Overview of Development for 351 Biological Products

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Disclaimer

My Comments are an informal communication and represent my own best judgment. These comments do not bind or obligate FDA.

Learning Objectives

- Recognize the role of FDA/CBER/OTAT
- Describe a 351 biological product
- Identify the structure of an IND and BLA
- Select the appropriate PDUFA meeting types for milestones in product development
- Identify resources available for industry

FDA's Role

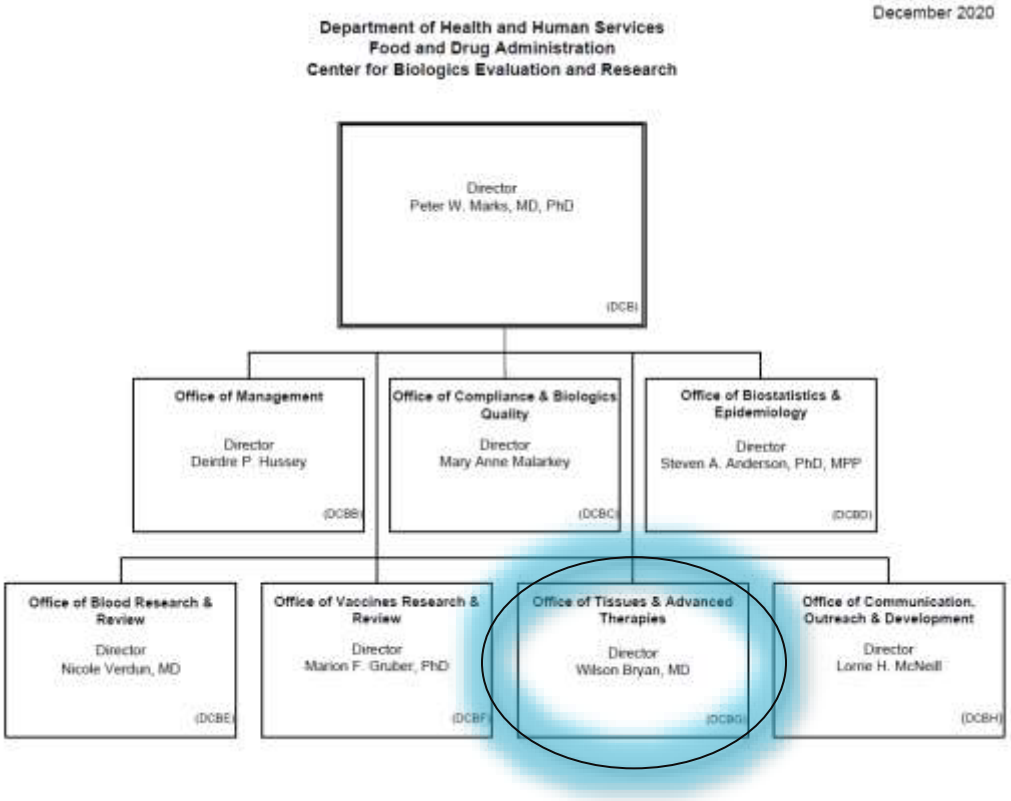

FDA
U.S. Department of
Health and Human Services
Food and Drug Administration

U.S. Food and Drug Administration (FDA)

FDA protects the public health by assuring the safety, efficacy, and security of:

- Human and veterinary drugs
- Biological products
- Medical and radiation-emitting devices
- Foods and cosmetics
- Tobacco Products

Center for Biologics Evaluation and Research (CBER)



CBER Regulates Complex Products

OTAT-Regulated Products

- **Gene therapies**
  - Ex vivo genetically modified cells
  - Non-viral vectors (e.g., plasmids)
  - Replication-deficient viral vectors (e.g., adenovirus, adeno-associated virus, lentivirus)
  - Replication-competent viral vectors (e.g., measles, adenovirus, vaccinia)
  - Microbial vectors (e.g., Listeria, Salmonella)
- **Stem cells/stem cell-derived**
  - Embryonic
  - Fetal (e.g., neural)
  - Perinatal (e.g., placental, umbilical cord blood)
  - Adult (e.g., hematopoietic, neural, cardiac, adipose, mesenchymal)
  - Induced pluripotent stem cells (iPSCs)
- **Functionally mature/differentiated cells** (e.g., retinal pigment epithelial cells, pancreatic islets, chondrocytes, keratinocytes)
- **Products for xenotransplantation**
- **Therapeutic vaccines and other antigen-specific active immunotherapies**
  - Peptide vaccines
  - Cellular immunotherapy (e.g., natural killer cells)
- **Blood- and Plasma-derived products**
  - Coagulation factors
  - Fibrin sealants, Fibrinogen, Thrombin, Plasminogen
  - Immune globulins
  - Anti-toxins, Snake venom antisera
- **Tissues**
- **Devices**
- **Combination products**
  - Engineered tissues/organs

U.S. Paradigm for Medical Product Regulation

Centralized (federal) authority for oversight	• FDA oversees the entire lifecycle of a medical product from investigational product development to post-marketing surveillance/study
Applicable laws with enforcement provisions	• Medical products subject to laws and regulations regarding clinical investigations and marketing authorization
Documented policies and guidelines available to public	• Federal Register (FR) • FDA Guidance Documents
Transparency / forum for public discussion	• FDA advisory committees; FDA-sponsored public workshops • FDA presentations at public meetings

What is a 351 biological product?

What is a 351 Biological Product?

- Section 351 of the Public Health Service Act of 1944 (PHS Act)
  - "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings."

**Section 351 of the Public Health Service Act (42. U.S.C § 262)*

* Federal Food, Drug, and Cosmetic Act (FD&C Act)

** Selected part of Title 21 Code of Federal Regulations (e.g., parts 300s, 600s, 1271s)*

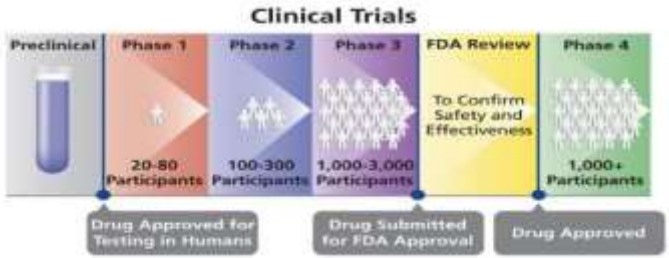
Biologics Regulation

- Biological drugs and biological devices licensed under PHS Act
- Additionally, regulated under the Federal Food, Drug, and Cosmetic Act (FD&C Act)
  - Title 21 Code of Federal Regulations (CFR)

21 U.S. Code § 355 (FD&C Act Sec. 505)

Regulatory Pathway for Biologics

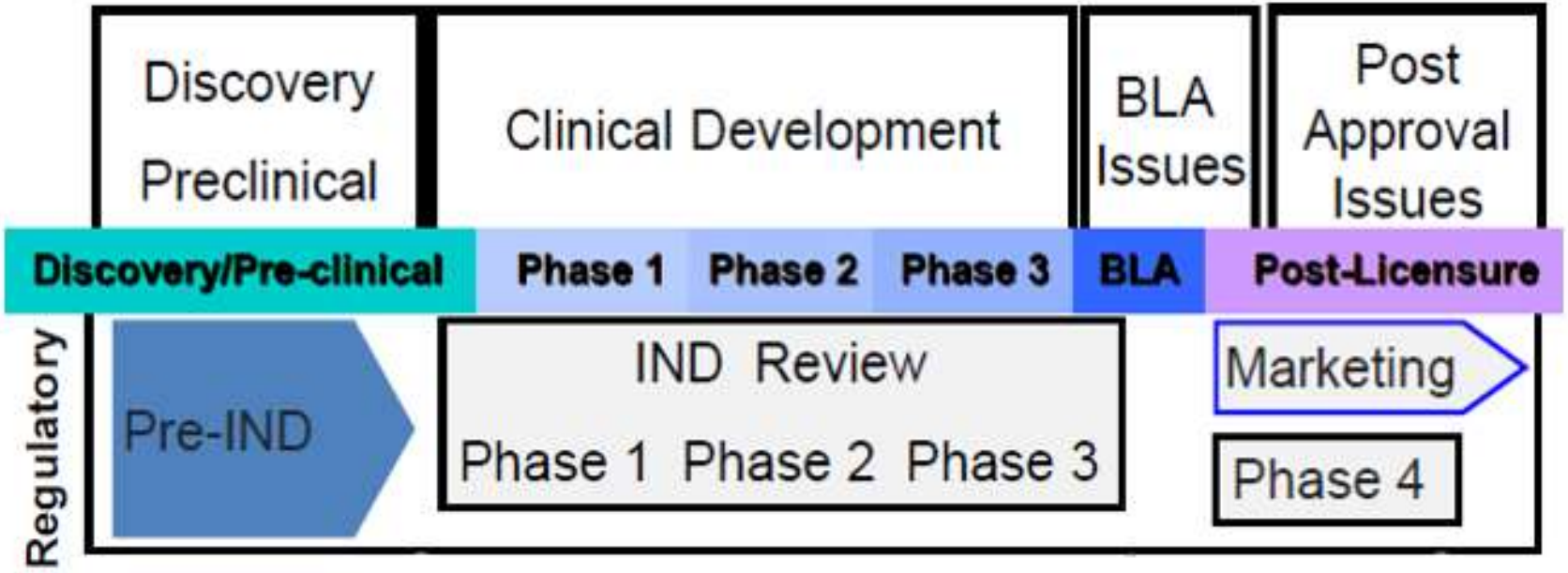
- A new biologic may be introduced into interstate commerce if an application has been approved by the FDA demonstrating the product's safety and effectiveness (BLA – Biologics License)



- Prior to licensure, an investigational biological product can only be distributed to clinical investigators and/or administered to humans with an Investigational New Drug application (IND) that is in effect

Lifecyle approach

Regulatory and Lifecycle Overview



*Prescription Drug User Fee Act (PDUFA VI)

Clinical Development: Investigational New Drug Application (IND)

Investigational New Drug (IND) Application

- The FDA regulates US clinical investigations of biological products
- Clinical investigations of an unapproved biologic must be conducted under an IND

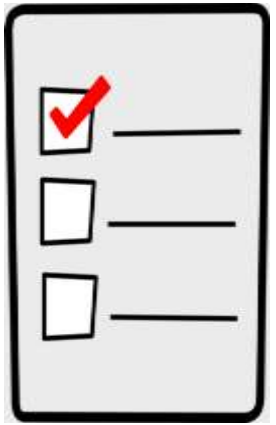
  -Ensure subjects' safety and rights (all phases)

  - Phases 2 and 3: ensure the scientific evaluation's quality is adequate to permit an evaluation of the product's effectiveness and safety.

  (21 CFR 312.22)

IND Submission Requirements

Investigational New Drug Applications (INDs) for CBER-Regulated Products



- 21 CFR 312
  - IND Requirements
    - 312.23 IND Content and Format
    - 312.47 Meetings
    - 312.50 – 312.69 Responsibilities of Sponsors/Investigators
- Forms FDA 1571 and 1572

IND Submission Process

1. Possible INTERACT and/or Pre-IND meeting (highly recommended for new products, new dosage forms, new routes of administration and new indications)

2. Submission of a complete IND application package

   – Electronic Common Technical Document (eCTD), Paper/PDF version to the DCC by email *

3. Conduct initial 30-day review for safety

   – Regulatory Actions: Study may Proceed/Active, Hold, Partial Hold

**Due to the current public health emergency, our normal business processes have temporarily changed.*

IND Interactions and Meetings

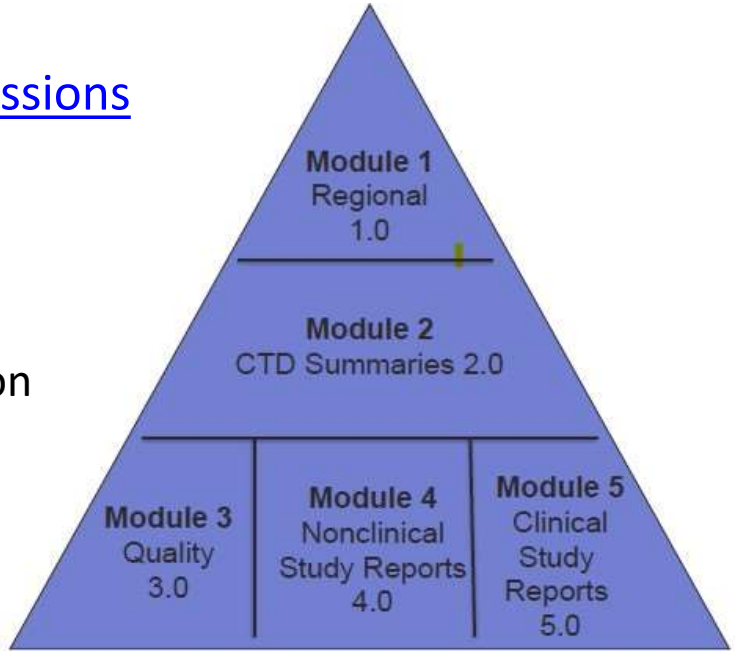
- Original submission – reviewers may contact sponsors by email during the 30-day review phase to request additional information (IR)
- Submitted as a formal amendments to the IND file
  - IND milestone meetings:
    - End of Phase 2/Pre-BLA
  - Others as needed for expedited programs
    - Breakthrough (BT)
    - Regenerative Medicine Advanced Therapy (RMAT) Designations

Marketing Phase: Biologics License Application (BLA)

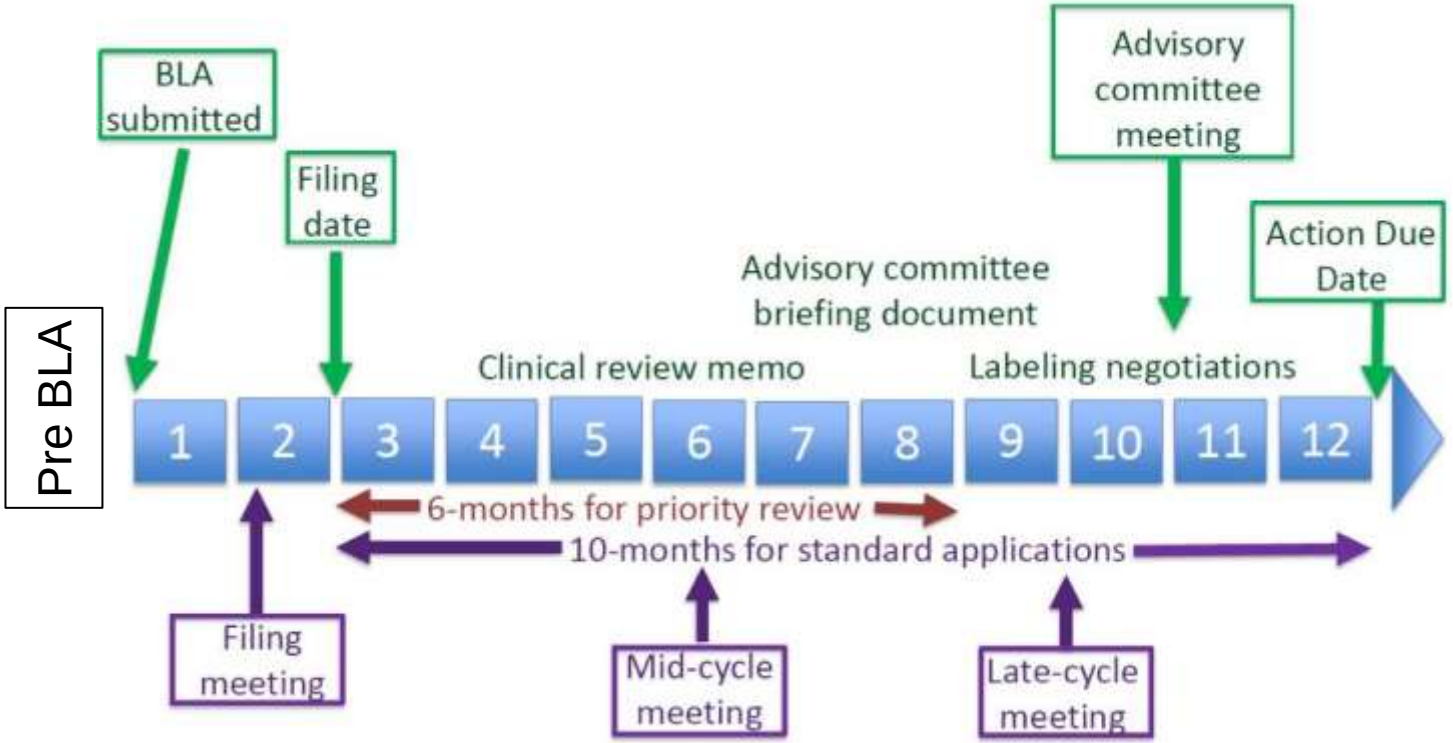
Biologics License Application (BLA)

- BLA requirements to support safety, purity, and potency *(21 CFR Part 601.2)*
- Submit Using eCTD via FDA Electronic Submissions Gateway (ESG) (Section 745A(a) of the FD&C Act)
  - Form FDA 356h
  - Administrative information
  - Product and manufacturing (CMC) information
  - Preclinical studies
  - Clinical studies
  - Labeling

(21 CFR 600-680)



Original BLA Review Cycle



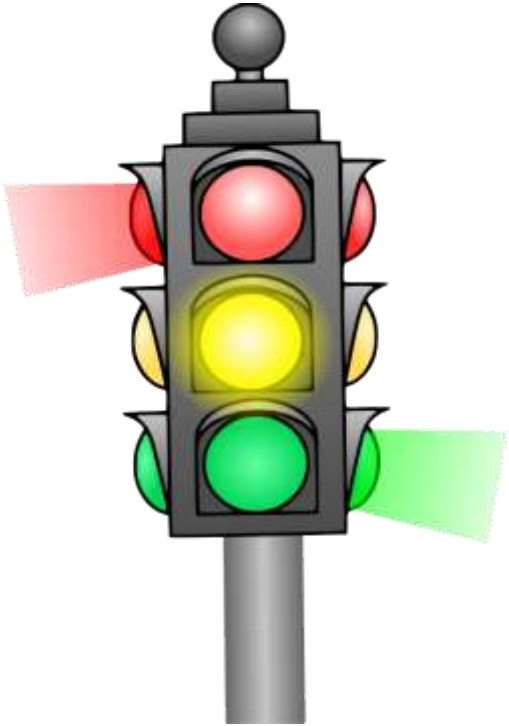
BLA Timeline

- Evaluation on a case-by-case basis to determine if the review timeline will be priority or standard.
- **Priority**: Products are eligible for priority review if they provide a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious or life-threatening disease.

Guidance for Industry: Expedited Programs for Serious Conditions - Drugs and Biologics

BLA Actions

- Actions by the FDA
  - Filing Action (60days)
    - Filing Letter or Refuse to File (RTF) (21 CFR 601.2(a))
  - Complete Response (stops the clock)
    - SOPP 8405.1: Procedures for Resubmission of an Application/Supplement
    - Class 1=2mo vs Class 2=6mo
  - Approval ☺
- Actions by the Sponsor
  - Withdraw (*75% if before Filing Action)



BLA Interactions and Meetings

- BLAs reviewed under PDUFA will have
  - Mid Cycle Communication
    - Generally, a teleconference/email with the applicant
  - Late Cycle Meeting
    - Typically, the last official meeting with the applicant to discuss any outstanding issues
- FDA may send information requests (IR) as needed
- Other: Application Orientation Meeting (AOM), Labeling, Advisory Committee (AC), REMS, and pre-license inspections at manufacturing facilities

Advisory Committee (AC) Meetings

- As needed, determined near BLA filing action date
- Should occur no later than two months (standard review) or no later than six weeks (priority review) prior to the user fee goal date

Guidance for Industry: Advisory Committee Meetings-Preparation and Public Availability of Information Given to Advisory Committee Members

BLA Amendments

- Responses to IRs, Proprietary Name Reviews (PNR), late/agreed to submissions
- Unsolicited amendment
  - May not be reviewed
- Major Amendment
  - Substantial amount of new data or a major reanalysis
  - Extends the review clock by 3 months
  - Only ONE major amendment per review cycle

Interactions and Meetings under PDUFA VI

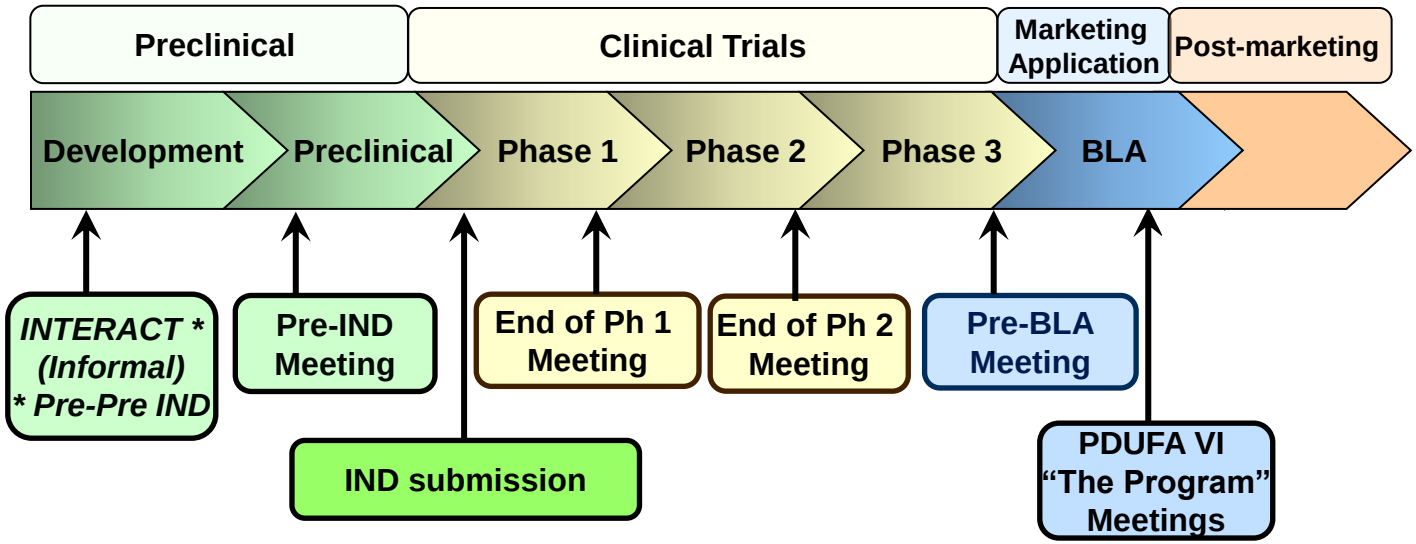
Formal Regulatory Meetings

- Provide guidance during product development and facility design, to facilitate compliance with regulations governing development and post-approval marketing of products (Dec 2017)

Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products Guidance for Industry

Best Practices for Communication Between IND Sponsors and FDA During Drug Development Guidance for Industry and Review Staff

Opportunities for Interaction During Product Development



INTERACT

Initial Targeted Engagement for Regulatory Advice on CBER producTs

(previously known as pre-pre-IND interactions)

- **Goal:** *To obtain early feedback on a product development program for a novel/innovative investigational agent*
- **Purpose**
  - A mechanism for early communication
  - Non-binding, informal scientific discussions between CBER review disciplines
  - Initial targeted discussion of specific issues
  - Meet specific requirements for requests to be granted

Meeting Types

(PDUFA VI)

- *Type A*
- *Type B*
- *Type B - End of Phase (EOP)*
- *Type C*

Type A Meetings

- Stalled product development
  - Important safety issues
  - Clinical Hold
    - Sponsor needs feedback on how to address hold issues
    - Sponsor responded, FDA reviewed, need new path forward
- Special Protocol Assessments (SPA) Nonagreement

***Contact FDA before requesting*

Type B Meeting

- Pre-IND *(21 CFR 312.82)*
- Pre-BLA *(21 CFR 312.47)*
- Breakthrough therapy (BT) Designation
- Regenerative Medicine Advanced Therapy Designation (RMAT)– designated product development program discussions *(21st Century Cures Act)*

Type B (EOP) Meeting

- End-of-phase (EOP) 1 for subpart E or H *(21 CFR 312.82)*
- EOP 2 / Pre-phase 3 *(21 CFR 312.47)*
  - Pediatric Study Plan (PSP) should have been discussed with applicant prior to BLA submission (EOP2 or pre-BLA) –agreed PSP must be part of the BLA or reference that an agreed PSP is in place

Pediatric Research Equity Act (PREA)

Type C Meetings

- Anything else related to development and review of a product
- Facility meetings with Division of Manufacturing and Product Quality (DMPQ)
- CMC issues with marketed product
- Special Type C Meeting for early consultation on use of a *new surrogate endpoint*

PDUFA Timelines

Meeting Type	Meeting Confirmation (after receipt)	Receipt of Meeting Package (before meeting)	Preliminary Response (before meeting)	Meeting to be held or WRO (after receipt)
A	14	With the request	2	30
B	21	30	2	60
B (EOP)	14	50*	5**	70
C	21	47*	5**	75
C (Surrogate EP)	21	With the request	5**	75, WRO does not apply***

* If meeting is scheduled earlier than Day 70 Type B (EOB)/Day 75 Type C, the package is due on Day 20 Type B (EOP)/Day 28 Type C

** Please respond within 3 days of receipt of preliminary response

*** Not a PDUFA mandate but a CBER policy

Meeting Formats

- Face-to-Face
  - Example: Pre-BLA meeting, EOP2, Type A
- Teleconference
  - Examples: INTERACT, Pre-IND
- Written Responses
  - Can be requested by the sponsor for any meeting type

  FDA may change a requested response format, pending review of the meeting request and/or package

  **The pandemic and OTAT's meeting workload may impact the format of the meeting granted*

Submitting to FDA/CBER

- Electronic

  *Setting up FDA Secure email : send request to *SecureEmail@fda.hhs.gov*

  – FDA Electronic Submissions Gateway (ESG) (all commercial, BLA, and phase 3 INDs)

  – Email single PDF to Document Control Center (DCC) or various personnel in CBER (Research, IR)

    - *CBERDCC_eMailSub@fda.hhs.gov . We will accept these submissions through this email option only during the COVID-19 public health emergency.*

- Mail in: ~~Paper or a CD or a USB drive to DCC *~~
- Request for pre-assigned Submission Tracking Number (STN) for CBER only

  – Please send your request for a pre-assigned STN to Regulatory Information Management Staff (RIMS) CBERRIMS@fda.hhs.gov . In your request, please include the name and address of the Sponsor (including city, state, zip), the contact person for the file (including phone #), the name of the specific biologic product and the anticipated submission date.

Challenge Questions

Challenge Question #1

The FDA regulates and approves biological products under the authority of:

A. 21 CFR 312

B. Section 351 of the PHS Act

C. Don’t Know

Challenge Question #2

Which regulatory pathway allows a new biological product to be exempt from restrictions on interstate shipment and administration?

A. IND

B. BLA

C. Don’t Know

Resources

Resources

- PHS Act
  - https://www.govinfo.gov/content/pkg/COMPS-8773/pdf/COMPS-8773.pdf
- Federal Food, Drug, and Cosmetic Act (FD&C Act)
  - https://www.fda.gov/regulatory-information/laws-enforced-fda/federal-food-drug-and-cosmetic-act-fdc-act
- Prescription Drug User Fee Act (PDUFA VI)
  - https://www.fda.gov/industry/fda-user-fee-programs/prescription-drug-user-fee-amendments
- 21 CFR 312 – Investigational New Drug Application Regulations
  - https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=312
- Biologics License Applications (BLAs)
  - https://www.fda.gov/drugs/types-applications/therapeutic-biologics-applications-bla

Resources

- FDA Regulation of CBER-Regulated Products
  - https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics)
- **IN**itial **T**argeted **E**ngagement for **R**egulatory **A**dvice on **C**BER produc**T**s (INTERACT)
  - https://www.fda.gov/vaccines-blood-biologics/industry-biologics/interact-meetings
- Submission of an Investigational New Drug Application (IND) to CBER
  - https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-applications-inds-cber-regulated-products/submission-investigational-new-drug-application-ind-cber
- CBER Standard Operating Procedures and Policies (SOPPs)
  - https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-procedures-sopps
- CBER Secure Email Policy Takes Effect October 1, 2018
  - https://www.fda.gov/vaccines-blood-biologics/workshops-meetings-conferences-biologics/cber-secure-email-policy-takes-effect-october-1-2018

Resources

- Forms & Submission Requirements
  - https://www.fda.gov/drugs/development-approval-process-drugs/forms-submission-requirements
- Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products Guidance for Industry
  - https://www.fda.gov/media/109951/download
- Best Practices for Communication Between IND Sponsors and FDA During Drug Development Guidance for Industry and Review Staff
  - https://www.fda.gov/media/94850/download
- Guidance for Industry: Advisory Committee Meetings-Preparation and Public Availability of Information Given to Advisory Committee Members
  - https://www.fda.gov/media/75436/download

Resources

- FDA Forms
  - https://www.fda.gov/about-fda/reports-manuals-forms/forms
- Electronic Submissions Gateway
  - https://www.fda.gov/industry/electronic-submissions-gateway
- Guidance for Industry: Electronic Common Technical Document (Submit Using eCTD)
  - https://www.fda.gov/media/135373/download
- eCTD Modules: *The Comprehensive Table of Contents Headings and Hierarchy*
  - https://www.fda.gov/media/76444/download

Resources

- Pediatric Research Equity Act (PREA)
  - https://www.fda.gov/media/71891/download
- Guidance for Industry: - Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans
  - https://www.fda.gov/media/86340/download
- Guidance for Industry: Expedited Programs for Serious Conditions - Drugs and Biologics
  - https://www.fda.gov/media/119293/download
- Guidance for Industry Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act
  - https://www.fda.gov/media/89049/download

Contact Information

- **Jennifer Albert, BSN, RN @** Jennifer.Albert@fda.hhs.gov
- **Regulatory Questions:**
  - **OTAT Main Line – 240-402-8190**
    Email: OTATRPMS@fda.hhs.gov
- **OTAT 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 Twitter:** https://www.twitter.com/fdacber

FDA Headquarters

Questions?

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