

Types of Regulatory Submissions (within CBER/OTP)

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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

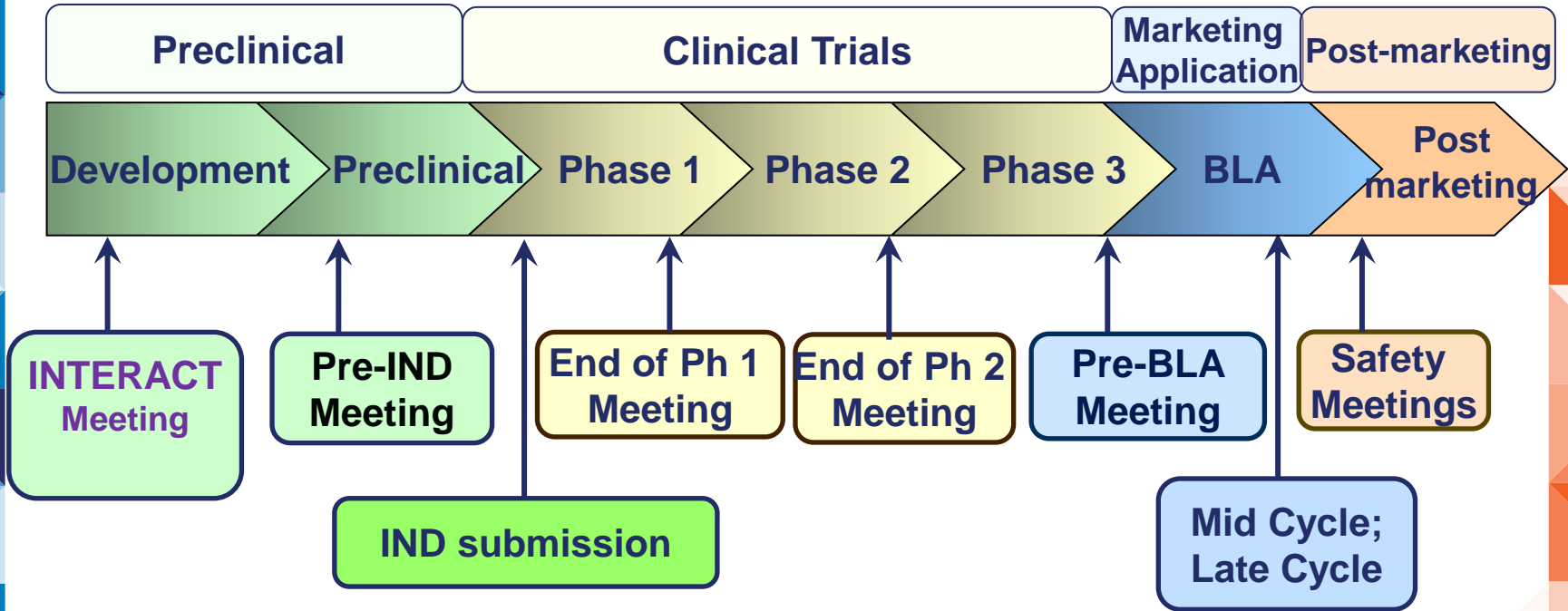
Pre-Marketing (Investigational) Application

- IND

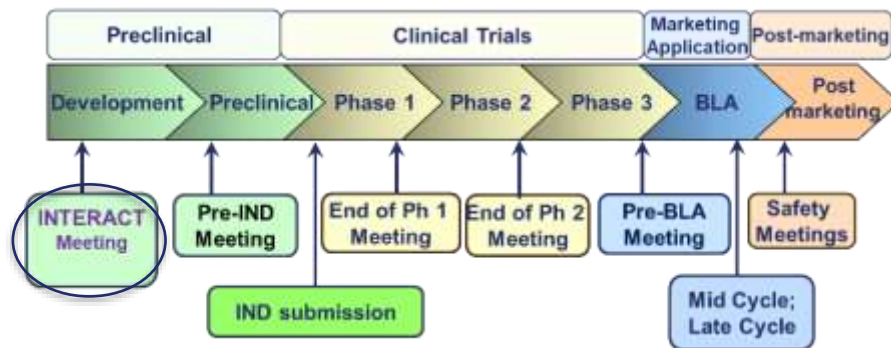
Marketing Application

- 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



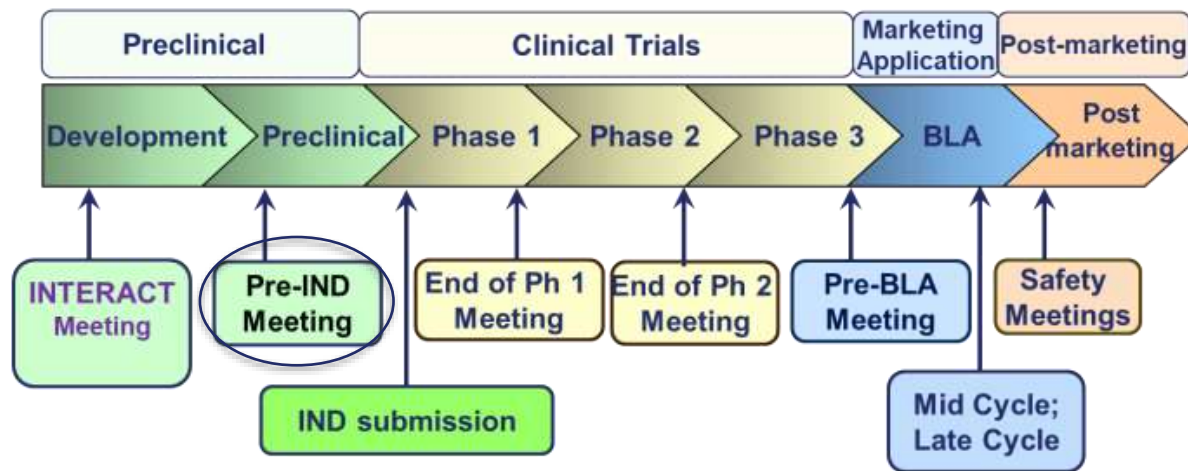
- Meeting package must accompany request with key issues and specific questions identified
- Refer to [CBER SOPP 8101.1](#): Regulatory Meetings with Sponsors and Applicants for Drugs and Biological Products
- Grant or deny decision within 21 days sent via email
- Written Response Only (WRO), teleconference,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



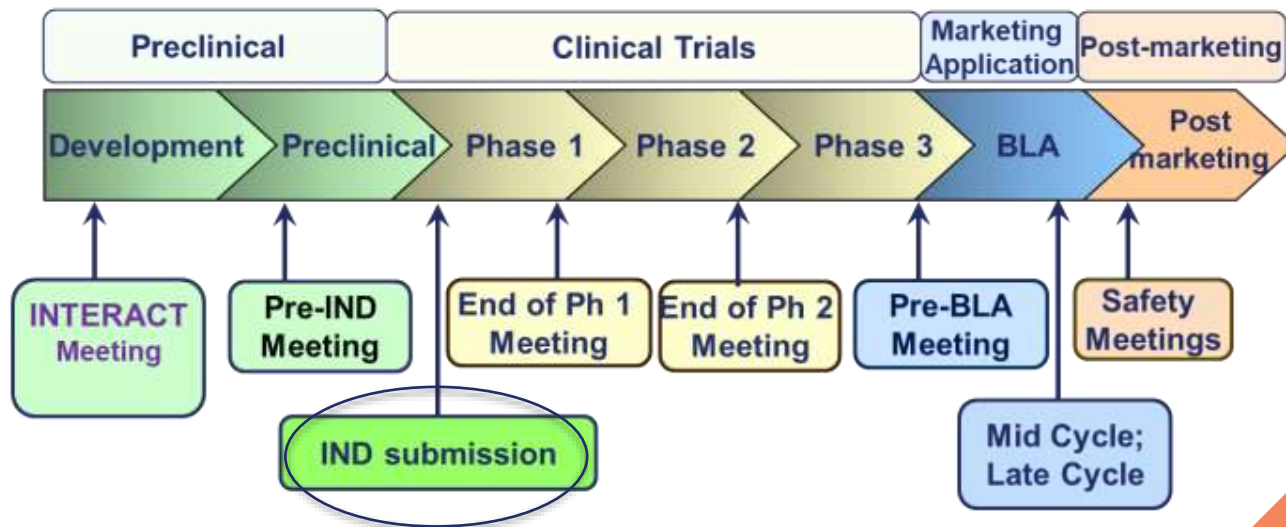
- Meeting scheduled within 60 calendar days
- WRO goal date by Day 60
- Meeting package due 30 days beforehand
- Preliminary Responses sent 2 days prior to meeting
- Sponsor response/agenda 1 day prior to meeting
- Formal meeting minutes within 30 days
- Request for clarifications within 20 days

Helpful INTERACT/pre-IND Tips



- Secure email (SecureEmail@fda.hhs.gov)
- 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

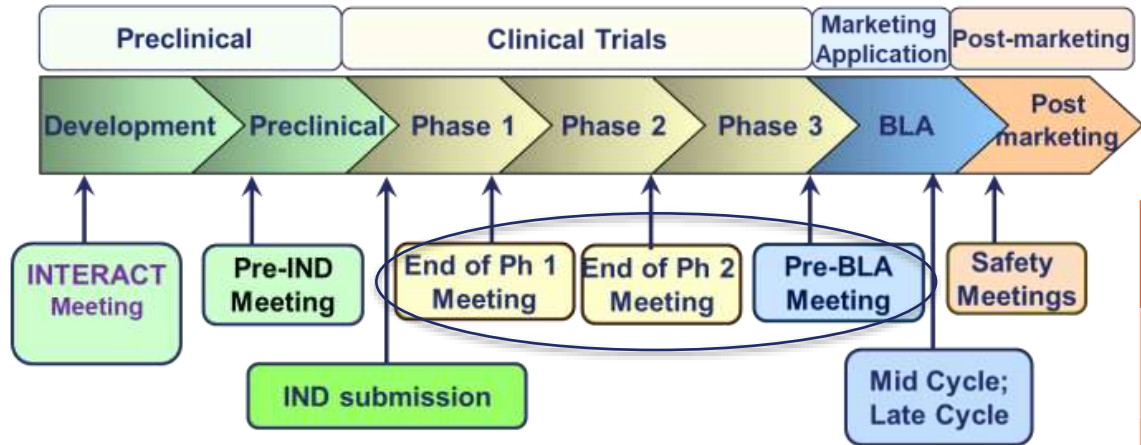
- Secure email
- Consider the 30-day timeline
 - Best days for submission M-W
 - Availability for email or telecon communications
 - Timely response

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

Biologics Master Files (MFs)

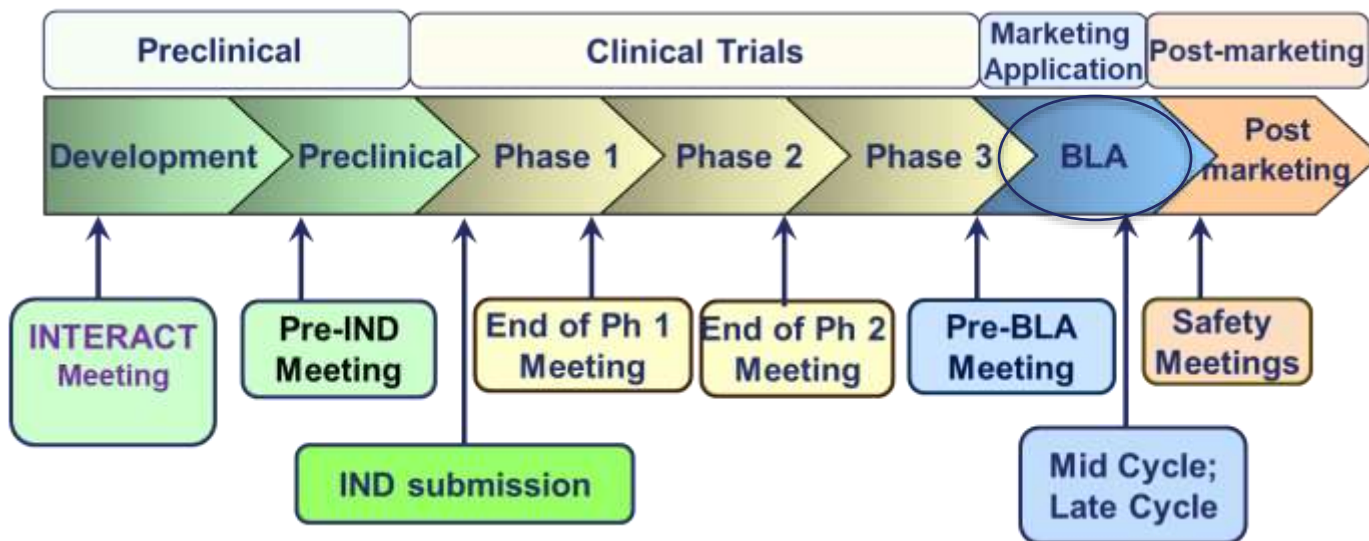
Master Files in CBER

- 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

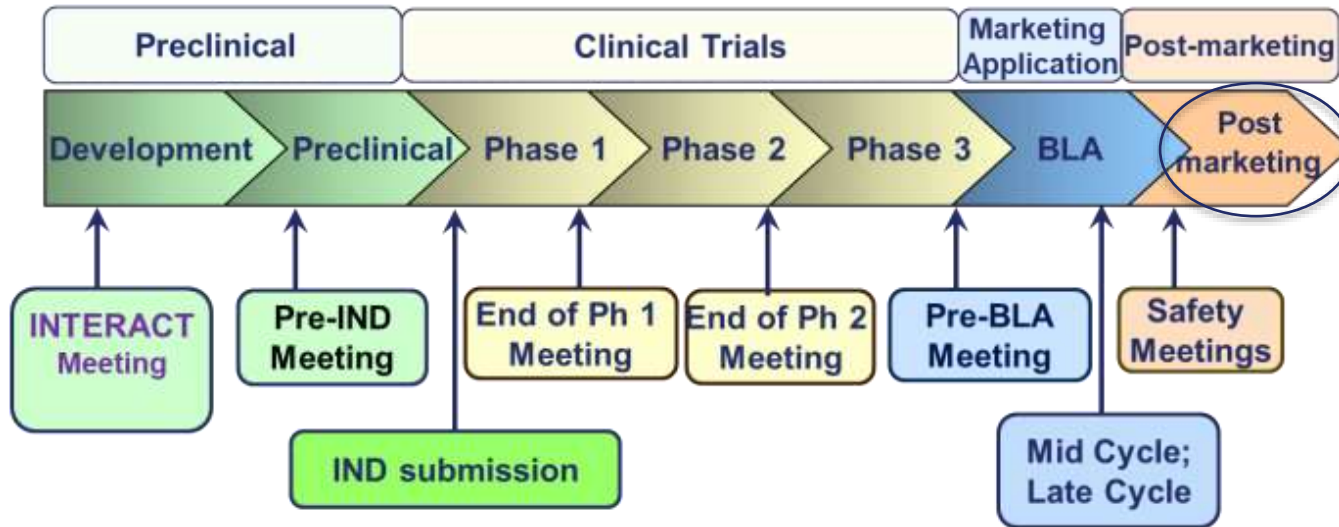
BLA Decisions

- 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



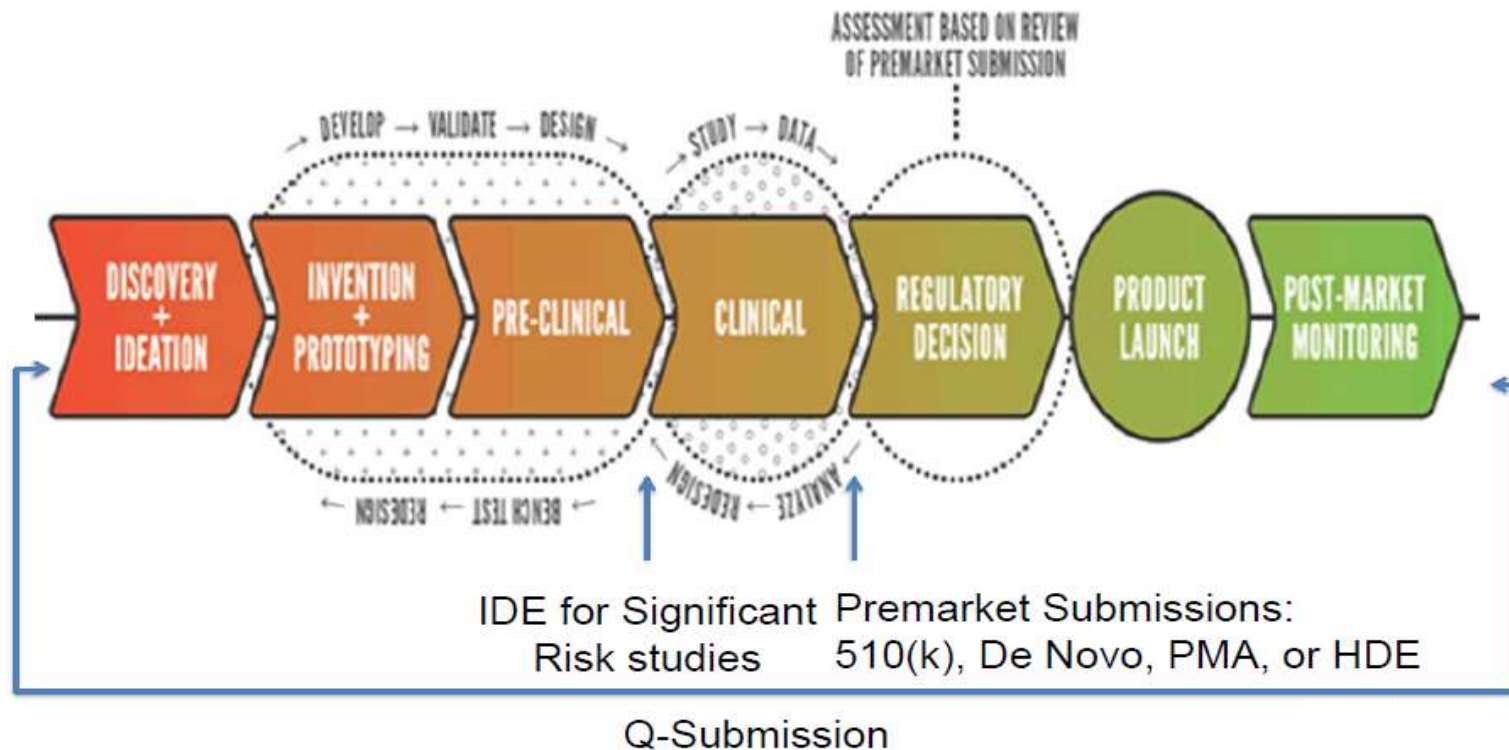
- Class I: Lowest Risk
 - Ex. Bandages, Hospital Bed
- Class II: Moderate Risk
 - Ex. Syringes, Mononuclear Cell collection for therapeutic use
- Class III: Highest Risk
 - Ex. Tissue and Cell Processing Devices at Point-of-Care

Devices Reviewed in OTP

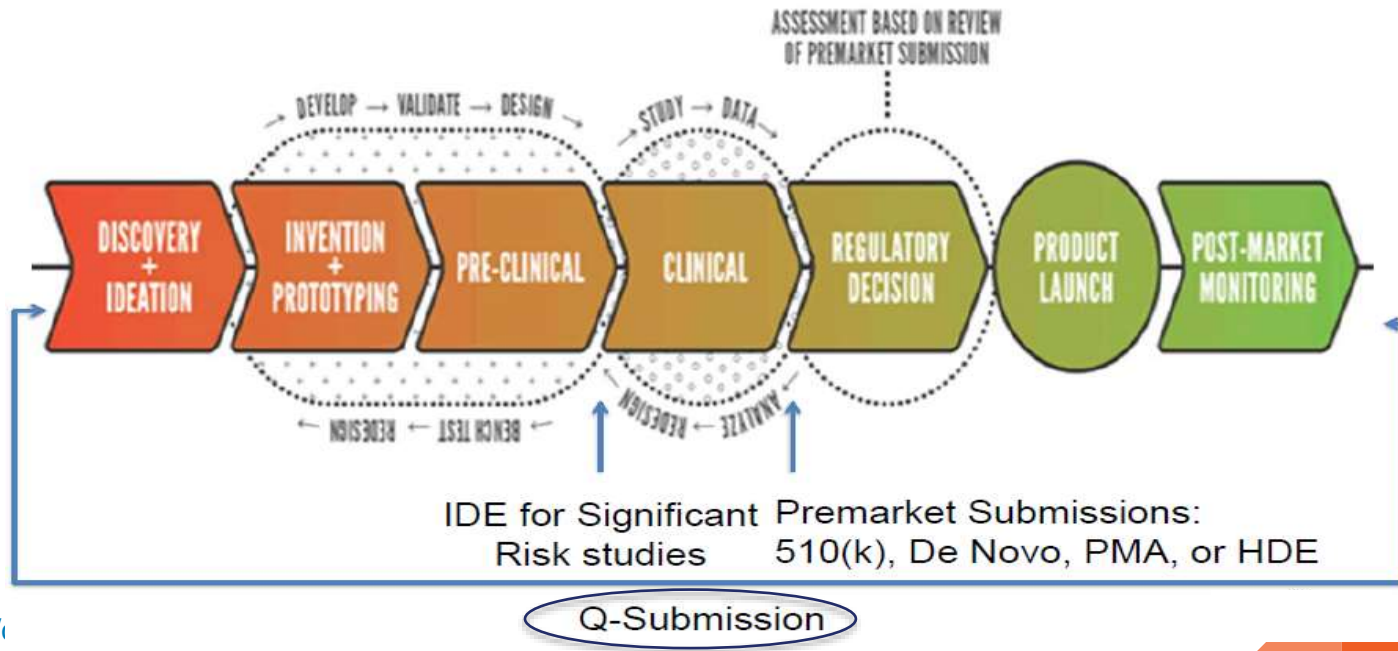


- Devices intended to process HCT/Ps (Human cells, tissues and cellular and tissue-based products) or other biologics *ex vivo* to generate device output at point-of-care
 - Therapeutic effect mediated by device output
 - Device output can be combined with another regulated article *in vitro* to generate 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-Submissions (Q-Subs)



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

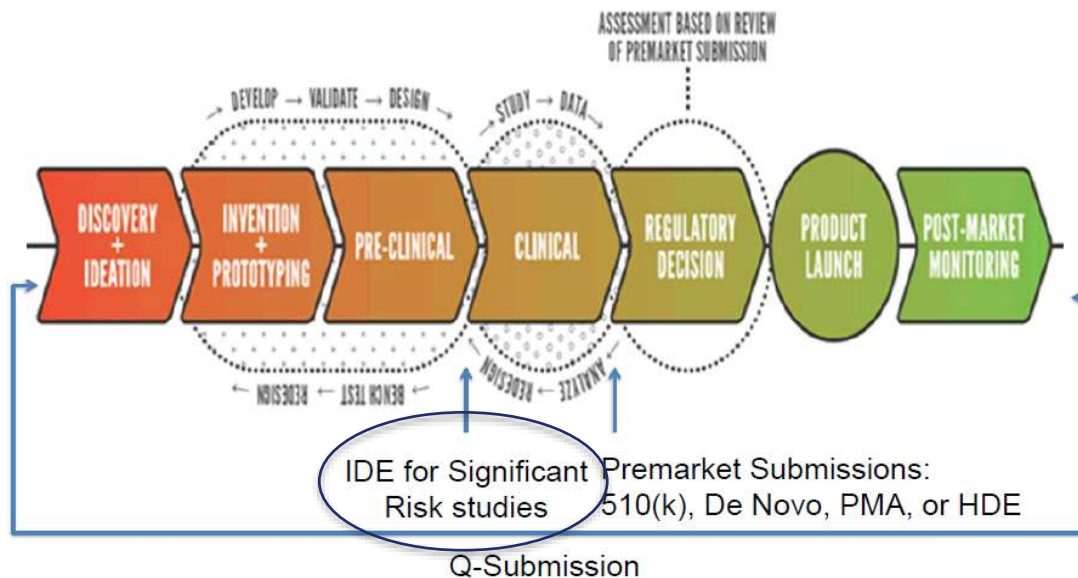


Table 1 – Q-Sub types and corresponding feedback mechanisms and timelines

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 or Written Feedback	If SIR is received within 60 days of FDA's marketing submission letter: 21 days as resources permit
		If SIR is received more than 60 days 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

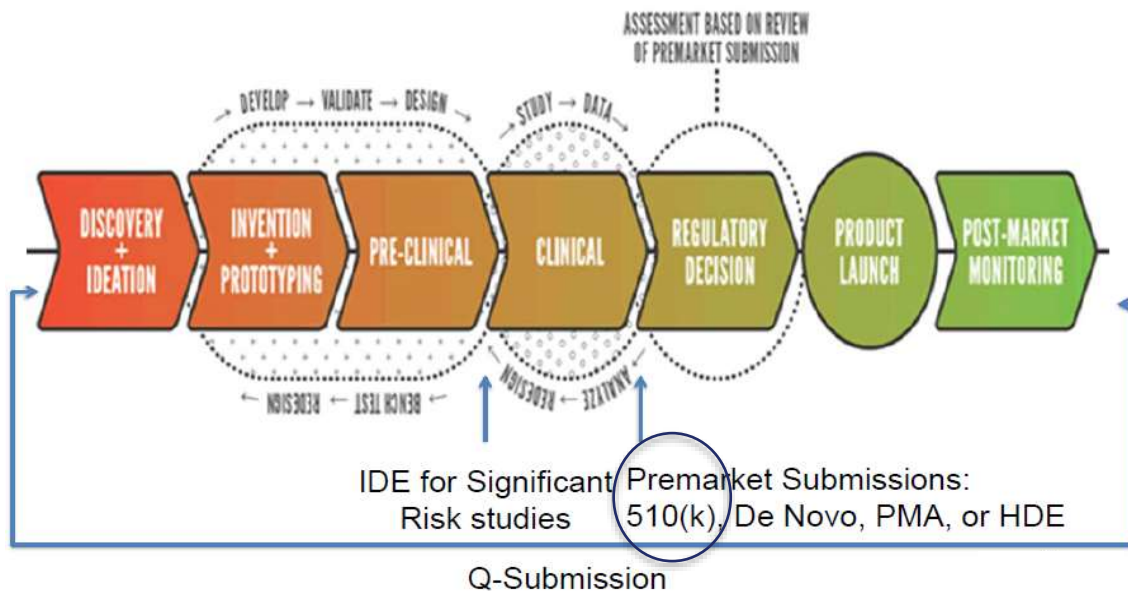
IDE Study Types

- 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

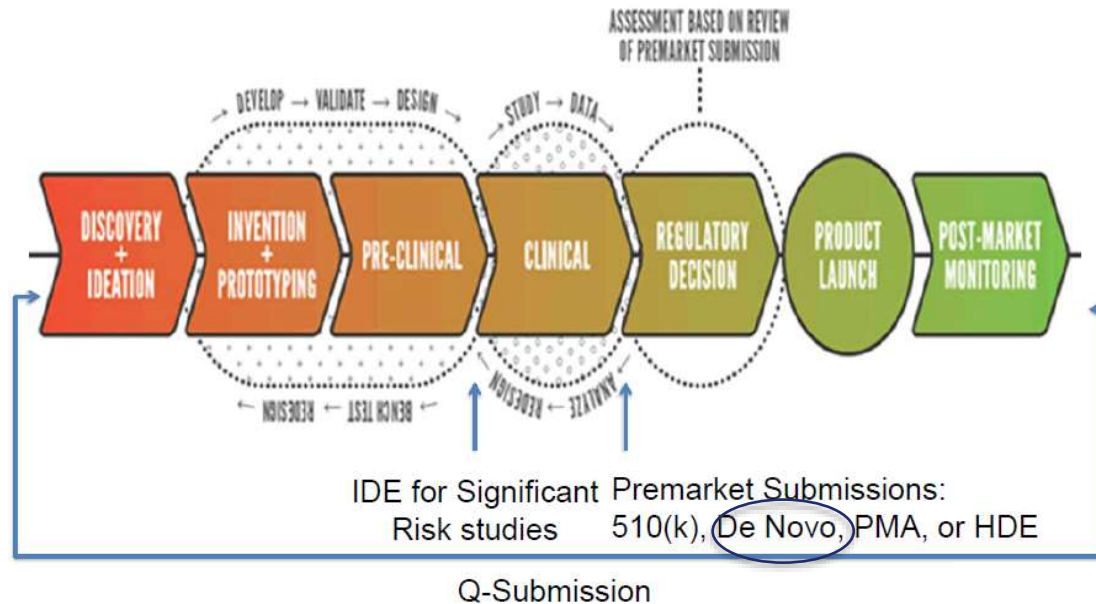
510(k) Submission



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

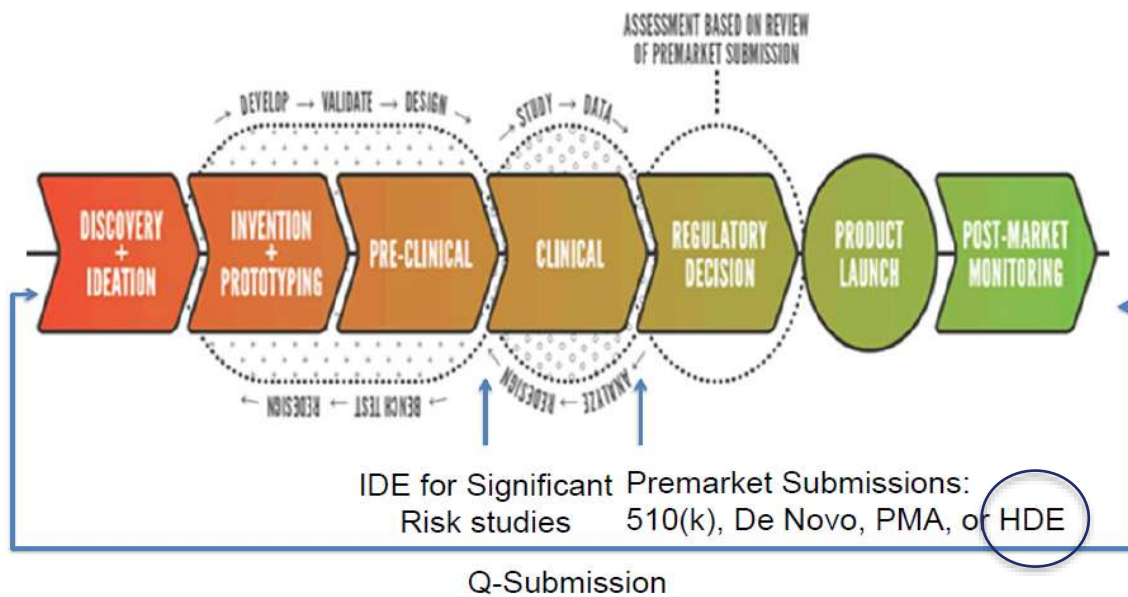


What is a De Novo?



- 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



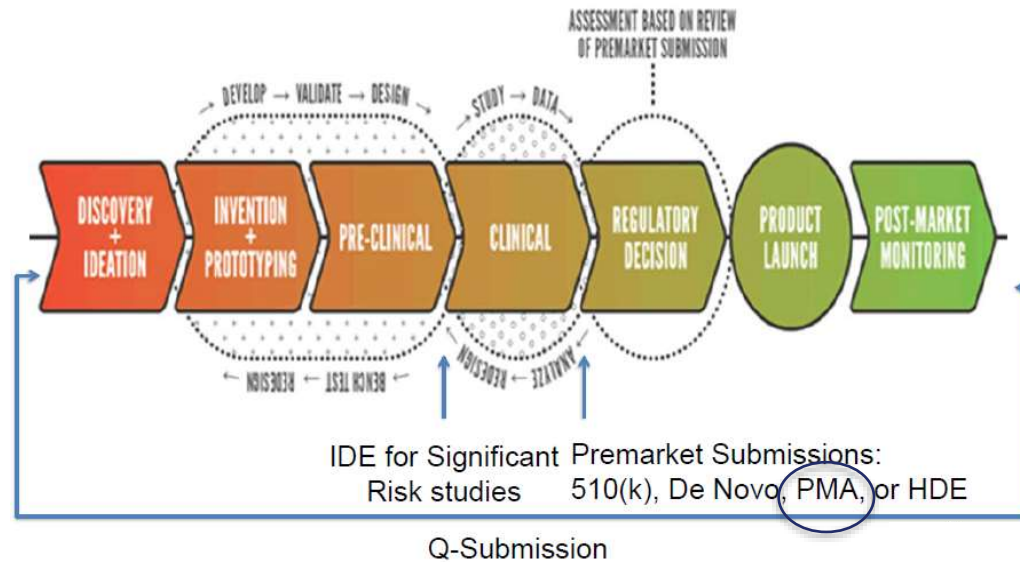
What is an HDE?



- 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)

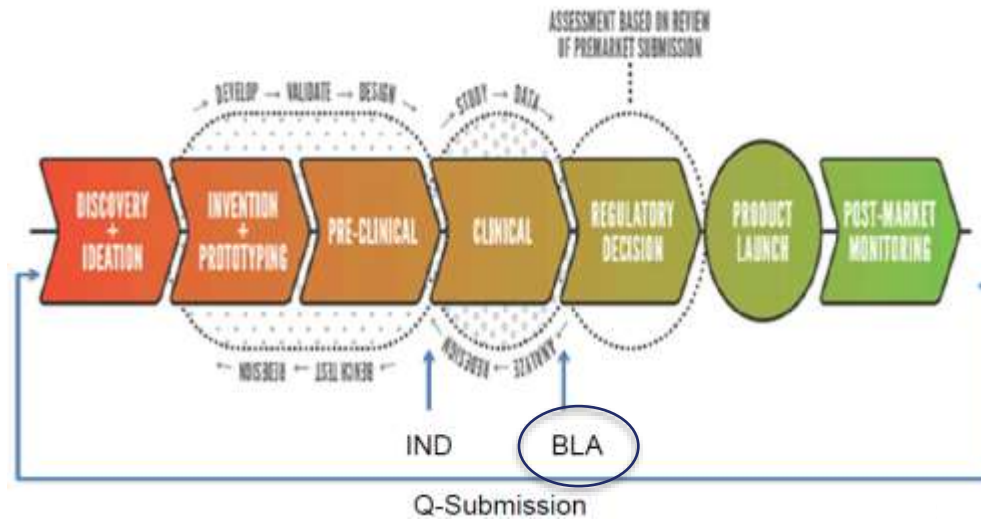


What is a PMA?



- 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

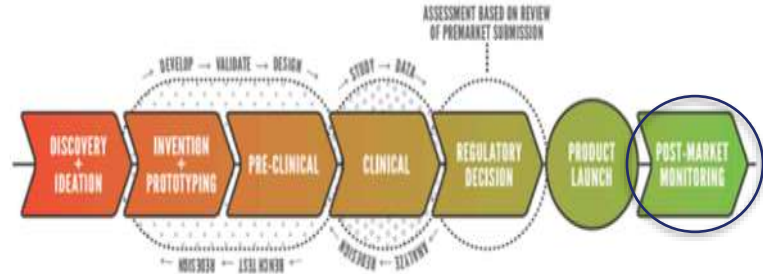
Device Biologics License Application (Device BLA)



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](#)

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

Contact Information



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- **Regulatory Questions:**
 - **OTP Main Line – 240 402 8190**
 - **Email:** 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
- **Phone:** 1-800-835-4709 or 240-402-8010
- **Consumer Affairs Branch:** ocod@fda.hhs.gov
- **Manufacturers Assistance and Technical Training Branch:** industry.biologics@fda.hhs.gov
- **Follow us on X, formerly twitter:** <https://www.twitter.com/fdacber>

