FDA Regulatory Considerations: Pathways for Innovative, Safe and Effective Dental Medical Products

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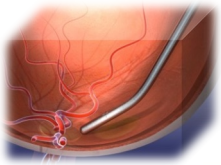
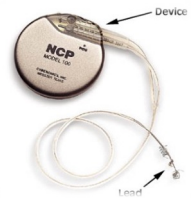
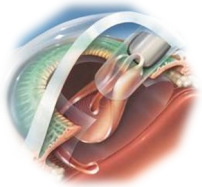
Center for Devices and Radiological Health (CDRH) Regulates Medical Devices





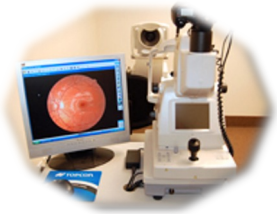









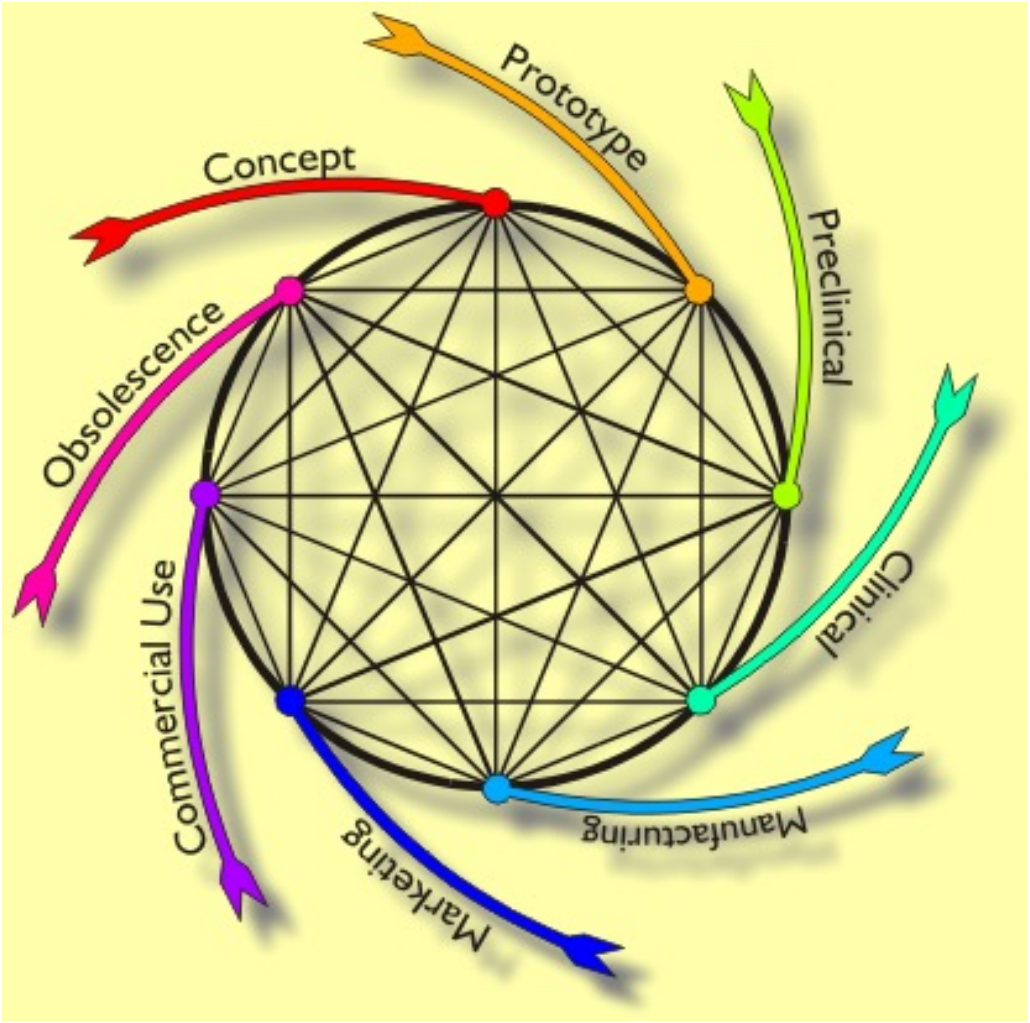




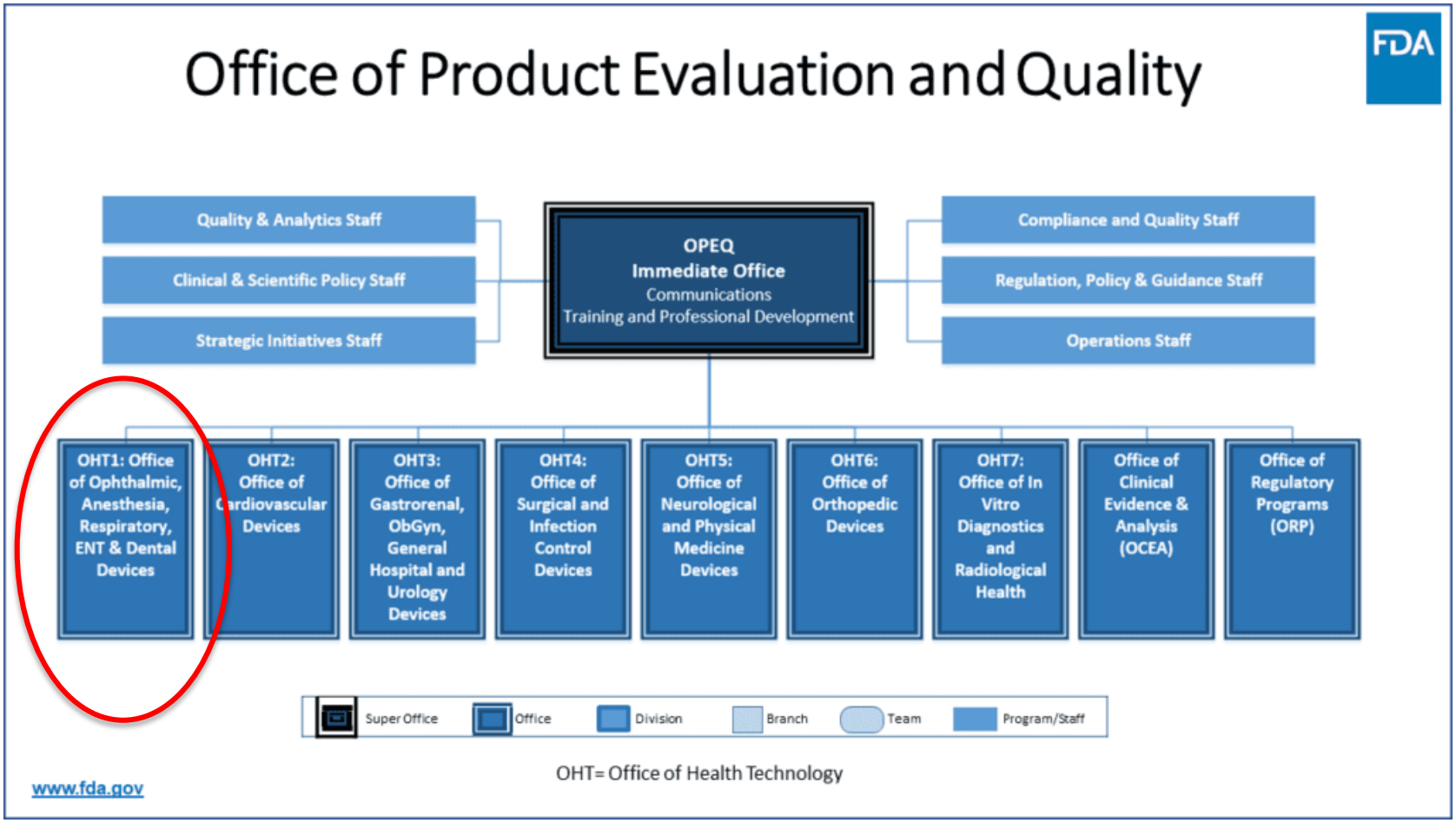

CDRH Mission

- The mission of the Center for Devices and Radiological Health (CDRH) is to protect and promote the public health.
- We assure that patients and providers have timely and continued access to safe, effective, and high-quality medical devices and safe radiation-emitting products.
- We provide consumers, patients, their caregivers, and providers with understandable and accessible science-based information about the products we oversee.
- We facilitate medical device innovation by advancing regulatory science, providing industry with predictable, consistent, transparent, and efficient regulatory pathways, and assuring consumer confidence in devices marketed in the U.S.

Total Product Lifecycle



Total Product Lifecycle (TPLC) Organization

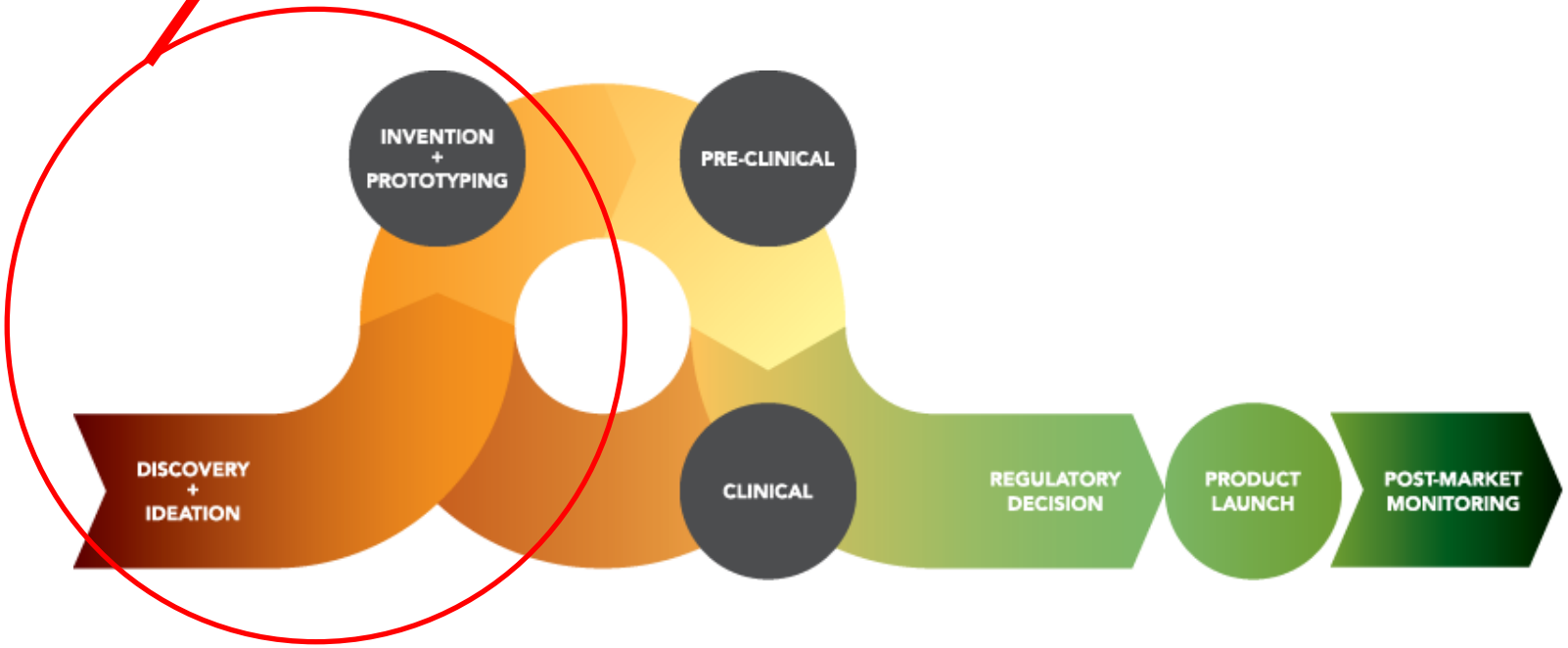


DEVICE INNOVATION IN CDRH

- CDRH Innovation activities that help accelerate patient access to safe, effective, and innovative medical devices: https://www.fda.gov/about-fda/center-devices-and-radiological-health/cdrh-innovation
- Provide early regulatory assistance to innovators and small businesses
  - ✓ Informational meetings
  - ✓ Pre-submissions

  https://www.fda.gov/media/114034/download
- Using Regulatory Science tools such as:
  - ✓ Consensus standards (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/search.cfm)
  - ✓ FDA Guidance documents (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/guidance-documents-medical-devices-and-radiation-emitting-products
  - ✓ Medical Device Development Tools (https://www.fda.gov/medical-devices/medical-device-development-tools-mddt)
  - ✓ Other (https://www.fda.gov/medical-devices/science-and-research-medical-devices/catalog-regulatory-science-tools-help-assess-new-medical-devices)

- **Product Type /Classification (RFD)**
- **IFU (HUD)**
- **Summaries of Approvals/Clearances**
- **FDA Meeting / Q - sub**



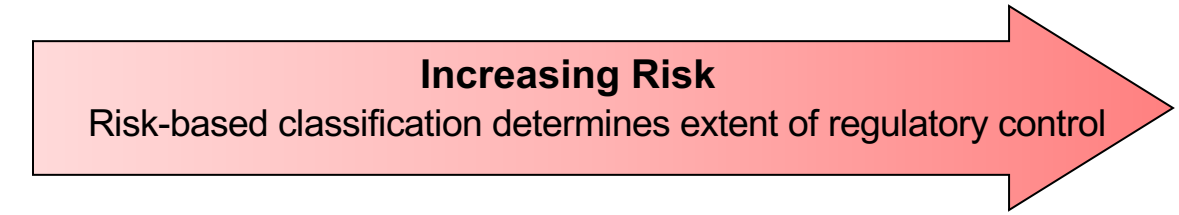
Dental Products

- Biological Product
- Drug
- Device
- Combination Product

It is a Medical Device if it:

- Diagnoses, Cures, Mitigates, Treats or Prevents a Disease or Condition, or
- Affects the Function or Structure or the Body, and
- Does Not Achieve Intended Use Through Chemical Action, and
- Is Not Metabolized

Risk-Based Oversight of Medical Devices



Class I
- General Controls
- Most exempt

Class II
- General controls
- Special controls
- Typically 510(k)

Class III
- General controls
- Premarket approval (PMA)

General Controls
- Prohibition of adulteration, misbranding
- Registration of Facilities
- Electronic Device Listing
- Premarket Notification [510(k)] (unless exempt)
- Quality Systems
- Labeling
- Medical Device Reporting (MDR)

Special Controls (addressing Risk)
- Guidelines (e.g., Glove Manual)
- Mandatory Performance Standard
- Recommendations or Other Actions
- Special Labeling (e.g., 882.5970, Cranial Orthosis)

Dental Device examples

Class	Examples
Class I	Toothbrush, Manual and Powered Orthodontic appliances Handpieces
Class II	Dental composites Intraoral devices (snoring and OSA) Aligners Bone cutting drills Stereotaxic navigation systems Dental Implants Bone plates Bone grafting materials Tympanostomy Tube
Class III	TMJ implants Bone grafting materials (combination product)

FDA Resources

- Device Classification and Advice

  www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/default.htm

  Device Advice: Comprehensive Regulatory Assistance | FDA

- Request for Information (513(g))
  - Means for obtaining the agency's views about the classification/regulatory requirements that may be applicable to a particular device

  http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm209841.htm

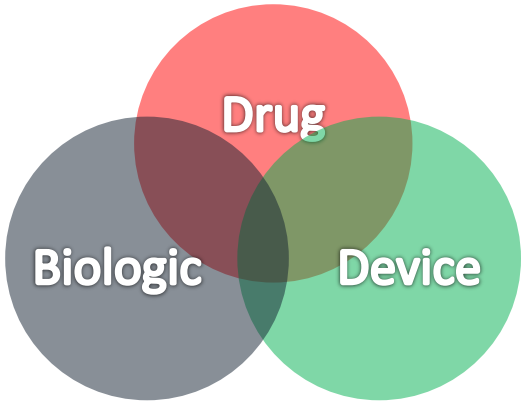
Premarket Submission Types

- A **510(k)** is a premarketing submission made to FDA to demonstrate that the device to be marketed is as safe and effective, that is, substantially equivalent (SE), to a legally marketed device (predicate) that is not subject to premarket approval (PMA)
- **Premarket Approval (PMA)** is the most stringent type of device marketing application required by FDA. A PMA is an application submitted to FDA to request approval to market. Unlike premarket notification, PMA approval is to be based on a determination by FDA that the PMA contains sufficient valid scientific evidence that provides reasonable assurance that the device is safe and effective for its intended use or uses
- A Humanitarian Use Device (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 8,000 individuals in the United States per year. An **HDE application** for a HUD is similar in both form and content to a premarket approval (PMA) application, but is exempt from the effectiveness requirements of a PMA
- The **de novo classification** option provides an alternate pathway to classify novel devices of low to moderate risk that do not have a legally marketed predicate device. Devices that are classified through the de novo process may be marketed and used as predicates for future 510(k) submissions

What is a Combination Product?

Combinations of 2 or more DIFFERENT products:

- Drug + Device
- Device + Biologic
- Drug + Biologic
- Drug + Device + Biologic



How do I get a Classification / Center Jurisdiction Assignment?

- Informal guidance:
  - Email: combination@fda.gov
  - Simple issues, uncertainty, process concerns
  - Determine whether an RFD is needed
  - Non-binding; can submit RFD if disagree with informal guidance
- Formal process:
  - Submit a Request for Designation (RFD)
  - Formal, binding determination – **60** days
  - Complex issues or dispute / uncertainty
  - Requirements in 21 CFR 3.7

When to submit an RFD or informal inquiry?

Submit an RFD or informal inquiry **BEFORE** any submission (i.e., pre-submission / marketing submission)

<u>Why?</u>

FDA may stop the review clock
while a determination is being made
(21 CFR 3.10)

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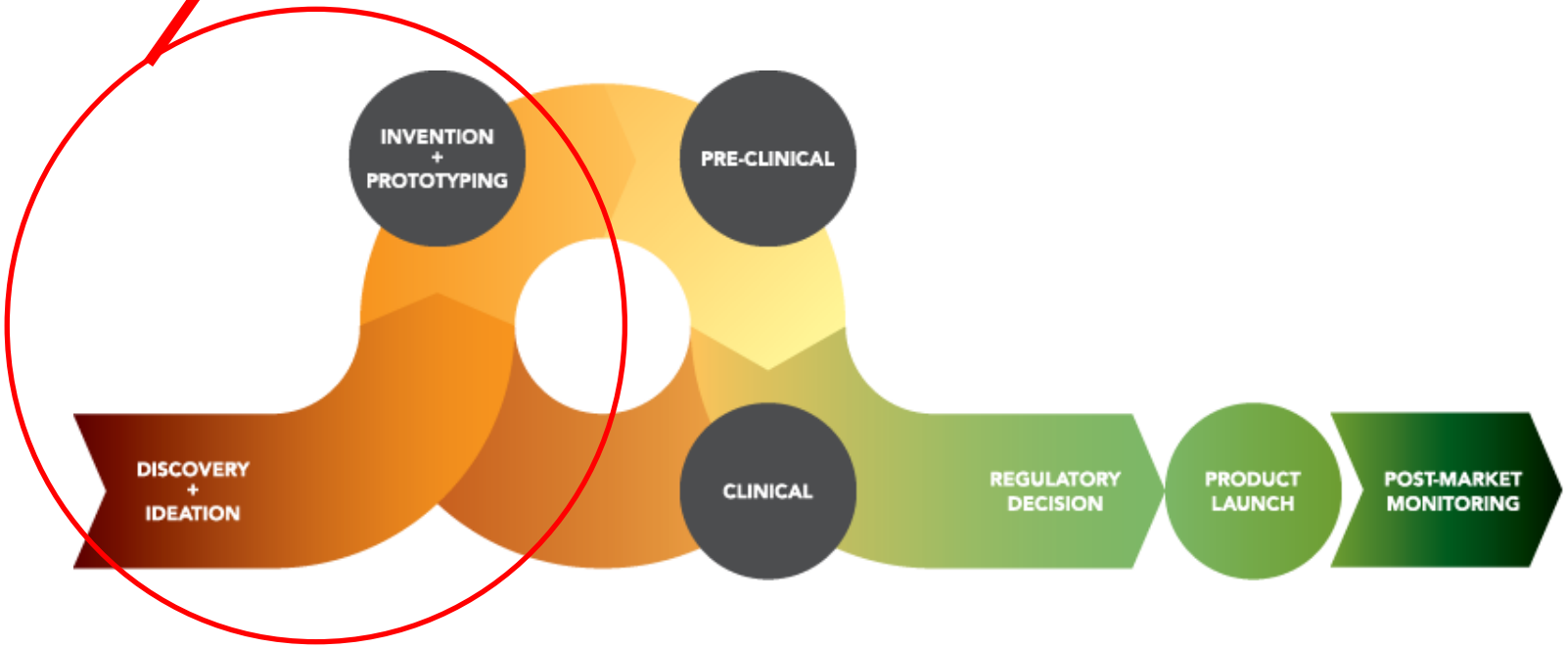


Indication for Use (IFU)

- General description of the disease or condition the device will diagnose, treat, prevent, cure or mitigate, including a description of the patient population for which the device is intended [21 CFR 814.20]
  - Clinical/non-clinical study design informed by the IFU

HUD Definition

A Humanitarian Use Device (HUD) is a medical device intended to benefit patients in treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8,000 individuals per year in the United States.

https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/humanitarian-use-device-hud-designation-program

HDE Approval

- **Safety**
  - does not pose unreasonable risk of illness or injury
  - same threshold as PMA devices

- **Probable benefit**
  - outweighs the risks of using the device, taking into account the probable risks and benefits of alternative therapies
  - exempt from effectiveness
  - different from PMA devices (reasonable assurance of effectiveness)

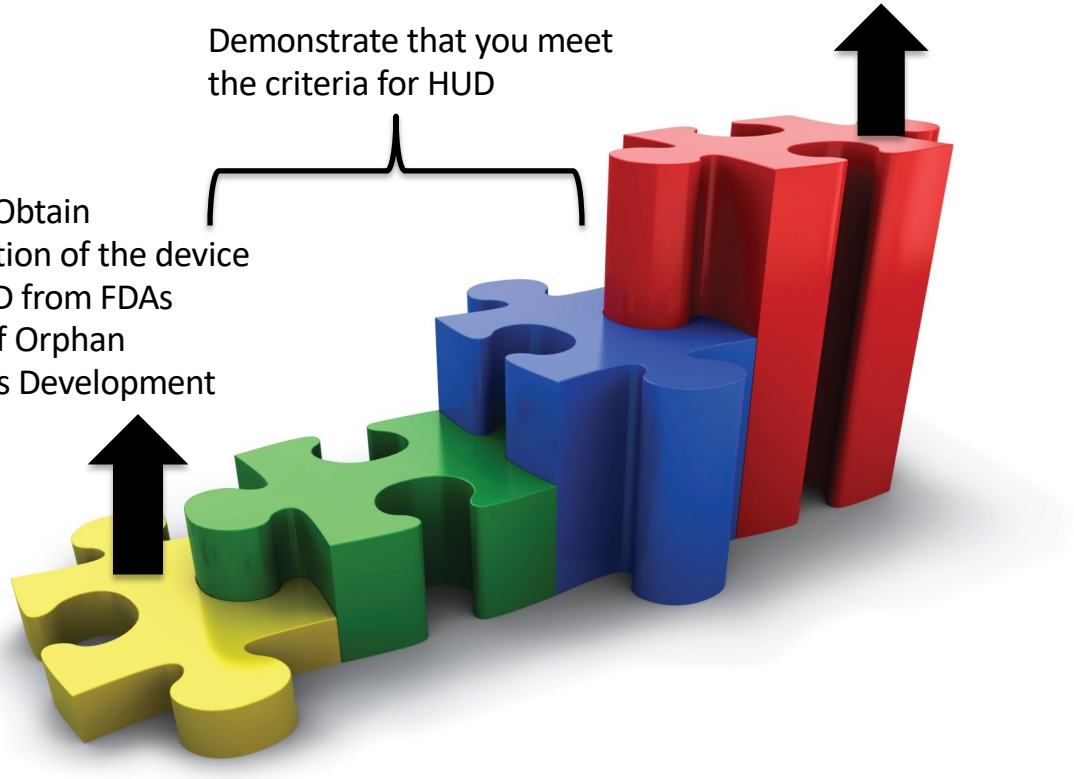
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/humanitarian-device-exemption-hde-program

HDE Application Process

Step 2: After HUD is granted, submit an IDE/HDE application to CDRH/CBER

Demonstrate that you meet the criteria for HUD

Step 1: Obtain designation of the device as a HUD from FDAs Office of Orphan Products Development (OOPD)



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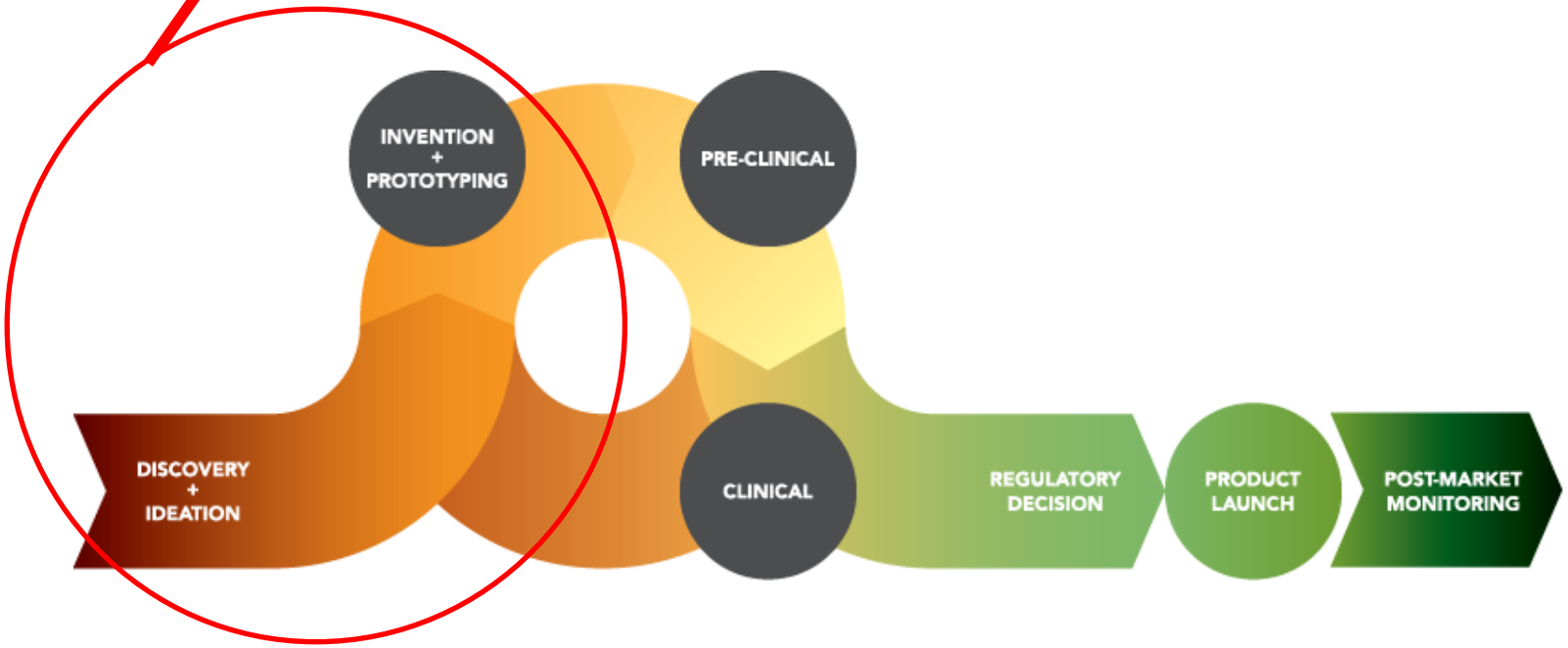

FDA Resources: Summaries

- Summary of Safety and Effectiveness
  - http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm
- Summary of Safety and Probable Benefit
  - http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/HDEApprovals/ucm161827.htm
- 510(k) Summaries
  - http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/510kClearances/default.htm
- De Novo Summaries
  - https://www.fda.gov/about-fda/cdrh-transparency/evaluation-automatic-class-iii-designation-de-novo-summaries

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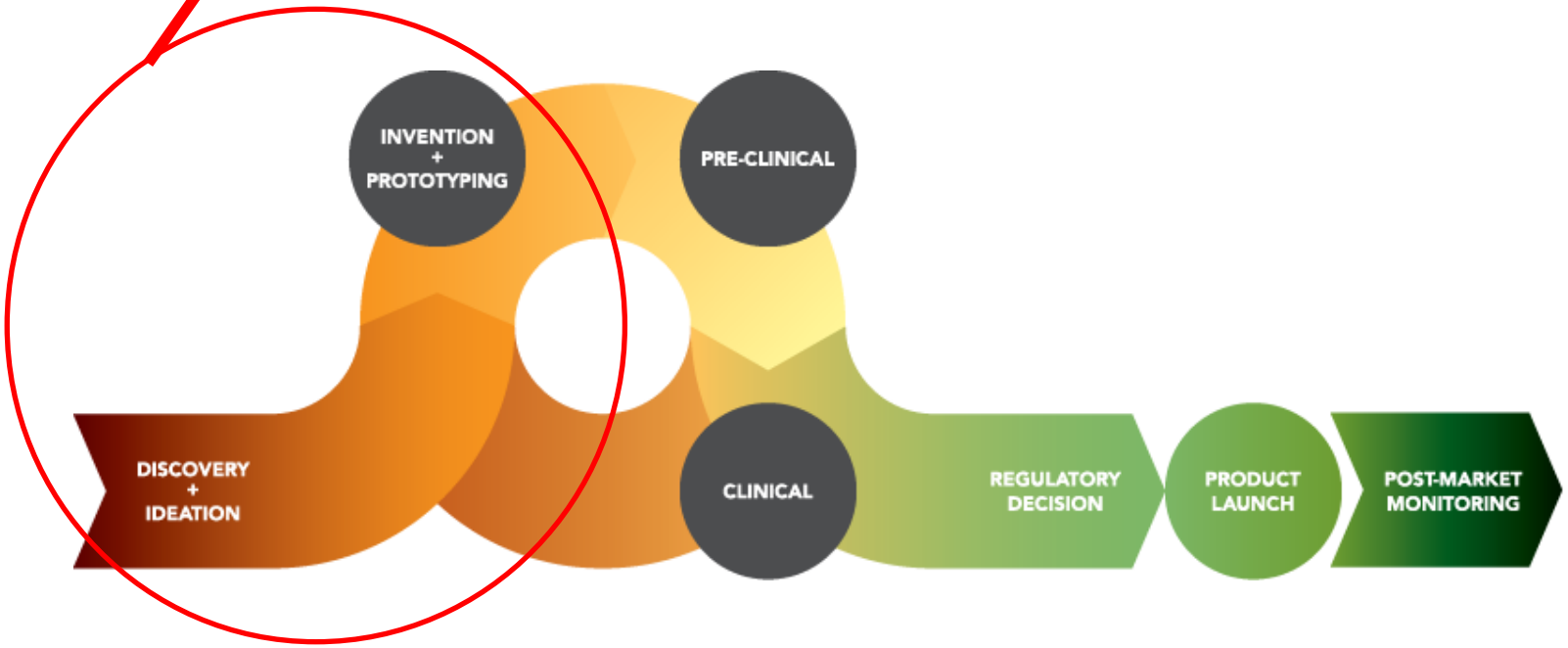


Q-submission Program

- The Q-Submission Program provides a mechanism to request interactions with the FDA related to medical device submissions
- Q-sub guidance: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf.
- Feedback mechanisms addressed in guidance:
  - Pre-Submissions
  - Informational Meetings
  - Study Risk Determinations
  - Formal Early Collaboration Meetings
  - Submission Issue Requests
  - Day 100 Meetings for PMA Applicants

Q-Sub type: Pre-Submissions

- Facilitates device development / innovation by providing FDA feedback on proposed:
  - Preclinical testing plan
  - Animal Study design
  - Clinical trial design (e.g., control group, endpoints, inclusion/exclusion criteria, statistical analysis plan)
  - Proposed indications for use
- Provides an opportunity for a meeting/teleconference with the FDA
  - Within 75-90 calendar days (21 days for submission issues)
  - Written feedback 5 days before teleconference/meeting or by Day 70 if meeting is set for later date
  - No user fee
  - Written email feedback only is also an option

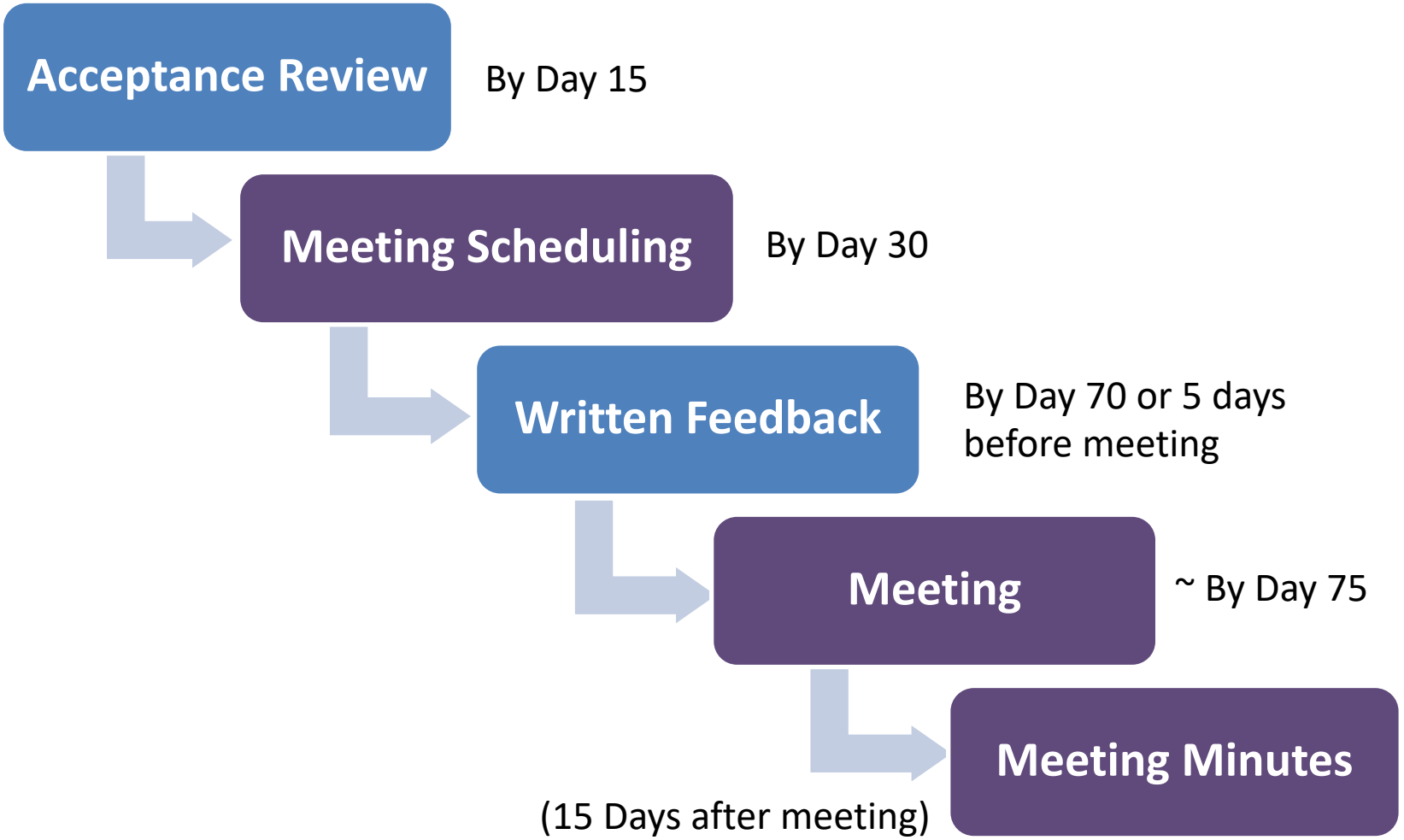
Key Information in a Pre-submission

- Detailed Device Description
- Proposed Intended Use/Indications for Use
- Summary of Previous Discussions or Pre-Submissions or Submissions Regarding the Same Device
- Specific Questions for FDA Feedback
- Preferred method to receive FDA Feedback
- *Meeting Format, Preferred Dates and Times, Planned Attendees, and Audiovisual Equipment Needs, if meeting or teleconference is requested*

Pre-Submission Reminders

- FDA review of a Pre-Sub does not guarantee approval or clearance of future premarket submissions
- FDA intends to stand behind their feedback
- Sponsors should reference Pre-Sub feedback received in subsequent submissions

Pre-Submission Process



Preparing your Pre-Submission

Do

- While conducting research consider when initial interactions with FDA would be helpful
- Include only relevant information in your package
- Include specific questions you wish to ask the FDA

Don't

- Have broad questions
- Have too many questions
- Expect a pre-review of your marketing submission

The Meeting

Do

- Use FDA's written feedback to refine your meeting agenda
- Plan the meeting time (usually 1 hour) to get most out of it (e.g., prepare slides and send to FDA in advance if possible)
- Ensure the right people are at the meeting

Don't

- Feel obligated to hold meeting if written feedback meets needs
- Don't expect immediate FDA feedback on significant new information presented during the meeting

After the Meeting

Do

- Do submit meeting minutes within 15 days
- Check in if significant time has elapsed since receiving feedback
- Include summary of Pre-Sub discussions in subsequent pre-market submissions and how you addressed feedback

Don't

- Include new discussion topics in the meeting minutes and expect FDA feedback on these

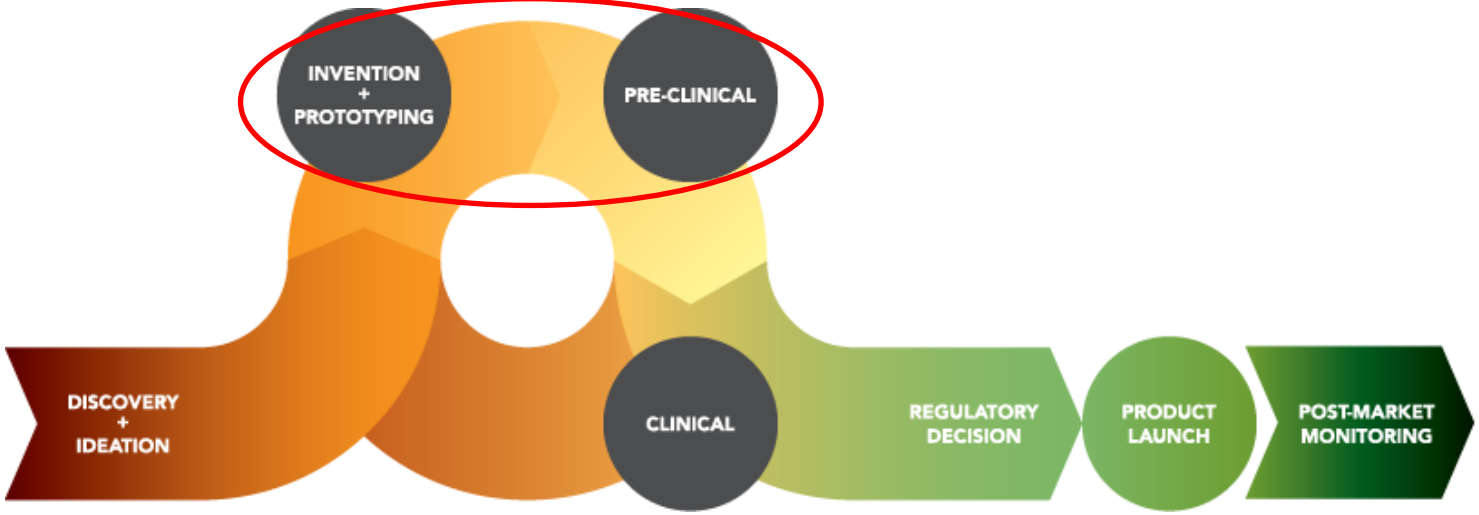
Q-Sub Type: Informational Meeting

- A meeting with the intent to share information with FDA without the expectation of receiving feedback
- FDA is in listening mode
- Timeframe: 90 days, resource permitting
- Provide an overview of ongoing device development
- Familiarize reviewers about new device with significant differences in technology from currently available devices

Q-Sub Type: Study Risk Determination

- FDA will help sponsors, clinical investigators, or institutional review boards (IRB) make a study risk determination for not exempt studies
- FDA will provide a study determination letter
- Detailed Device Description and how it will be used in the study
- Clinical Study Protocol
- Description of the study population

- Q-Sub
- Guidance / Standards
- Pre-clinical
- MDDT



FDA Guidance

- Guidance describes FDA's interpretation of, or policy on, a regulatory issue
  - Submissions
  - Labeling
  - Manufacturing
- Guidance for Clinical Studies
  - Regulatory Pathway
  - Study Design
  - Data Analysis
- Check availability of FDA Guidance

  www.fda.gov/cdrh/guidance.html

Recognized Standards

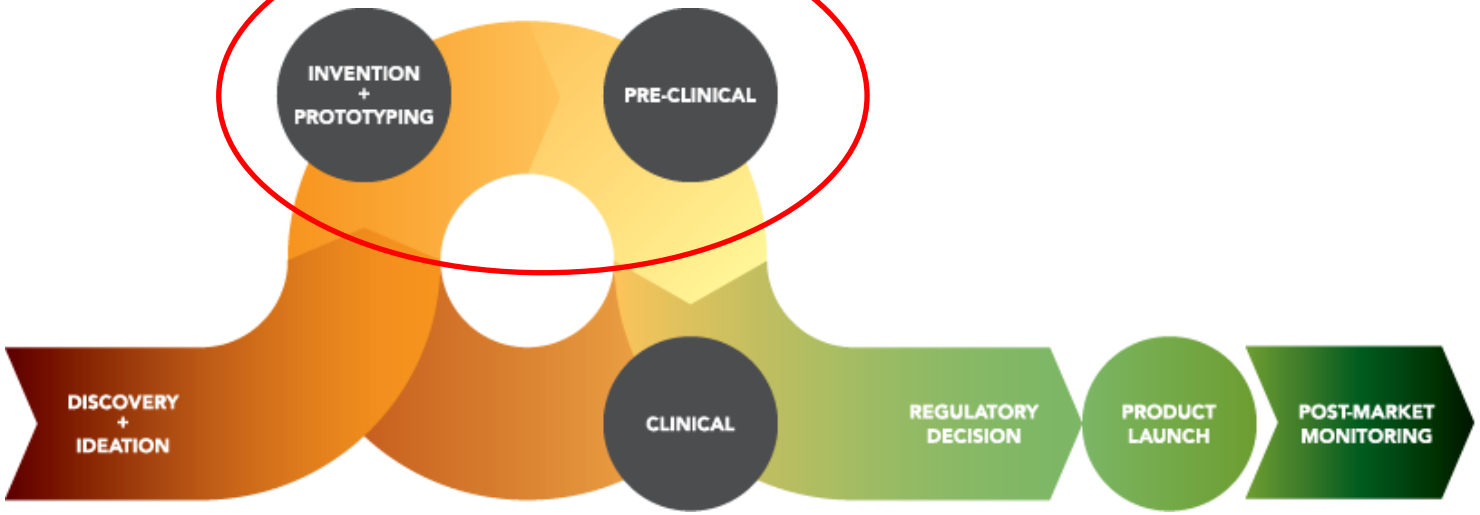
- A consensus standard which FDA has recognized for use in satisfying a premarket submission requirement

- Outlines:
  - Parameters needed for evaluation of a specific device
  - Pre-clinical testing needed prior to human testing
  - Recommended clinical trial

- Check recognized Standards

www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

- Q-Sub
- Guidance / Standards
- Pre-clinical
- MDDT



Pre-Clinical Testing

- Bench performance testing
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recommended-content-and-format-non-clinical-bench-performance-testing-information-premarket
- Animal/cadaver/model testing for preclinical safety (and performance)
  - General Considerations for Animal Studies Intended to Evaluate Medical Devices
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-considerations-animal-studies-intended-evaluate-medical-devices
- Biocompatibility testing
  - Use of International Standard ISO 10993-1
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-international-standard-iso-10993-1-biological-evaluation-medical-devices-part-1-evaluation-and
- Sterility/Viral Inactivation
  - https://www.fda.gov/medical-devices/general-hospital-devices-and-supplies/sterilization-medical-devices
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/medical-devices-containing-materials-derived-animal-sources-except-in-vitro-diagnostic-devices

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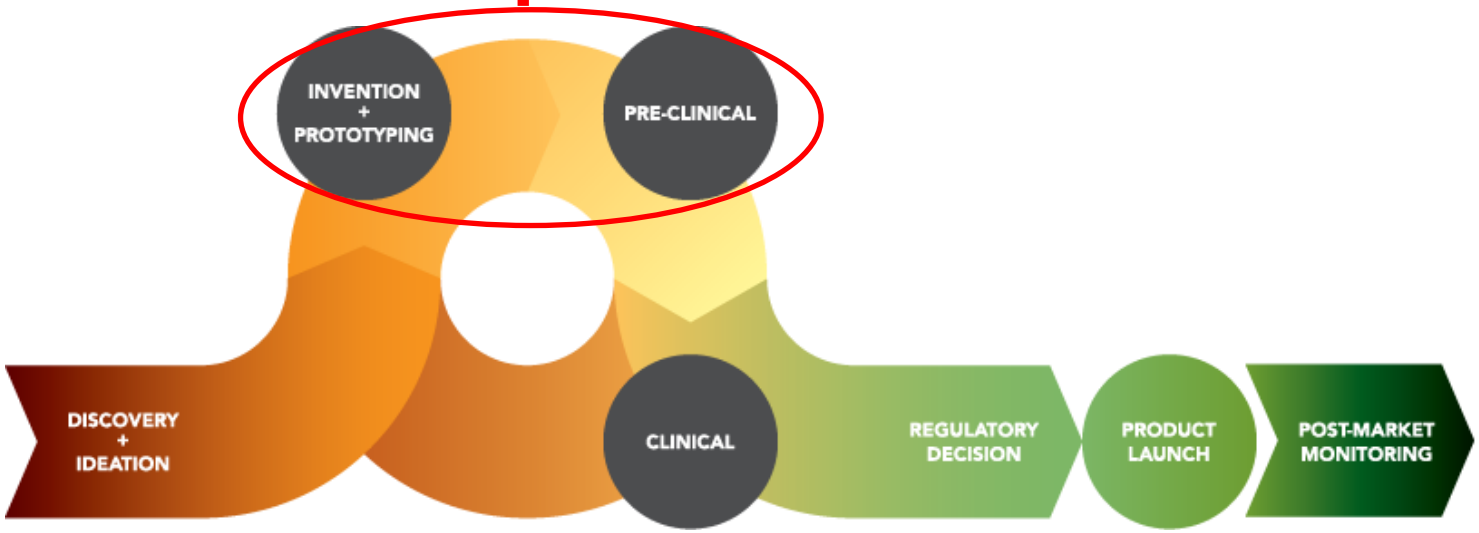


Medical Device Development Tool (MDDT)

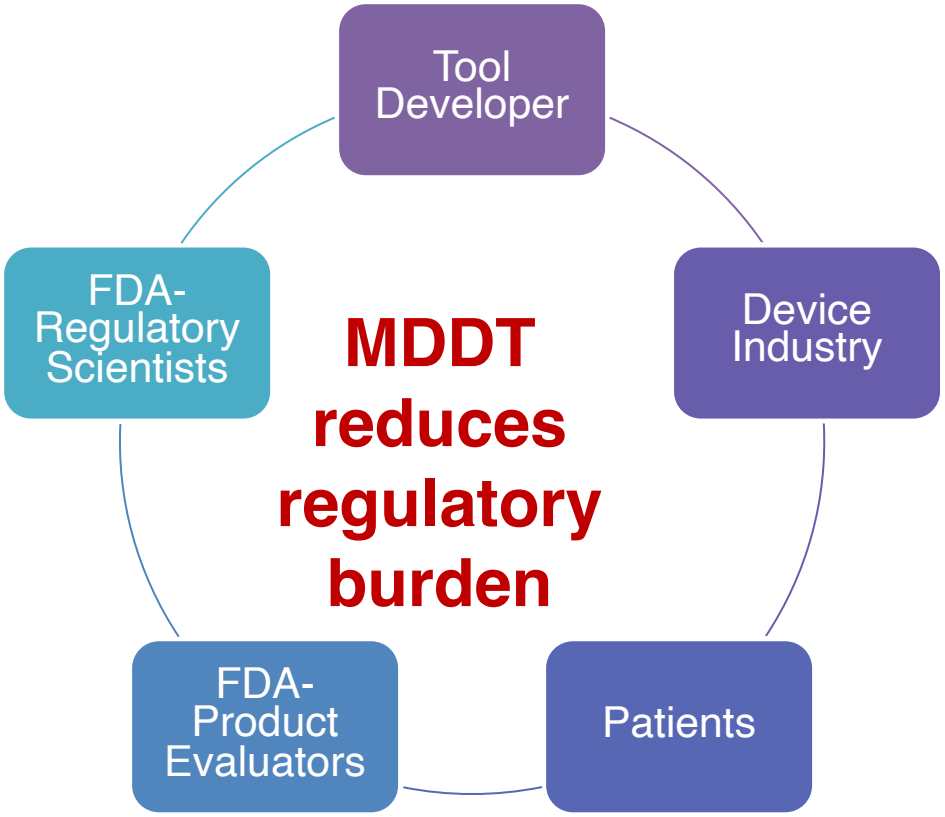
- **Medical Device Development Tool (MDDT)** is a method, material, or measurement used to assess effectiveness, safety, or performance of a medical device
  - MDDT Categories: Clinical Outcome Assessment (COA), Biomarker Test (BT), Nonclinical Assessment Model (NAM)
  - A MDDT is scientifically validated and qualified for a specific ***Context Of Use*** (COU) on the way the MDDT should be used
  - Qualification is an FDA conclusion that within the COU a MDDT has a specific interpretation and application in medical device development and regulatory review

Website:
http://www.fda.gov/MedicalDevices/ScienceandResearch/MedicalDeviceDevelopmentToolsMDDT/default.htm

Questions? email: MDDT@fda.hhs.gov

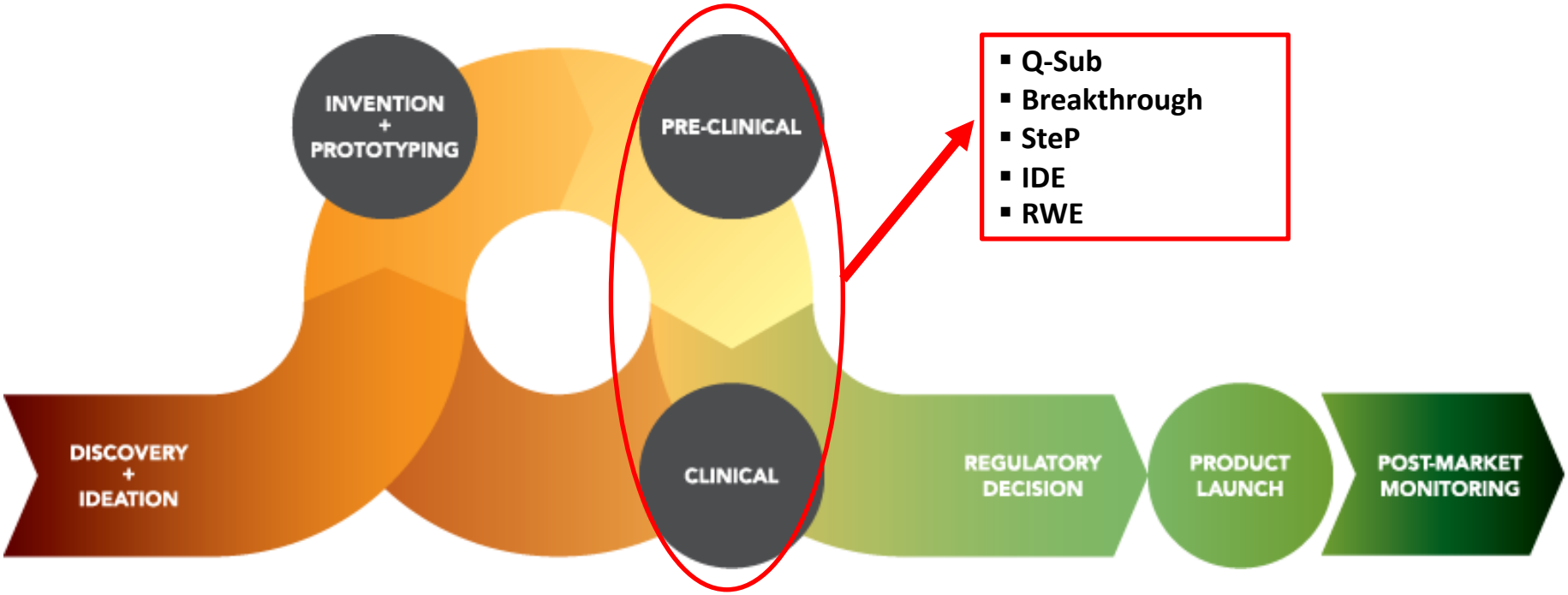
Medical Device Development Tool Program

Promotes Efficient Medical Device Development



Benefit of Qualifying Tools

- Fosters innovation
- Encourages collaboration
- Reduces resource expenditure
- Qualified MDDT applied in multiple device submissions
- Promotes efficiency in CDRH regulatory review resources
- Minimizes uncertainty in regulatory review process


INVENTION + PROTOTYPING
PRE-CLINICAL
CLINICAL
DISCOVERY + IDEATION
REGULATORY DECISION
PRODUCT LAUNCH
POST-MARKET MONITORING
Q-Sub
Breakthrough
SteP
IDE
RWE

Breakthrough Device Program

- Medical devices and CDRH led combination products
- Timely Interactions with FDA review team
- Identify areas of agreement
- Senior Management Engagement
- Priority Review
- https://www.fda.gov/medical-devices/how-study-and-market-your-device/breakthrough-devices-program

Criteria for Breakthrough Devices

- More effective treatment or diagnosis of life threatening or irreversibly debilitating disease

+

<u>At least one of the following:</u>

- Represents breakthrough technology
- No approved or cleared alternatives exist
- Offers significant advantages over existing approved/cleared alternatives
- Availability is in the best interest of patients (e.g., addresses an unmet medical need)

Breakthrough Device Process

Designation Request Q-Submission

- Applicant provides device description, proposed indication, rationale for meeting statutory eligibility criteria
- 60 day review clock

Follow On Q-Submissions

- Data Development Plan collaboration (optional)
- Requests for feedback similar to Pre-Submissions (highly interactive, prioritized review)
- Regular status updates in between submissions

IDEs and Marketing Submissions for Granted Breakthrough Devices

- Prioritized review, senior management involvement
- Potential to accept greater uncertainty for approval with the possibility of post-market data component

Safer Technologies Program (SteP)

- Medical devices and CDRH led combination products
- Reasonably expected to significantly improve the safety of currently available treatments or diagnostics that target an underlying disease or condition associated with morbidities and mortalities less serious than those eligible for the Breakthrough Devices Program
- Interactive and timely communications, early engagement on Data Development Plans, sprint discussions, and senior management engagement to support the program, as resources permit
- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safer-technologies-program-medical-devices

SteP Justification

- Justification for Meeting Specific STeP Eligibility Factors Eligibility Factor
  - 1: The device seeking inclusion in STeP is “not eligible for the Breakthrough Devices Program due to the less serious nature of the disease or condition treated, diagnosed, or prevented by the device.”
    - This section should provide a discussion regarding how the Eligibility Factor 1 is met by the proposed device and indications for use
- Eligibility Factor 2: The device seeking inclusion in STeP is 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.

Early Feasibility Study (EFS) Program

- Goal
  - Encouraging innovation in the US by supporting the study of new technology
- Guidance
  - http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279103.pdf
- Key Principle
  - Approval of an early feasibility clinical study may be based on less nonclinical data than would be needed to support the initiation of a larger clinical study on a more final device design

When is a Good Time to Talk to FDA About an EFS?

After…

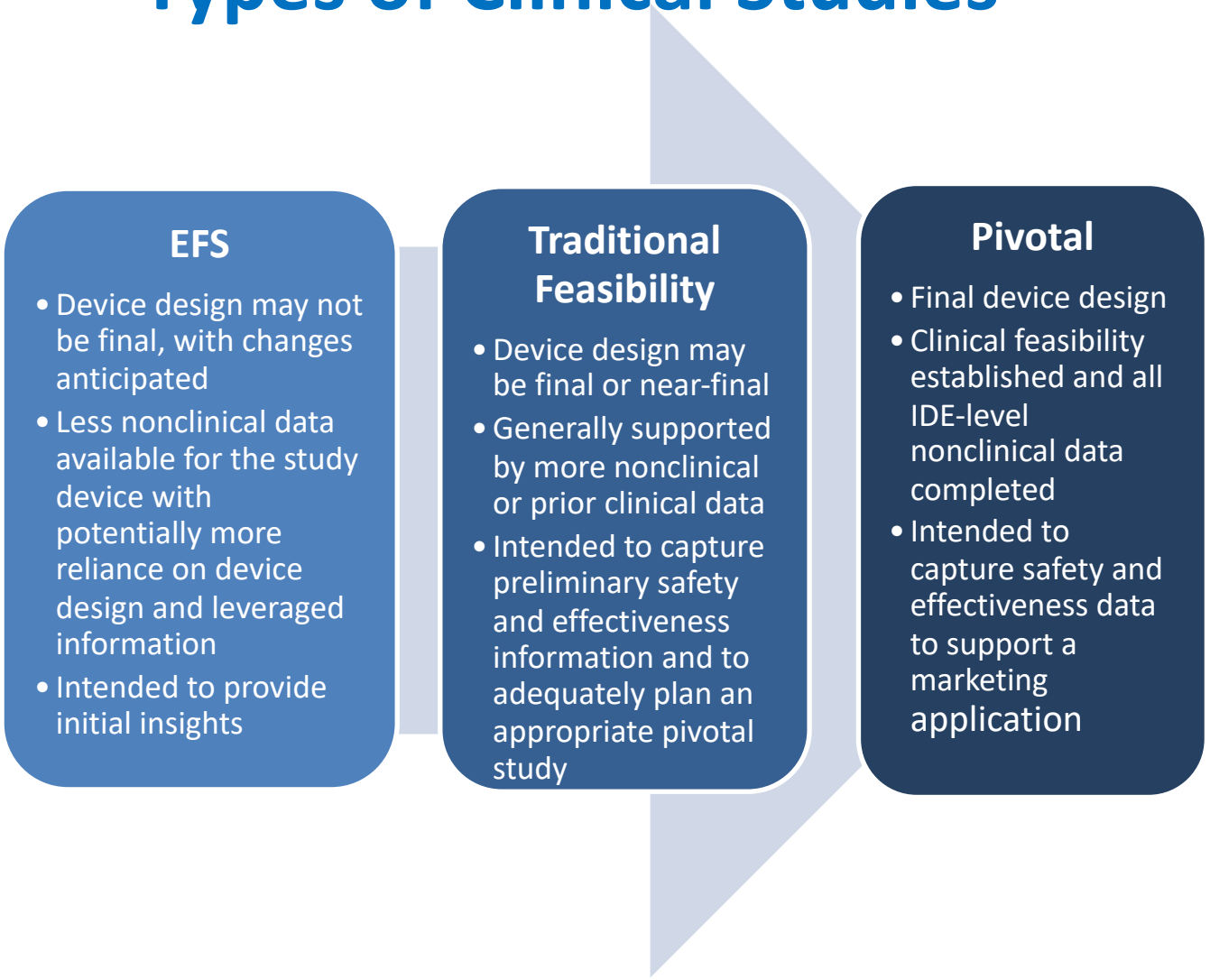
- You have established your general device design, intended use and what information you would like to gather from the EFS

Before…

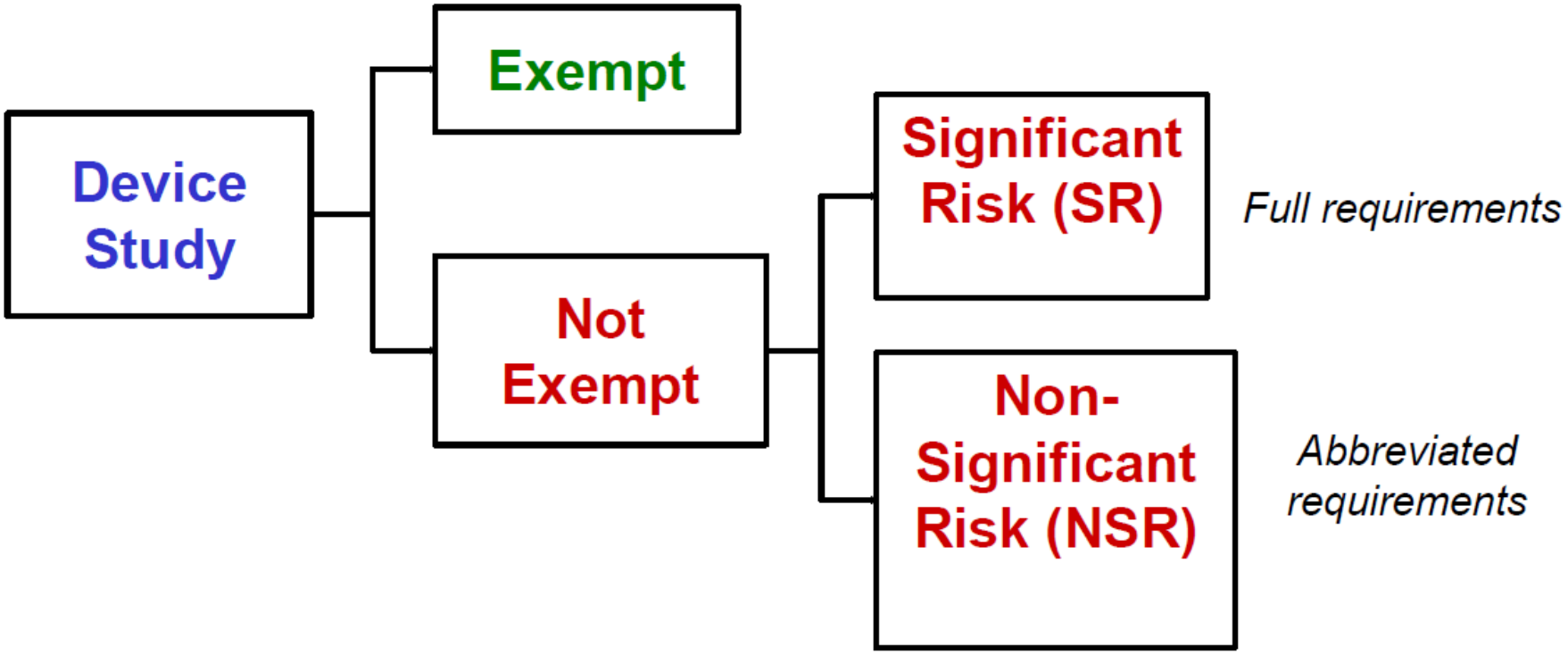
- Time and money spent on nonclinical testing

<u>Communication with FDA throughout the development process is recommended to optimize submission efficiency</u>

Types of Clinical Studies



Investigational Device Exemption (IDE)



https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/investigational-device-exemption-ide

Study Risk Determination

- Presents a potential for serious risk to the health, safety, and welfare of a subject and is:
  - an implant; or
  - used in supporting or sustaining human life; or
  - of substantial importance in diagnosing, curing, mitigating, or treating disease or preventing impairment of human health
  - otherwise poses a risk
- Sponsor makes initial determination
- IRB reviews the sponsor's determination
  - Information provided by the sponsor includes device description, prior investigations, investigational plan, subject selection, risk assessment and rationale used in making its SR or NSR determination
  - If the IRB disagrees with a sponsor's NSR assessment, the IRB must inform the clinical investigator/sponsor
  - Risk determination request sent to FDA in Qsubmission

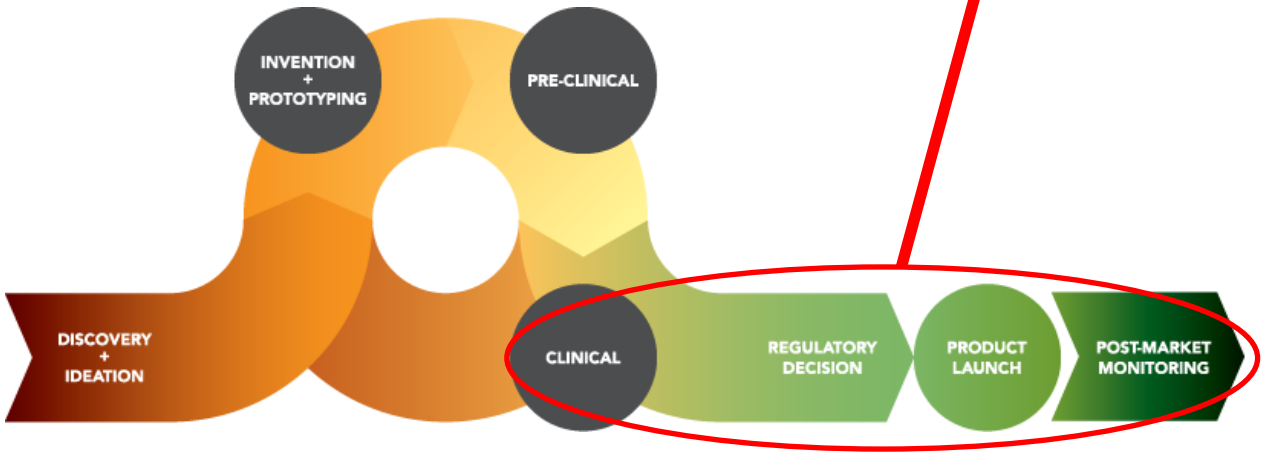
Real World Evidence(RWE)

Real-World Data (RWD)
Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources

Real-World Evidence (RWE)
Clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices - Guidance for Industry and Food and Drug Administration Staff (fda.gov)

- High quality submission (Complete, Well organized, Proofread)
- Submission Policies
- Inspection (Adequate procedures and manufacturing controls, acceptable validation data)
- Adverse Event Reporting



FDA MedWatch and Patient Safety

www.fda.gov/medwatch

http://www.fda.gov/downloads/forpatients/about/ucm410190.pdf

What Happens to Your Report

- Report captured in a database
- Database monitored continuously
- If needed, FDA can:
  - Work with manufacturer to facilitate product recall
  - Request a modification in product design
  - Request a modification in manufacturing process
  - Work with manufacturer to modify labeling

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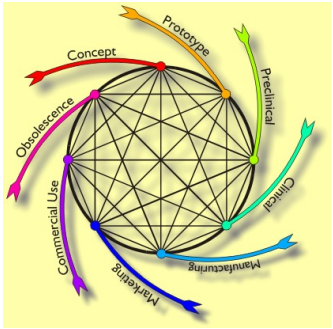
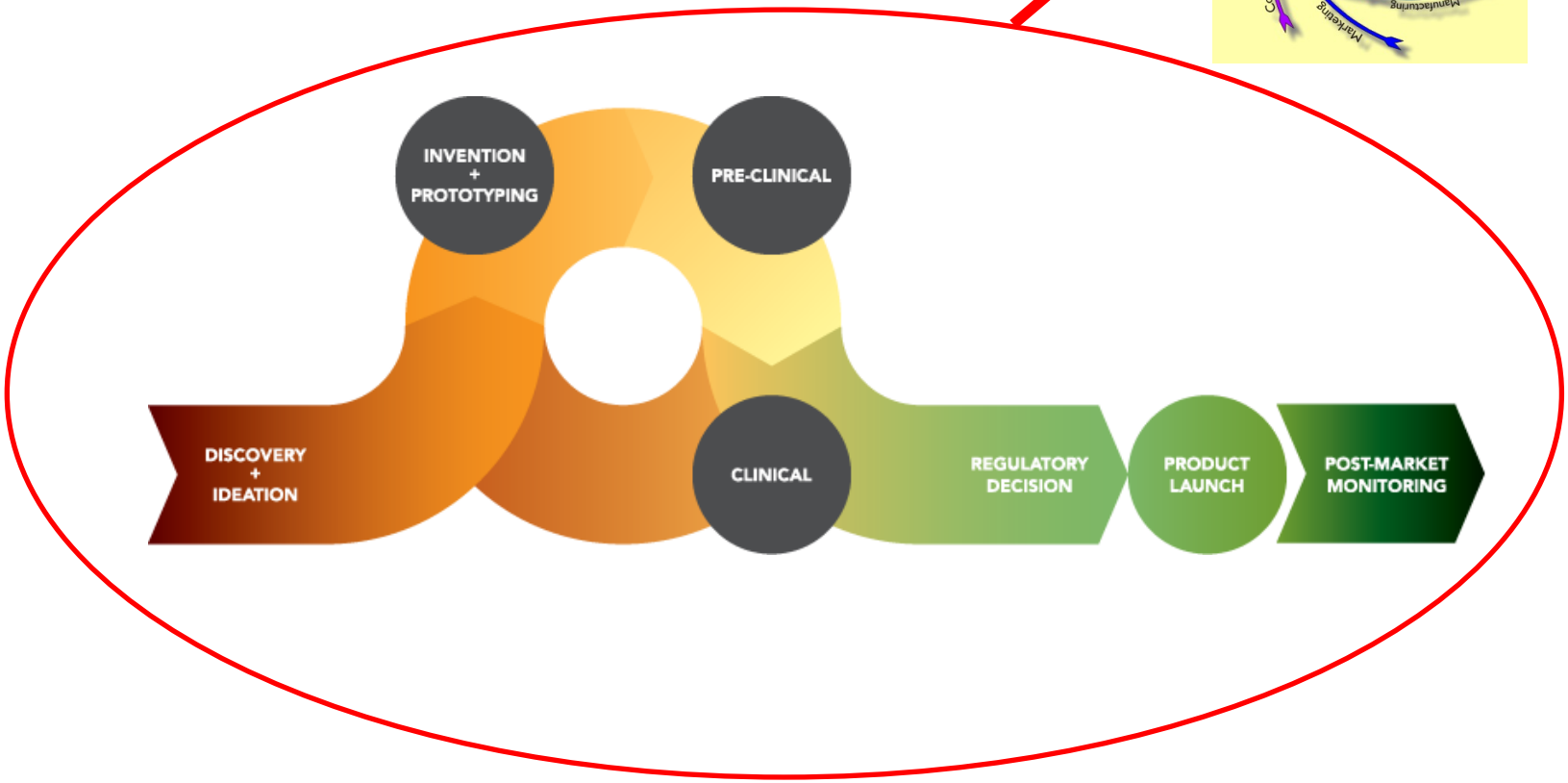
Total Product Life Cycle





Dental Teams Review Expertise

- Division of Dental and ENT Devices
  - Led by Srinivas “Nandu” Nandkumar (Srinivas.Nandkumar@fda.hhs.gov)
- Dental Devices Teams
  - Implantable dental devices team
    - Led by Andrew Steen (Andrew.Steen@fda.hhs.gov)
  - Restorative and Surgical dental devices team
    - Led by Michael Adjodha (Michael.Adjodha@fda.hhs.gov)
- Reviewers
  - Dentists / Periodontist / Oral Surgeon
  - Materials Scientists / Chemists / Biochemists
  - Biologists / Microbiologists
  - Biomedical Engineers
  - Compliance/Quality Systems Specialists


Questions?


THANK
YOU