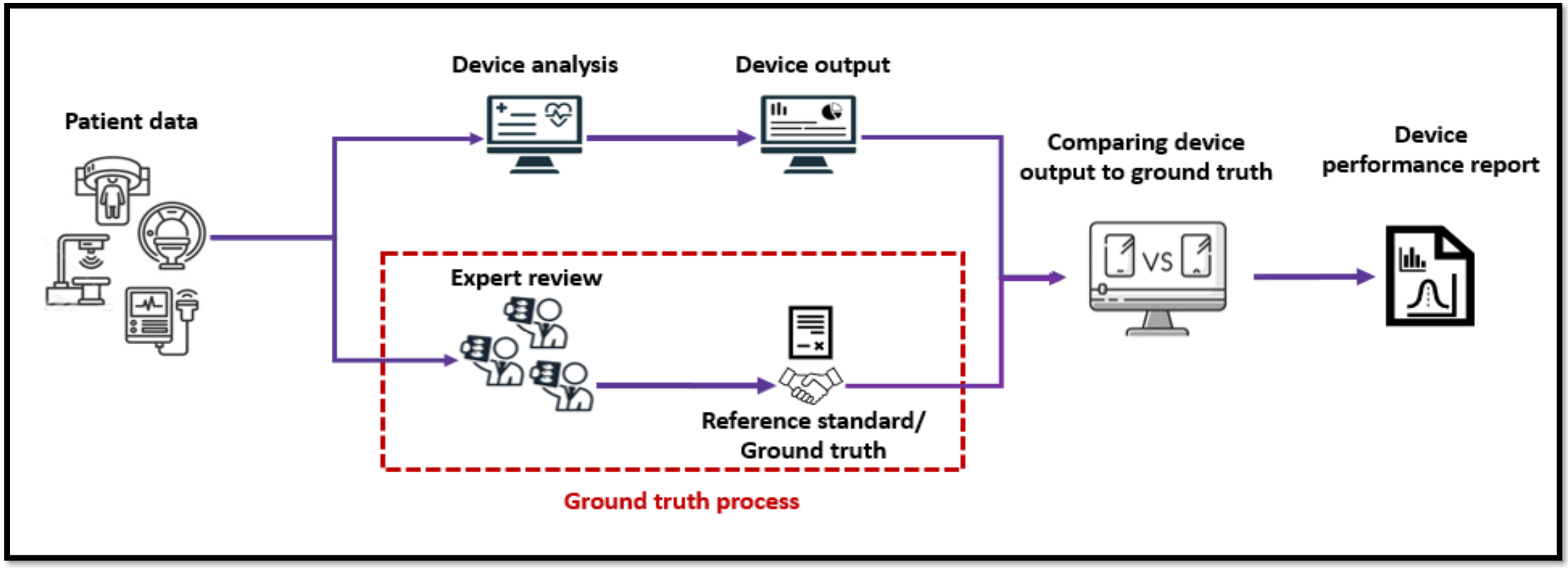
## Ground Truthing

- Establish reference standard based on Standard of Care (SOC) to compare to device output.



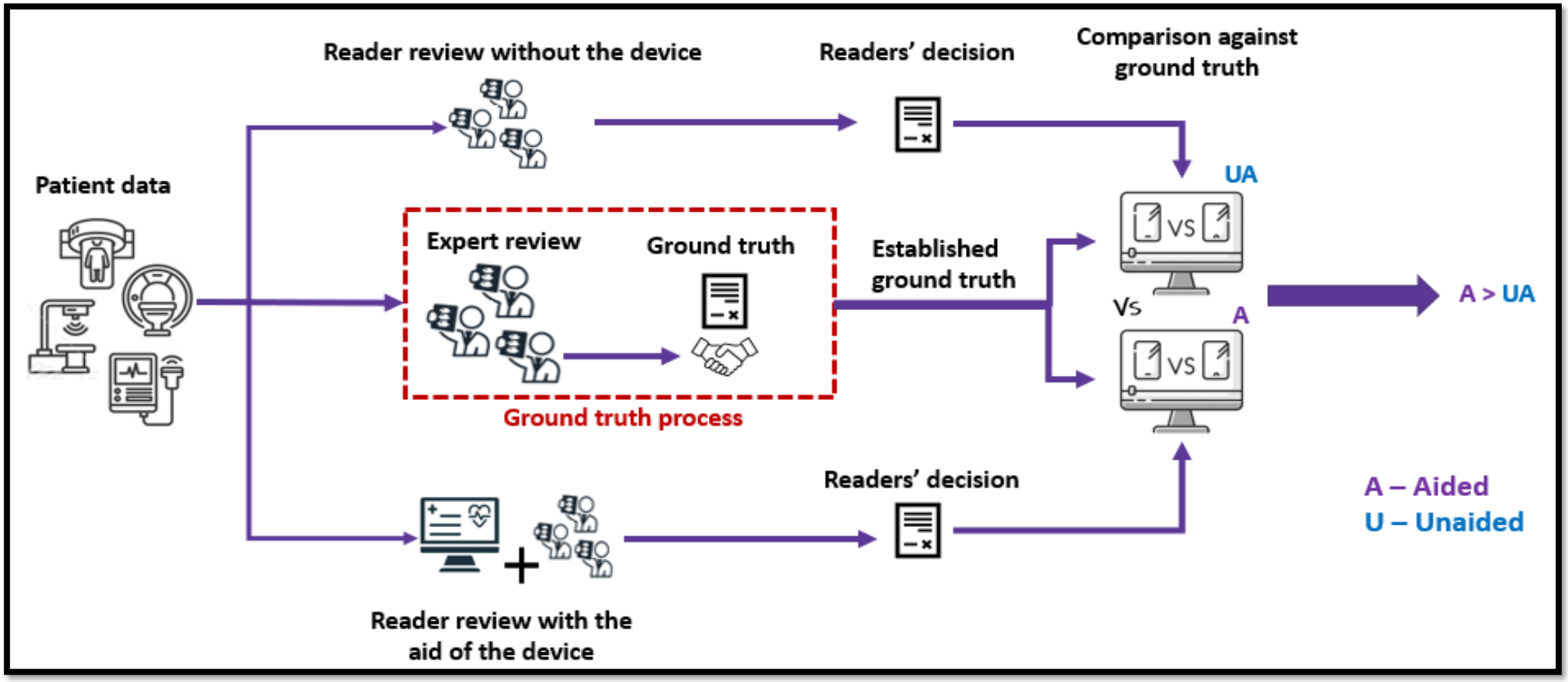
# Stand Alone Testing

- Comparing device output to reference standard



# Multi-Reader, Multi-Case

- Comparing Aided vs Un-Aided performance against established reference standard



MCRA Digital Health

# Thank you

MCRA Digital Health