

# Types of Regulatory Submissions (within CBER/OTP)

**Cara Pardon, MS**  
Regulatory Project Manager  
OTP/ORMRR/DRMRR1  
CBER | US FDA

REdI – May 29-30, 2024



# Learning Objectives

- Identify and define the types of regulatory submissions in the Biologics Life Cycle, under the PDUFA program, from INTERACT meetings through BLAs and post-market submissions
- Describe the timelines associated with PDUFA regulatory submissions
- Identify and define the types of regulatory submissions in the Medical Device Life Cycle, under the MDUFA program, from Q-submission meetings through premarket applications/notifications and post-market submissions
- Identify best practices for submissions and interaction with CBER/OTP during submission review

# PDUFA



- Prescription Drug User Fee Act
- Congress created in 1992
- Authorizes FDA to collect user fees

# Types of PDUFA Submissions



## Pre-Submission Meetings

- INTERACT
- Pre-IND

## Other

- Master File

## Post-Marketing Submissions

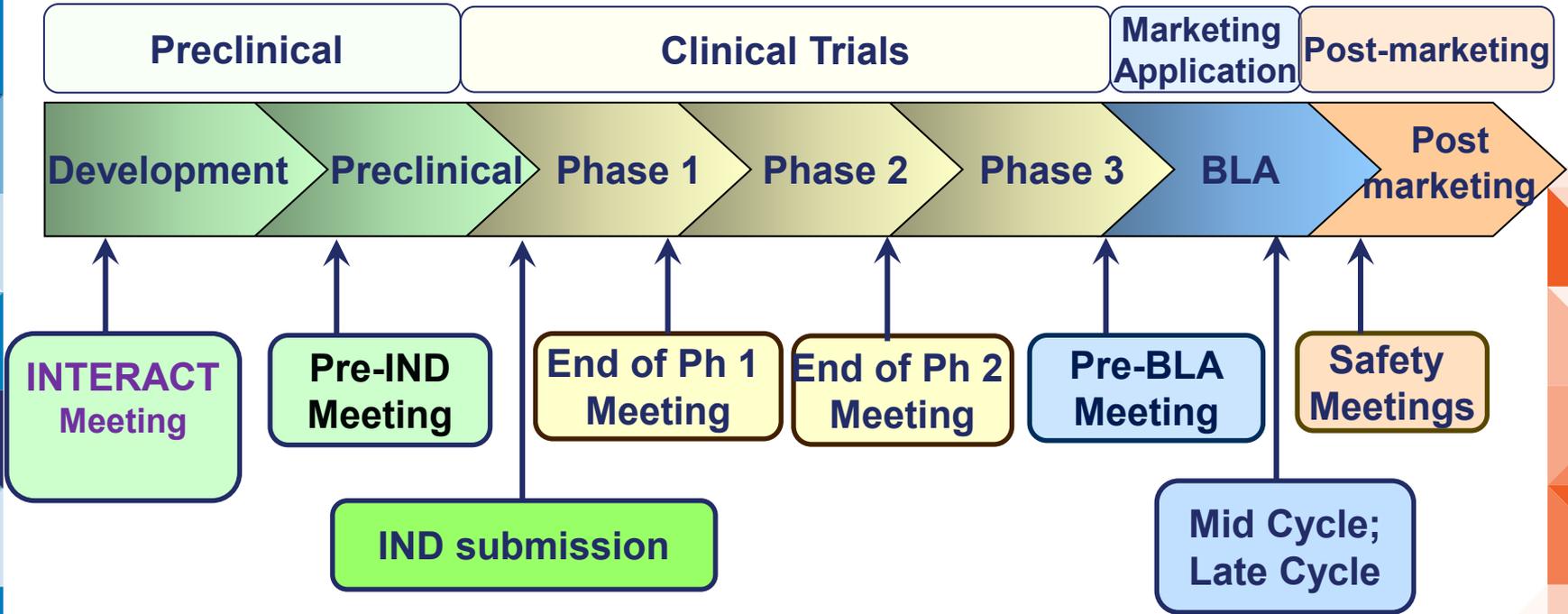
## Pre-Marketing (Investigational) Application

- IND

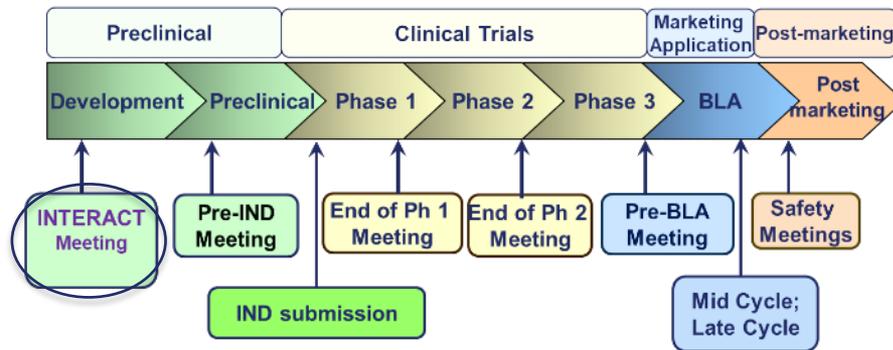
## Marketing Application

- BLA

# PDUFA Product Life Cycle



# Initial Targeted Engagement for Regulatory Advice on CBER Products (INTERACT) Meetings



# What is an INTERACT Meeting?



- Formal Meeting under PDUFA VII
- For novel therapies and unique development challenges
- For sponsors to obtain early feedback
- Specific pre-investigational product chosen
- One INTERACT Meeting

# INTERACT Discussions

- Choice of preclinical models, toxicology studies, and design of proof-of-concept (POC) studies
- Chemistry, manufacturing, and controls strategies to demonstrate product safety to support first in human (FIH) studies
- Clinical trial recommendations for FIH studies in clinical population

# INTERACT Request and Review

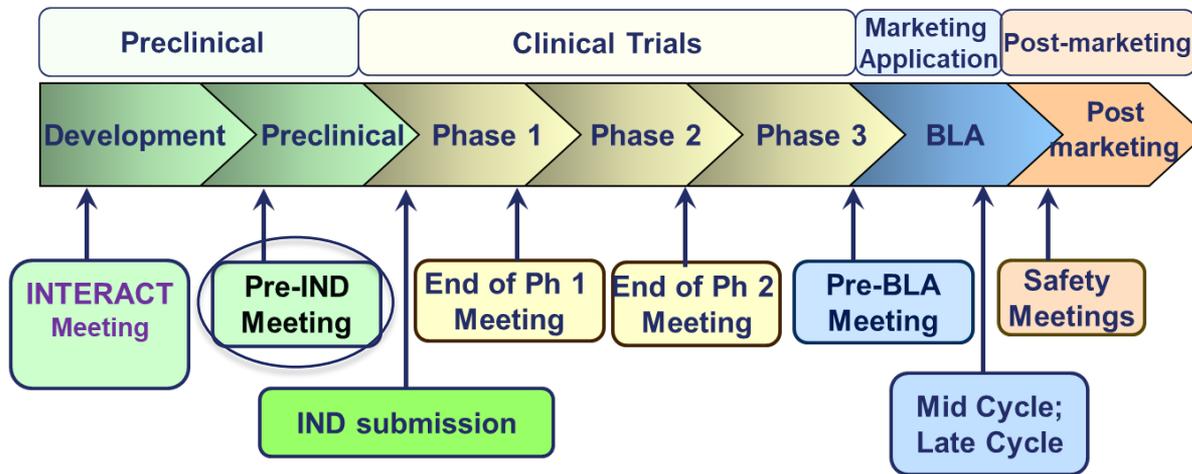


- Meeting package must accompany request with key issues and specific questions identified
- Refer to [CBER SOPP 8101.1](#): Regulatory Meetings with Sponsors and Applicants for Drugs and Biological Products
- Grant or deny decision within 21 days sent via email
- Written Response Only (WRO), teleconference, face-to-face (virtual), or face-to-face (in-person)

# INTERACT Meeting Timeline

- Meeting scheduled within 75 calendar days
- WRO goal date by Day 75
- Preliminary Responses sent 5 days prior to meeting
- Sponsor response/agenda 2 days prior to meeting
- No formal meeting minutes
- Annotated preliminary responses within 30 days if advice changed
- Requests for clarification within 20 days

# Pre-**Investigational New Drug (Pre-IND)** Meetings



# What is a pre-IND Meeting?

- Formal Type B Meeting
- For sponsors to obtain early feedback
- Defined manufacturing process developed
- Completed proof-of-concept (POC) and some preliminary safety/toxicology studies

# Pre-IND Discussions

- To discuss IND-enabling Chemistry, Manufacturing, and Controls (CMC), Pharmacology/Toxicology (P/T), and clinical trial design
- Specific questions

# Pre-IND Request and Review



- Meeting package does not need to accompany request; summary and draft questions included
- Refer to [CBER SOPP 8101.1](#): Regulatory Meetings with Sponsors and Applicants for Drugs and Biological Products
- Meeting confirmation or denial within 21 days sent via secure email
- Same 4 meeting format type options

# Pre-IND Meeting Timeline



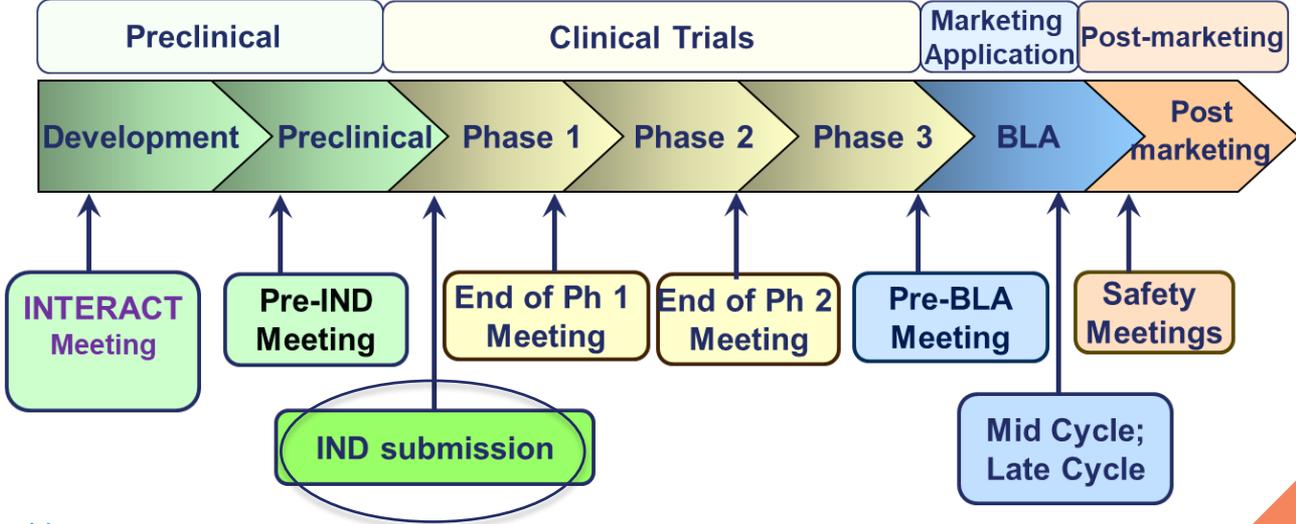
- Meeting scheduled within 60 calendar days
- WRO goal date by Day 60
- Meeting package due 30 days beforehand
- Preliminary Responses sent 2 days prior to meeting
- Sponsor response/agenda 1 day prior to meeting
- Formal meeting minutes within 30 days
- Request for clarifications within 20 days

# Helpful INTERACT/pre-IND Tips



- Secure email ([SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov))
- INTERACT vs pre-IND
  - Consider stage of development
  - 1 of each/1 or the other
- Timely communications
- Meeting package and meeting agenda guidance

# Investigational New Drug (IND) Application



# What is an IND?



- Under [21 CFR 312](#), any use in the United States (US) of a drug (or a biological product) not previously authorized for marketing in the US requires submission of an IND application to the FDA
- For an investigational drug to be used in clinical studies to collect safety and efficacy data
- Any human research study must be conducted under an IND application if the research:
  - Involves [a drug](#) (or a biological product);
  - Is [a clinical investigation](#);
  - Is [not exempt](#) from the IND requirements

# IND Safety is Priority

“FDA’s primary objectives in reviewing an IND are, in all phases of the investigation, to assure the **safety** and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug’s effectiveness and safety...”

[IND Regulations [21 CFR 312.22 (a) -General Principles of the IND Submission]

# What's in an IND Submission?



<input type="checkbox"/>	Form FDA 1571	21 CFR 312.23(a)(1)
<input type="checkbox"/>	Table of Contents	21 CFR 312.23(a)(2)
<input type="checkbox"/>	Introductory statement and general investigational plan	21 CFR 312.23(a)(3)
<input type="checkbox"/>	Investigator's Brochure	21 CFR 312.23(a)(5)
<input type="checkbox"/>	Clinical Protocol(s)	21 CFR 312.23(a)(6)
<input type="checkbox"/>	Chemistry, manufacturing, and control data	21 CFR 312.23(a)(7)
<input type="checkbox"/>	Pharmacology and Toxicology (P/T) data	21 CFR 312.23(a)(8)
<input type="checkbox"/>	Previous human experience	21 CFR 312.23(a)(9)
<input type="checkbox"/>	Additional information	21 CFR 312.23(a)(10)

# Original IND Timeline

- Acknowledgment letter by Day 14
- 30-day Interactive Review process
- Safe to Proceed (STP), Clinical Hold, or Partial Clinical Hold

# Helpful IND Tips

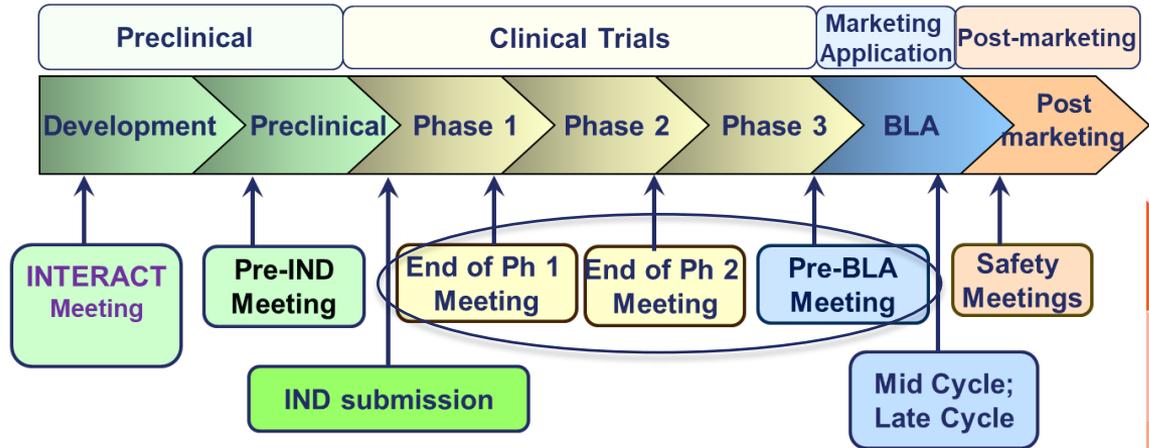
- Secure email
- Consider the 30-day timeline
  - Best days for submission M-W
  - Availability for email or telecon communications
  - Timely response

# Helpful IND Tips (cont.)

- Provide a complete submission
  - Correct format
  - Point of Contact (POC) information
  - Letter(s) of Authorization (LOAs)
- Consider previous INTERACT/pre-IND recommendations

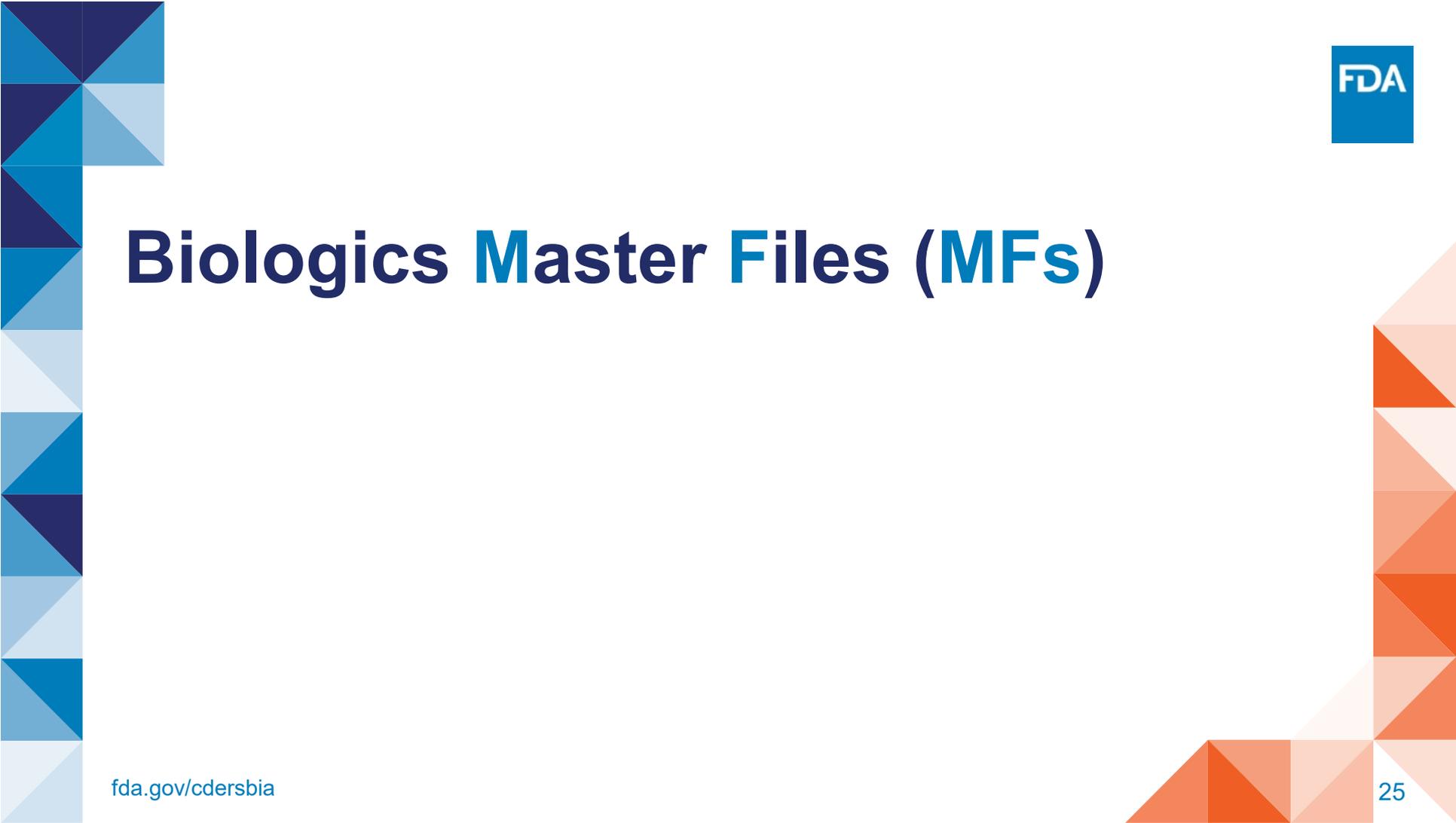
# IND Meetings

- End-of-Phase 1
- End-of-Phase 2
- Type A
- Type B
- Type C
- Type D
- Pre-BLA



Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products | FDA

CBER SOPP 8101.1

The slide features decorative geometric patterns. On the left, a vertical column of blue and dark blue triangles points downwards. On the right, a vertical column of orange and light orange triangles points upwards. The main title is centered in a large, bold, dark blue font.

# Biologics Master Files (MFs)

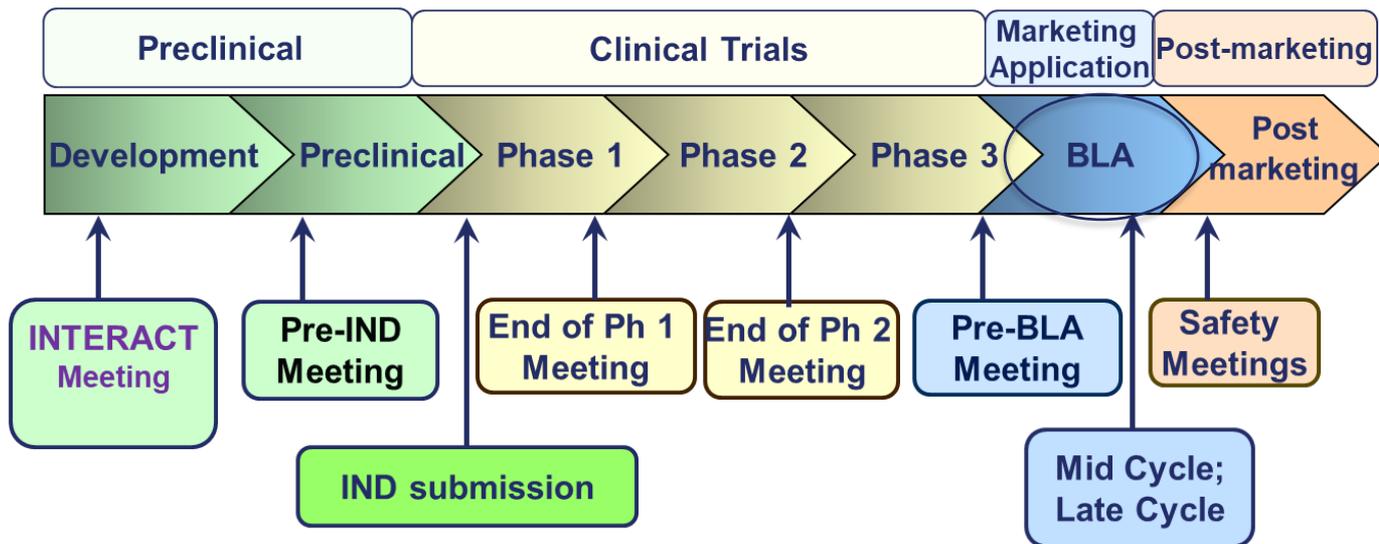
# Master Files in CBER

- Types II, III, IV, and V
- Device Master Files
- Information on facilities, processes, or articles for manufacturing, processing, packaging, or storing a product
- Not independently reviewed, nor approved
- Reviewed in context of an application

# Helpful MF Tips

- CBER submission for CBER application
- Letter of Authorization (LOA)
- Cross-reference section of Forms FDA-1571, FDA-356h, FDA-3514
- CDER Drug Master Files (DMFs)
- CDRH Device Master Files (MAFs)

# Biologics License Application (BLA)



# What is a BLA?

- A request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce (21 CFR 601.2)

# Original BLA Timeline

- Filing Notification by day 60
- Standard review – 12 months
- Priority review – 8 months

# Original BLA Meetings

- Application Orientation Meeting (AOM)
- Dataset walkthrough
- Mid-Cycle Communication
- Late-Cycle Meeting
- Advisory Committee

# During BLA Review

- Information requests
- Pre-license Inspection
- Major Amendment (adds 3 months to review)
  - a substantial amount of new data not previously submitted to or reviewed by the Agency.
  - a substantial amount of new manufacturing or facility information not previously submitted to or reviewed by the Agency.
  - a new analysis of studies not previously submitted to the pending application or supplement.
- Post-marketing and Labeling negotiations

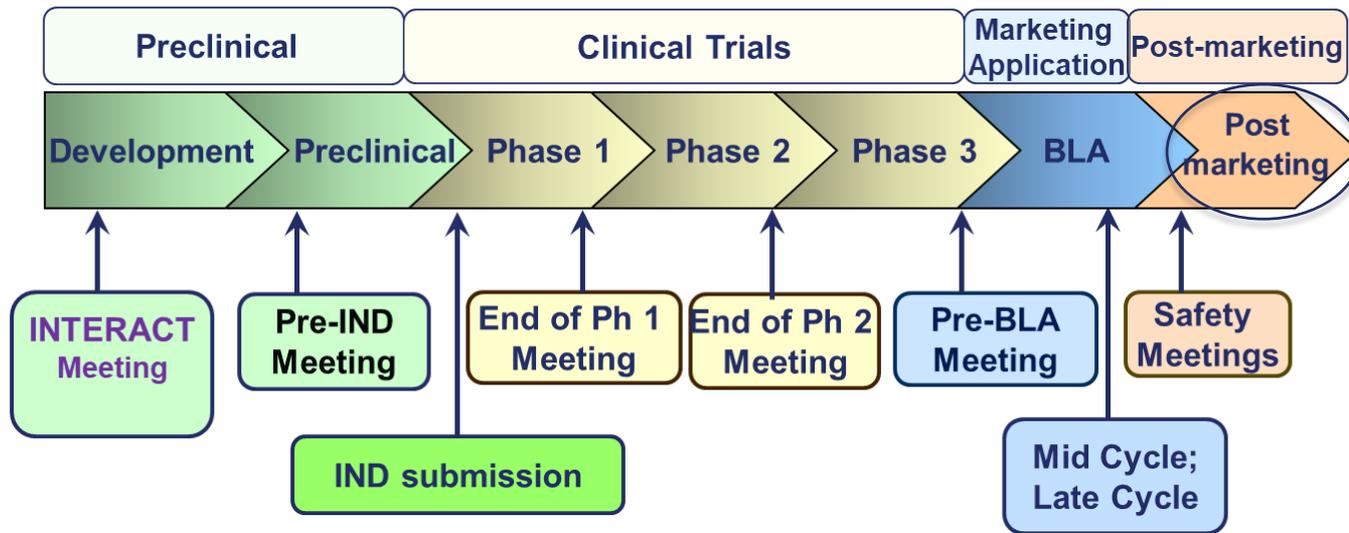
# BLA Decisions

- Approval
- Complete Response (CR)
  - Resubmission within 1 year
    - Extension request
    - Type A Meeting request

# Helpful BLA Tips

- Complete Application
- Prepared for Inspection
- Timely communications
- Form FDA-356h
  - Submission Tracking Number (STN): 12345/00/06

# Post-Approval Submissions



# Types of Post-Approval Submissions



- Manufacturing
- Labeling
- Efficacy
- Annual Reports
- Product Correspondences
- Post-marketing requirements/Post-marketing commitments (PMR/PMCs)
- Risk Evaluation and Mitigation Strategies (REMS)
- Pediatric Research Equity Act (PREA)
- Promotional Materials

# Supplement Types & Timelines



Submission Type	Supplement Type	Review Schedule
Changes Being Effected Immediately-CBE	Manufacturing	6 month
Changes Being Effected in 30 Days-CBE30	Manufacturing	6 month
Prior Approval Supplement-PAS	Manufacturing	4 month
Prior Approval Supplement-Efficacy	Efficacy Supplement	Priority 6 month or Standard 10 month
Labeling (PAS or CBE)	Labeling Supplement	6 month
Response to Complete Response (CR)	Original Supplement Type	2 or 6 months

# PDUFA Submission Guidance



- Submission to CBER Document Control Center (DCC): [Regulatory Submissions in Electronic and Paper Format for CBER-Regulated Products | FDA](#)
- Refer to [Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Submissions Under 745\(a\) of the Federal Food, Drug, and Cosmetic Act](#)
  - Identifies submissions required to be in eCTD format, submitted via the ESG

# Learning Objectives

- Identify and define the types of regulatory submissions in the Medical Device Life Cycle, under the MDUFA program, from Q-submission meetings through premarket applications/notifications and post-market submissions
- Identify best practices for submissions and interaction with CBER/OTP during submission review

# MDUFA



- Medical Device User Fee (and Modernization) Act
- Signed into law in 2002
- Authorizes FDA to collect user fees

# Types of MDUFA Submissions



## Pre-Applications and Meetings

- Q-Submissions

## Investigational Submission

- IDE

## Post-Marketing Submissions

## Marketing Applications

- 510(k)
- De Novo
- HDE
- PMA
- BLA

# Device Classification



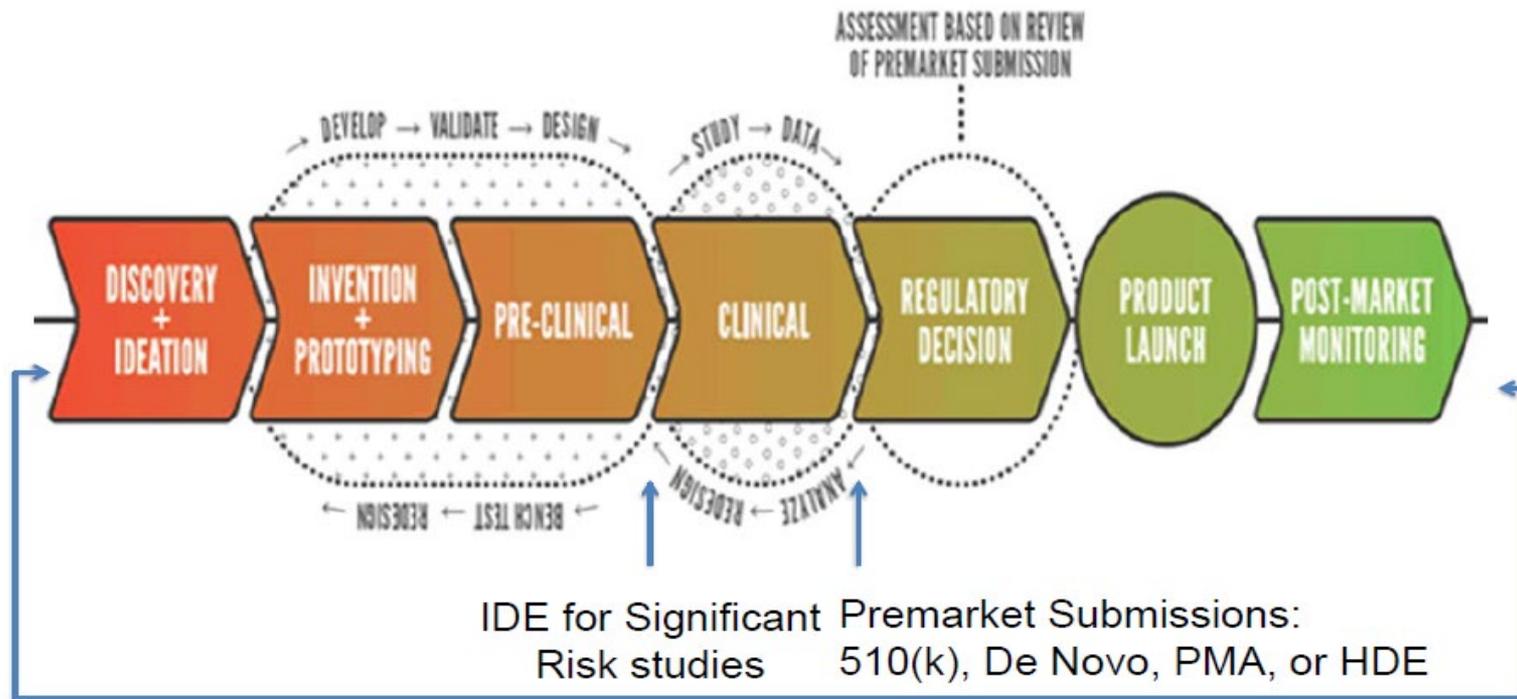
- Class I: Lowest Risk
  - Ex. Bandages, Hospital Bed
- Class II: Moderate Risk
  - Ex. Syringes, Mononuclear Cell collection for therapeutic use
- Class III: Highest Risk
  - Ex. Tissue and Cell Processing Devices at Point-of-Care

# Devices Reviewed in OTP



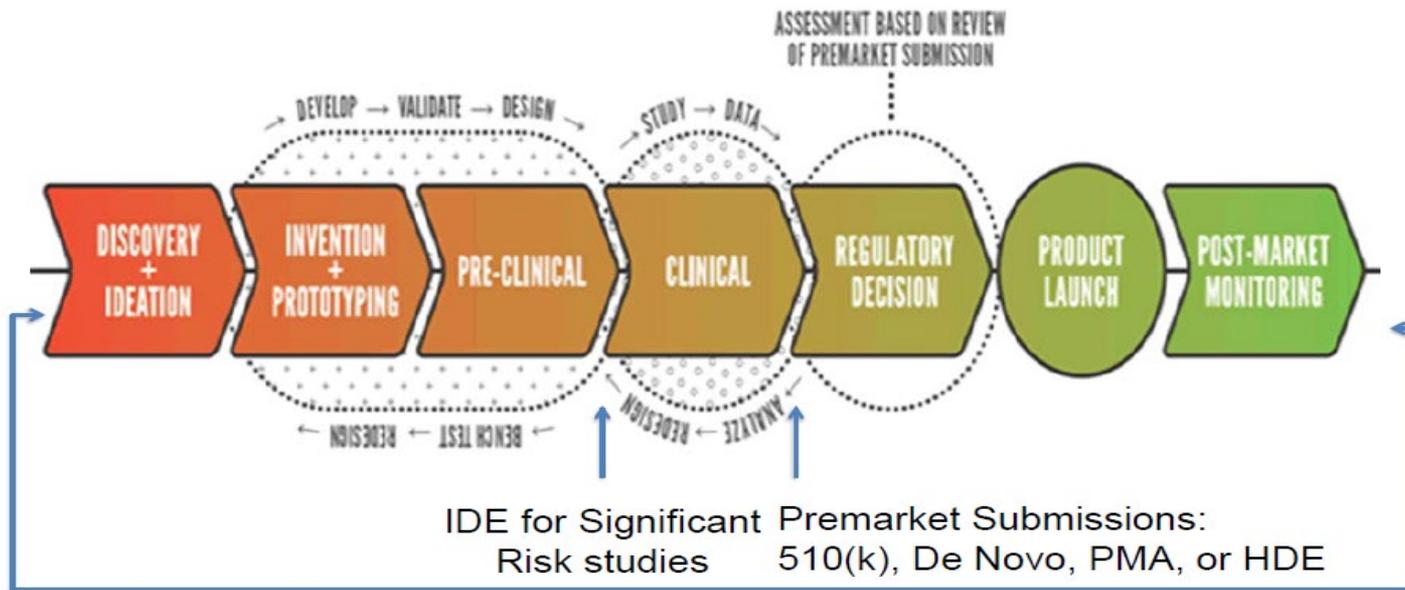
- Devices intended to process HCT/Ps (Human cells, tissues and cellular and tissue-based products) or other biologics *ex vivo* to generate device output at point-of-care
  - Therapeutic effect mediated by device output
  - Device output can be combined with another regulated article *in vitro* to generate tissue-engineered product or live cell construct
- Devices intended to
  - Collect, process, and/or store HCT/Ps or bone marrow (BM)
  - Deliver plasma protein therapeutics, cell/tissue and gene therapy products for specific clinical indications
  - Process blood, BM, or blood-BM mixture to generate platelet-rich plasma (PRP), platelet concentrate, or BM concentrate for therapeutic use
- *In vitro* diagnostic devices (IVD) intended to enumerate HCT/Ps
- Combination products

# Medical Device Development Pathway



Q-Submission

# Q-Submissions (Q-Subs)



Q-Submission

# What is a Q-Sub?

- Request for feedback or meeting for medical devices

# Types of Q-Subs

- Pre-Submissions (Pre-Subs)
- Submission Issue Requests (SIRs)
- Informational Meetings
- Study Risk Determinations (SR/NSR)
- Breakthrough Device Program
- Safer Technologies (STeP) Program

# Q-Sub Timelines

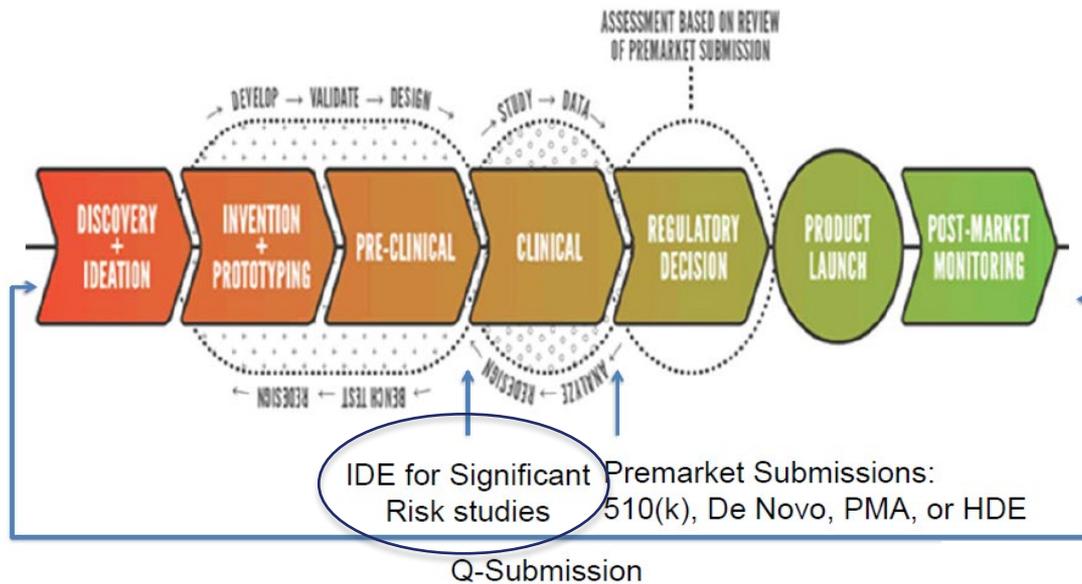


**Table 1 – Q-Sub types and corresponding feedback mechanisms and timelines**

Q-Sub Type	Method of Feedback	Timeframe for Sending Feedback or Scheduling Meeting (from receipt of submission)
Pre-Submission	Meeting with written feedback provided in advance	Written Feedback: 70 days or 5 days prior to scheduled meeting, whichever is sooner Meeting: Date based on mutual agreement (typically day 70-75)
	Written Feedback Only	70 days
Submission Issue Request (SIR)	Meeting <b>or</b> Written Feedback	If SIR is received <b>within 60 days</b> of FDA’s marketing submission letter: 21 days as resources permit
		If SIR is received <b>more than 60 days</b> after FDA’s marketing submission letter: 70 days as resources permit
Study Risk Determination	Formal Letter	90 days
Informational Meeting*	Meeting	90 days

\*When used to track requests that do not meet the definition of a Q-Sub type, Informational Meeting timeframe and feedback mechanism can vary. Typically, informational meetings do not include FDA feedback.

# Investigational Device Exemption (IDE) Application



# What is an IDE?

- For an investigational (significant risk) device to be used in clinical studies to collect safety and efficacy data

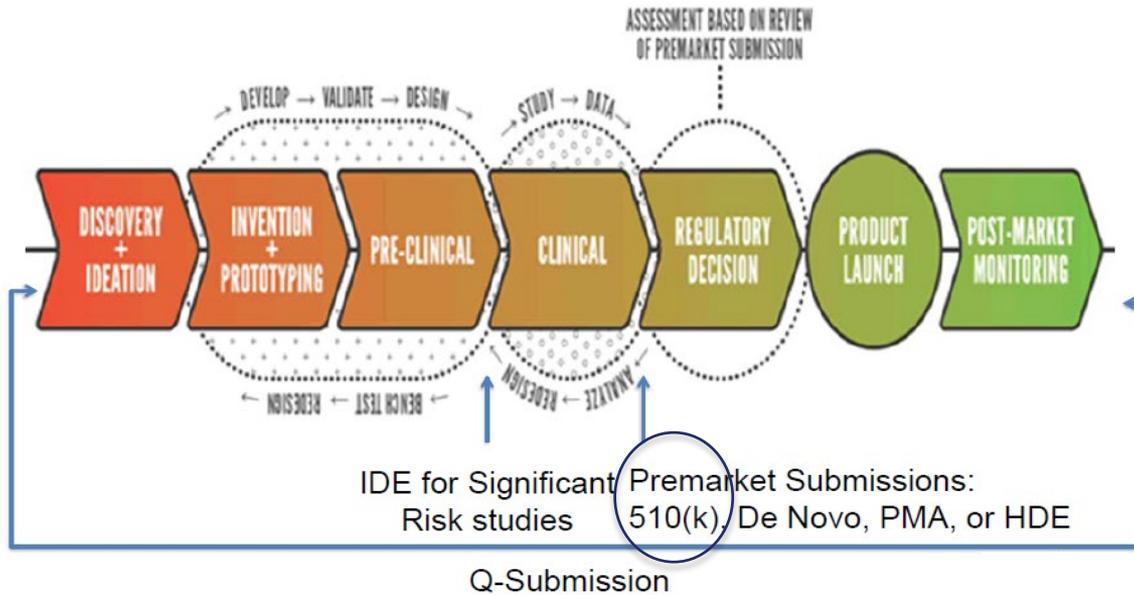
# IDE Study Types

- Early Feasibility Study
- Traditional Feasibility Study
- Pivotal Study
- Continued Access Study
- Observational Registry
- Supporting/Confirmatory Study
- Other

# IDE Timeline

- Acknowledgment letter by Day 5
- 30-day Interactive Review process
- Approval, Conditional Approval, Disapproval letter

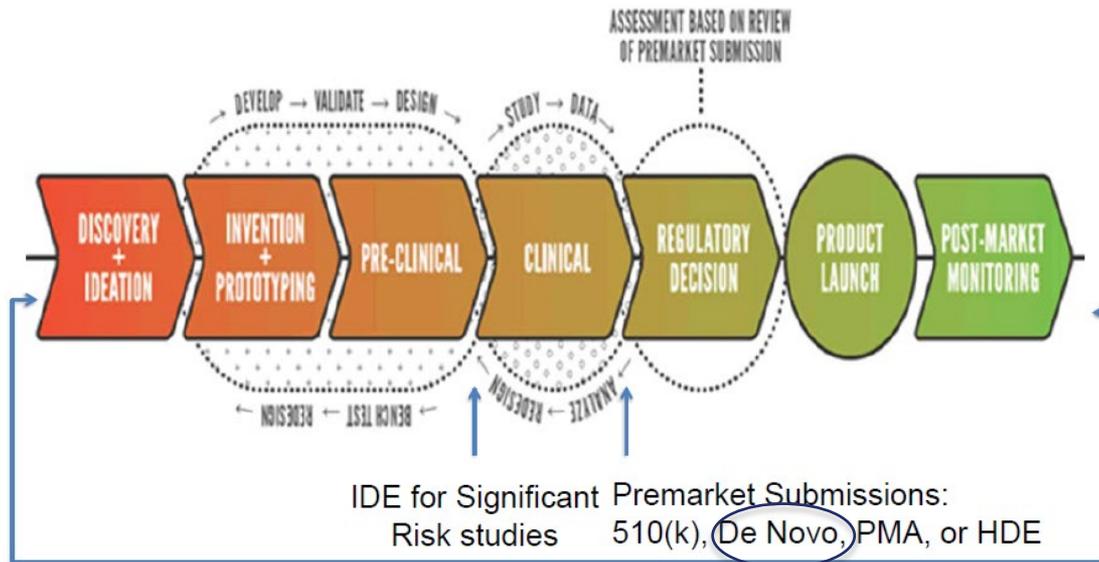
# 510(k) Submission



# What is a 510(k)?

- Pre-market notification for moderate risk devices (Class II and some Class I) to allow a device to enter interstate commerce by demonstrating substantial equivalence (SE) to a predicate device (defined in 21 CFR 807.92(a)(3))
- **Goal:** Demonstrate SE
- Decision options:
  - SE or SE w/ limitations: “Cleared”
  - NSE

# De Novo Request

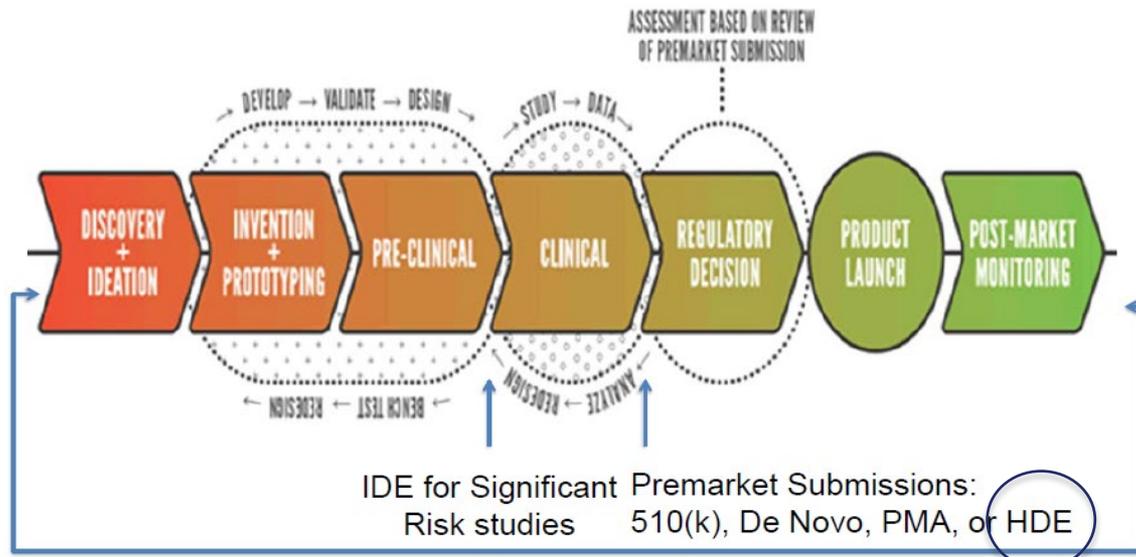


Q-Submission

# What is a De Novo?

- Classification Process
  - Risk-based
  - For new devices, whose type was not previously classified (automatically Class III) into Class I or II
- **Goal:** Classify new device into lower risk category
- Decision options:
  - Decline
  - Grant
    - Establishes new “device type” along with classification regulation, necessary controls, and product code
    - Device is eligible to serve as a predicate for new devices under 510(k) process

# Humanitarian Device Exemption (HDE) Application

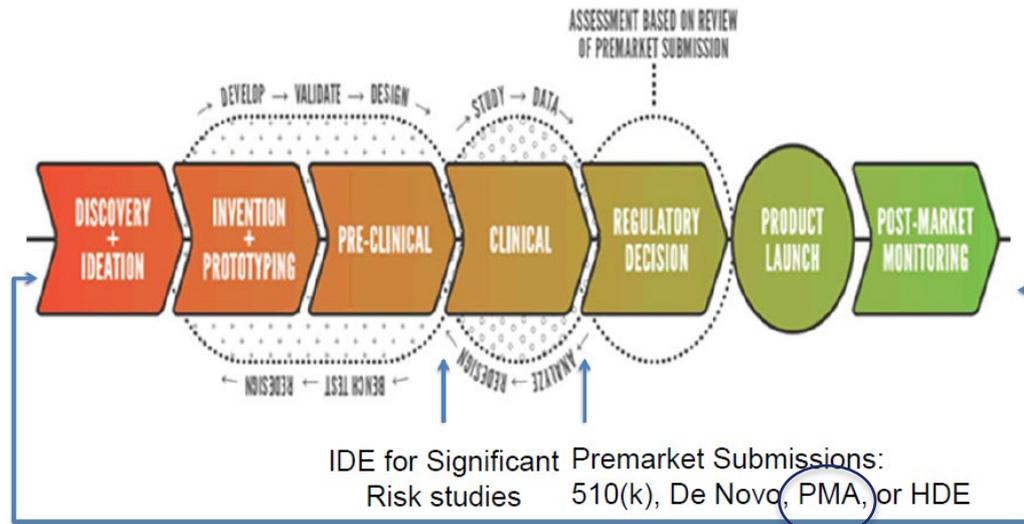


# What is an HDE?

- Marketing application for an HUD
  - HUD: a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8,000 individuals in the United States per year
- **Goal:** Demonstrate reasonable assurance of safety and probable benefit
- Exempt from the effectiveness requirements of sections 514 and 515 of the FD&C Act and subject to certain profit and use restrictions
- Decision Options:
  - Approval Order
  - Approvable Letter
  - Not Approvable Letter
  - Denial Order



# Pre-Market Approval Application (PMA)



IDE for Significant Premarket Submissions:  
 Risk studies 510(k), De Novo, **PMA**, or HDE

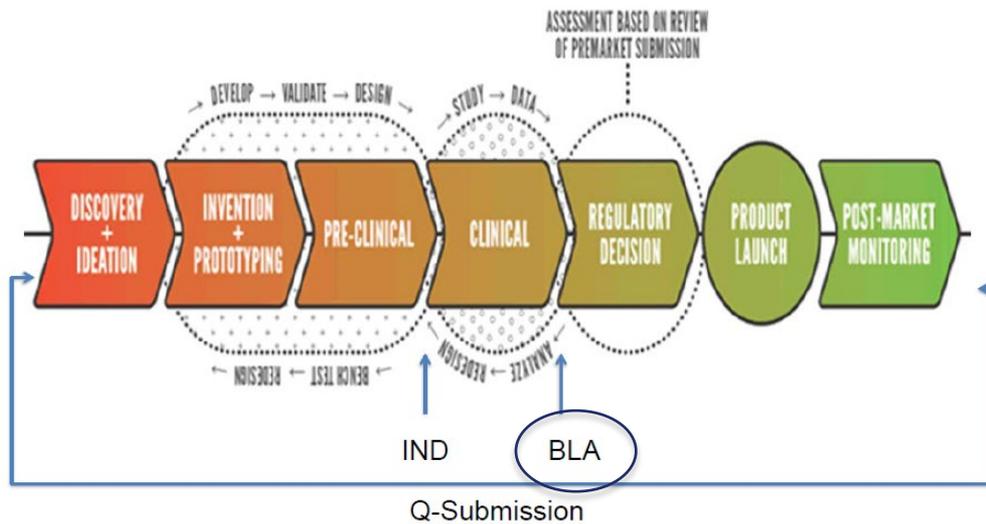
Q-Submission

# What is a PMA?



- To evaluate safety and effectiveness of highest risk medical devices (Class III)
  - Most stringent type of device marketing application
  - General and special controls alone are insufficient to assure S/E
- **Goal:** Demonstrate Safety and Efficacy
- Decision options:
  - Approval Order
  - Approvable Letter
  - Not Approvable Letter
  - Denial Order

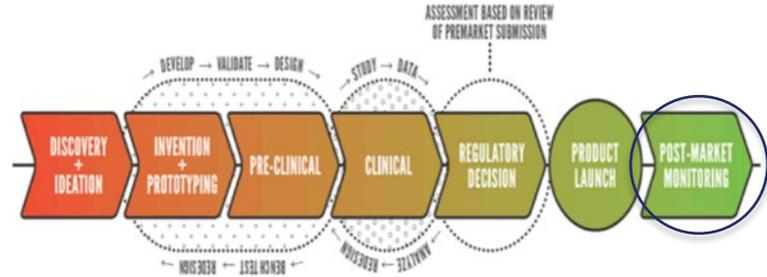
# Device Biologics License Application (Device BLA)



# Device Post-Market Submissions



- 522 Order
- 510(k) CBE
- 510(k) recalls, corrections, and removals
- PMA, HDE, and Device BLA Supplements
- PMA, HDE, and Device BLA Reports
- Device BLA Post-marketing requirements/Post-marketing commitments (PMR/PMCs)



# MDUFA Submission Guidance



- Secure email
- Submission to CBER Document Control Center (DCC): [Regulatory Submissions in Electronic and Paper Format for CBER-Regulated Products | FDA](#)
- [Guidance](#): eCopy Program for Medical device Submissions
- User Fees
- [eSTAR Program | FDA](#)
  - 510(k)

# Learning Objectives

- Identify and define the types of regulatory submissions in the Biologics Life Cycle, under the PDUFA program, from INTERACT meetings through BLAs and post-market submissions
- Describe the timelines associated with PDUFA regulatory submissions
- Identify and define the types of regulatory submissions in the Medical Device Life Cycle, under the MDUFA program, from Q-submission meetings through premarket applications/notifications and post-market submissions
- Identify best practices for submissions and interaction with CBER/OTP during submission review

# Challenge Question #1



Which of the following statements is **NOT** true?

- A. CBER Master Files are reviewed and approved as independent submissions
- B. To cross-reference a Master File in your IND submission, a Letter of Authorization (LOA) must be included
- C. A BLA Filing Notification decision will be provided within 60-days of receipt
- D. Secure email is required for regulatory communications

# Challenge Question #2



**IND and IDE submissions have a decision timeline of:**

- A. 60 days
- B. 90 days
- C. 30 days
- D. There is no specified timeline

# Challenge Question #3

**Which of the following statements is true?:**

- A. A PMA is required to evaluate safety and effectiveness of low-risk medical devices (Class I and II)
- B. An HUD is a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in more than 8,000 individuals in the United States per year
- C. A 510(k) is required when introducing a moderate risk device to the market for the first time (if there is predicate device)
- D. A De Novo submission may be Approved or Conditionally Approved

# Summary



- OTP reviews a wide array of regulatory submissions under the PDUFA and MDUFA programs
- There are many chances for interaction with OTP throughout the PDUFA and MDUFA product life cycles
- There are common best practices for regulatory submissions and communications with OTP

# Resources



- [Regulatory Submissions in Electronic and Paper Format for CBER-Regulated Products | FDA](#)
- [Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A\(a\) of the Federal Food, Drug, and Cosmetic Act | FDA](#)
- [Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products | FDA](#)
- [Best Practices for Communication Between IND Sponsors and FDA During Drug Development | FDA](#)
- [OTP INTERACT Meeting | FDA](#)
- [OTP Pre-IND Meetings | FDA](#)
- [Investigational New Drug Applications \(INDs\) for CBER-Regulated Products | FDA](#)
- [Master Files for CBER-Regulated Products | FDA](#)
- [Biologics License Applications \(BLA\) Process \(CBER\) | FDA](#)

# Resources (cont.)



- [Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program | FDA](#)
- [Investigational Device Exemption \(IDE\) | FDA](#)
- [The 510\(k\) Program: Evaluating Substantial Equivalence in Premarket Notifications \[510\(k\)\] | FDA](#)
- [De Novo Classification Request | FDA](#)
- [Humanitarian Device Exemption | FDA](#)
- [Premarket Approval \(PMA\) for CBER-Regulated Products | FDA](#)
- [eSTAR Program | FDA](#)
- [eCopy Medical Device Submissions | FDA](#)

**CDER/OTC looks forward to working with you during all stages of your product development.**

# Contact Information



- **Cara Pardon:** [cara.pardon@fda.hhs.gov](mailto:cara.pardon@fda.hhs.gov)
- **Regulatory Questions:**
  - **OTP Main Line – 240 402 8190**
  - **Email:** [OTPRPMS@fda.hhs.gov](mailto:OTPRPMS@fda.hhs.gov)
- **Interactions with Office of Therapeutic Products website:** [Interactions with Office of Therapeutic Products | FDA](#)
- **OTP Learn Webinar Series:** <http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm>
- **CBER website:** [www.fda.gov/BiologicsBloodVaccines/default.htm](http://www.fda.gov/BiologicsBloodVaccines/default.htm)
- **Phone:** 1-800-835-4709 or 240-402-8010
- **Consumer Affairs Branch:** [ocod@fda.hhs.gov](mailto:ocod@fda.hhs.gov)
- **Manufacturers Assistance and Technical Training Branch:** [industry.biologics@fda.hhs.gov](mailto:industry.biologics@fda.hhs.gov)
- **Follow us on X, formerly twitter:** <https://www.twitter.com/fdacber>

