

Biologics License Application (BLA)

Andy Papas, PhD, MBA

Vice President of Regulatory Affairs

NSF International

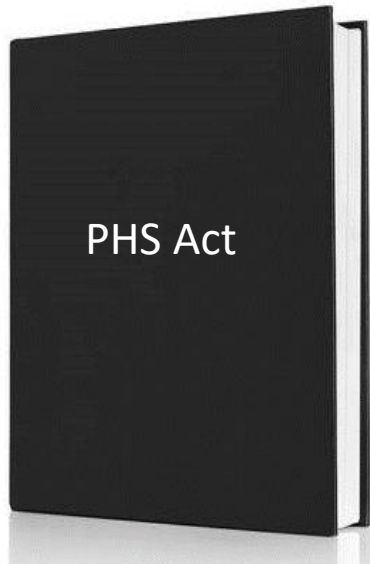


Objectives

- BLA approval standards
- BLA contents and organization
- FDA review timeline and milestones
- FDA's decision and post-approval commitments
- Other approaches



Approval Standard – Original BLA



PHS Act 351(a) (42 U.S.C. 262(a)(2)(C))

“The Secretary shall approve a biologics license application (i) on the basis of a demonstration that:

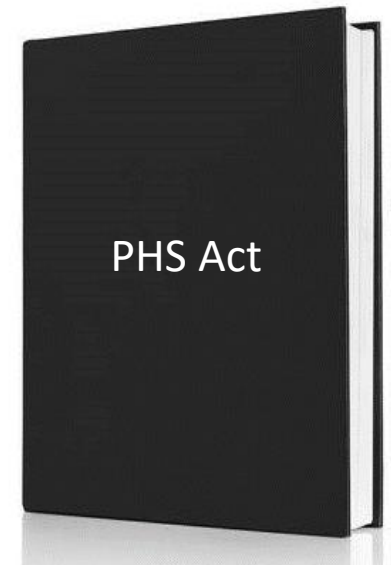
- (I) the biological product ... is **safe, pure, and potent**; and
- (II) the **facility** in which the biological product is manufactured, processed, packed, or held **meets standards** designed to assure that the biological product continues to be **safe, pure, and potent”**

Approval Standard – Biosimilar BLA

PHS Act 351(k) (42 U.S.C. 262(k)(3)):

“the Secretary shall license the biological product under this section if:

- a. ...information submitted...show[s] that the biological product—
 - i. is **biosimilar to the reference product**; or
 - ii. meets the standards [to be] **interchangeable with the reference product**; and
- b. ...the applicant...consents to inspection of facility ...”



Effectiveness

- **Potency** long been interpreted to include **effectiveness** (21 CFR 600.3(s))
- FDA generally considered **substantial evidence (SE)** of **effectiveness** to be necessary to support licensure:
 - Statute used to require two adequate and well-controlled trials
 - Changed in 1997 (FDAMA)
 - Rely on quality and quantity of SE (study design, endpoint(s), etc.)



Race and Ethnicity In New/Novel Drugs

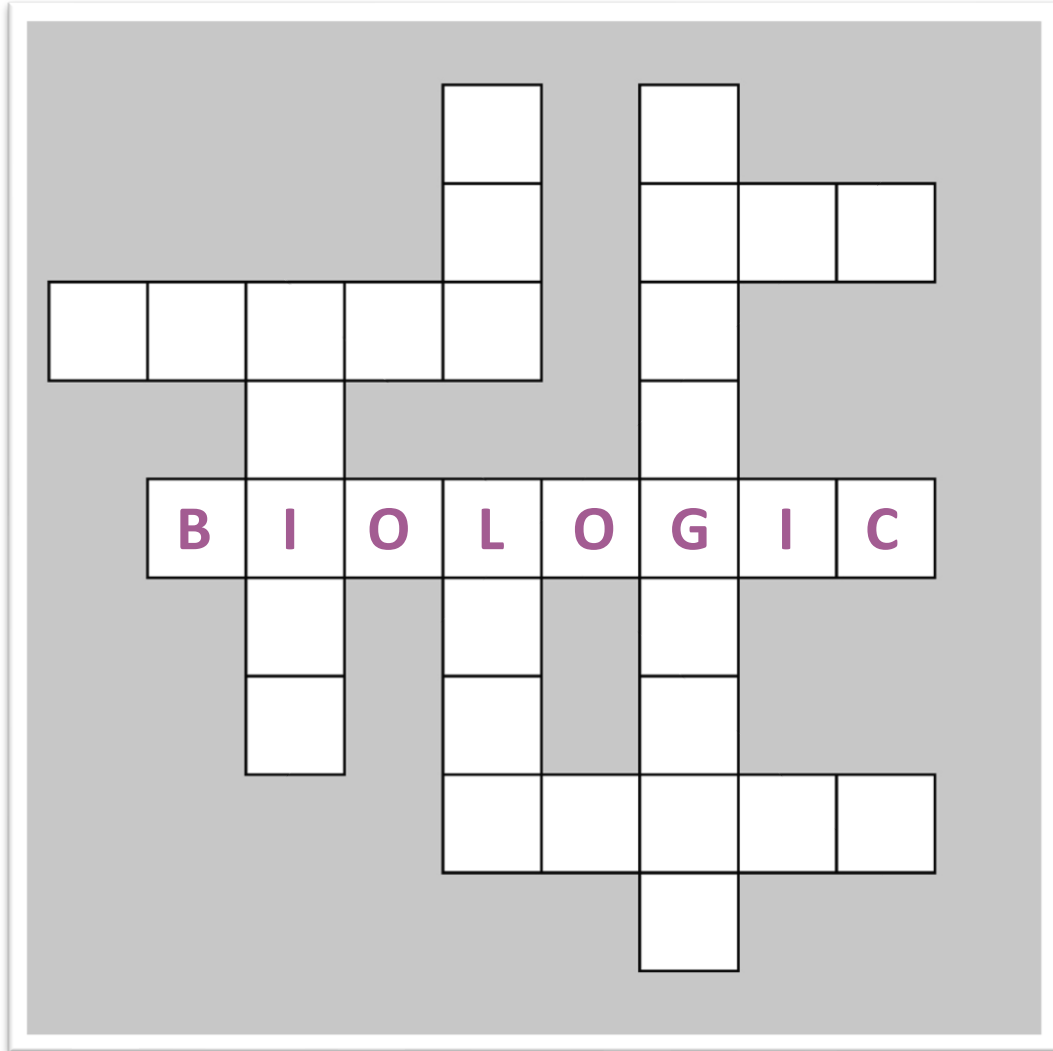
2020 NME/NBEs	Gender	Ethnicity				Age	US vs abroad
	Women vs Men	White	Black or African American	Asian	Hispanic	Age 65 or older	Conducted in US
Overall Average	56%	75%	8%	6%	11%	30%	54%

Clinical data, on average, getting a lot smaller, more female, less diverse [2015 to 2020]*

*FDA Today, The clinical data behind new drug approvals, Alexander Gaffney, Politico's AgencyIQ, 22-JAN-2021

BLA Contents and Organization

Legal Definition of Biologic



- Virus
- Therapeutic serum
- Toxin, antitoxin
- Vaccine
- Blood, blood component or derivative
- Allergenic product
- Protein (except any chemically synthesized polypeptide)
- Arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound)
- Applicable to the prevention, treatment, or cure of disease or conditions of man

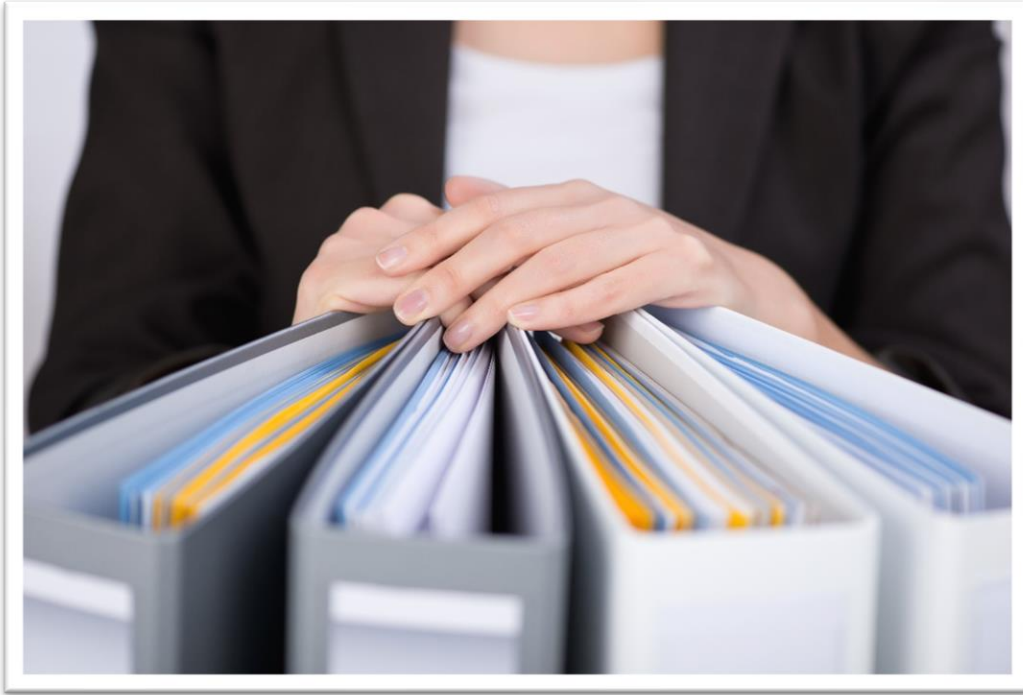
Question #1

Which of the following type of biological product is NOT overseen by CBER?

- a. Virus
- b. Therapeutic serum
- c. Toxin, antitoxin
- d. Vaccine
- e. Blood, blood component or derivative
- f. Allergenic product
- g. Protein (except any chemically synthesized polypeptide)



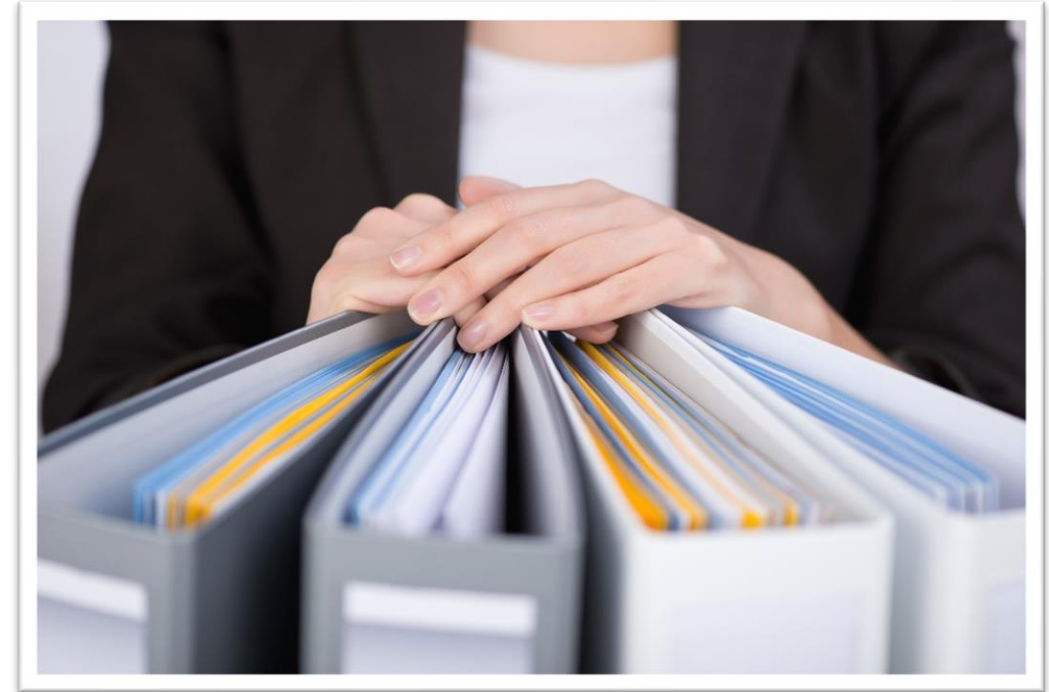
BLA Content and Organization



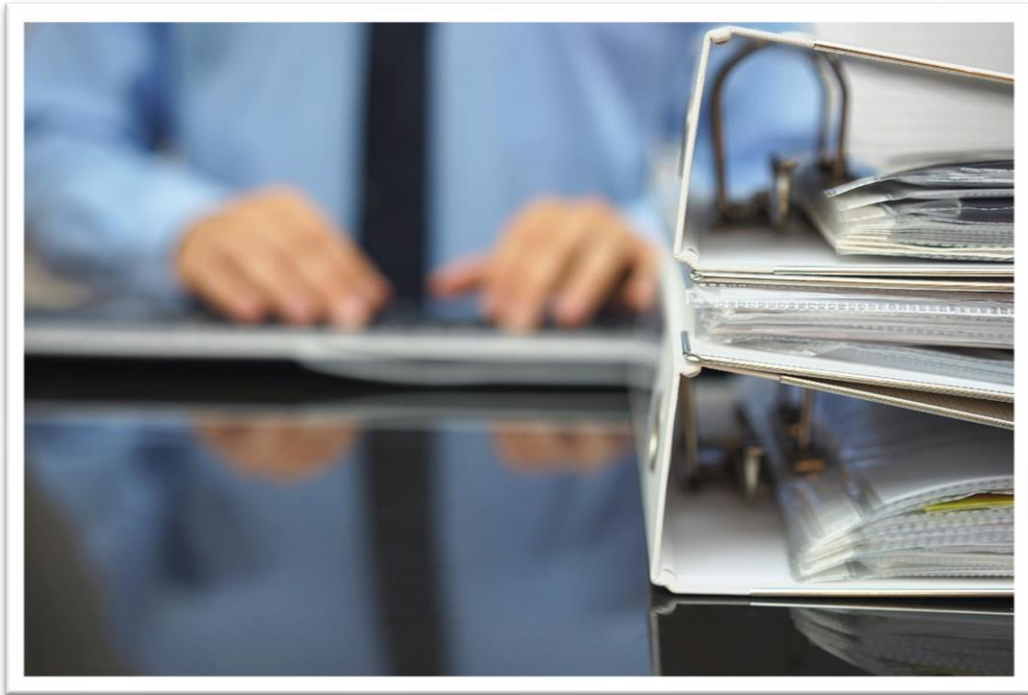
1. Administrative information
2. Non-clinical study data demonstrating **safety**
3. **Effectiveness**: All human clinical study data and related information:
 - Early safety and preliminary efficacy data
 - Pivotal possibly multi-center **efficacy** studies
 - Literature references
4. Product **quality**:
 - Manufacturing facilities, validated processes and controls
 - Validate analytical methods, batch results, product specifications
 - Product stability data for shelf-life determination

351(k) BLA Content and Organization

1. Administrative information
2. Non-clinical study data:
 - **Comparative** non-clinical data
3. All human clinical study data and related information:
 - **Comparative** clinical data
4. Product quality:
 - Manufacturing facilities, validated processes and controls
 - Validate analytical methods, batch results, product specifications
 - Product stability data for shelf-life determination
 - **Extensive comparative analytical characterization data**



BLA Content and Organization



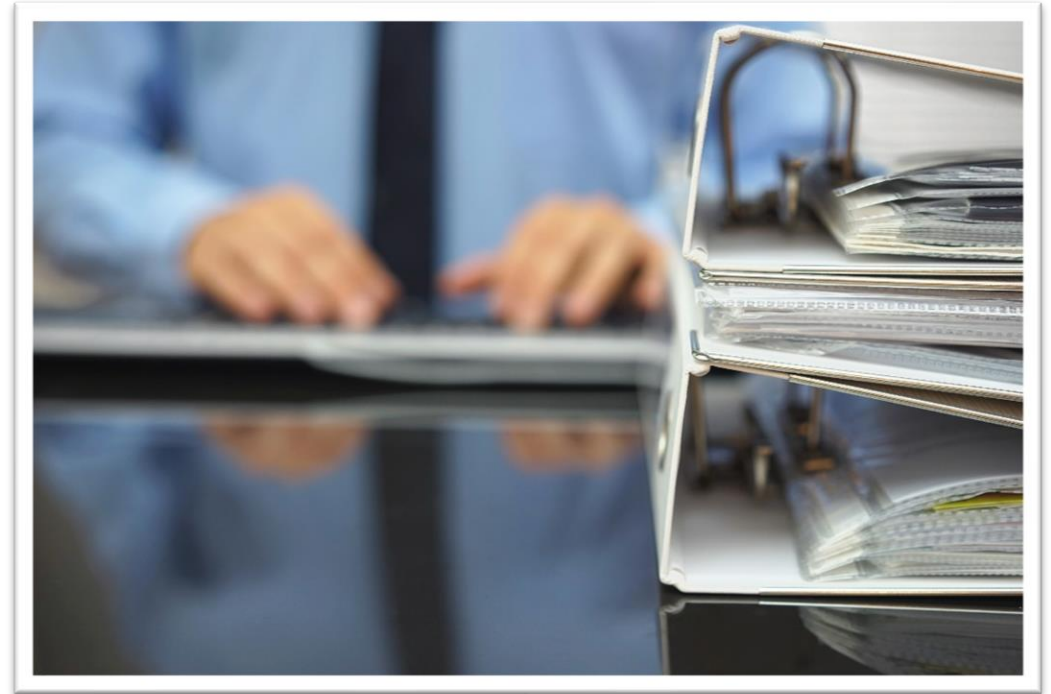
Administrative content (incomplete list):

- Statements of conformance
 - GLP conformance
 - Debarment certification
 - ClinTrials.gov compliance certification
- Financial disclosures of clinical investigators
- Patent information
- Proposed professional labeling
 - Fundamentally based on pivotal clinical trials results

BLA Content and Organization

Administrative content (continued):

- All significant interactions with FDA:
 - Meeting requests (PIND, EOP2, pre-BLA, type C meeting, etc.), briefing documents and minutes; other correspondences from agency interactions
- Letter(s) of Authorization to Drug Master Files (DMF) and/or BMF
- PDUFA User Fee Cover sheet

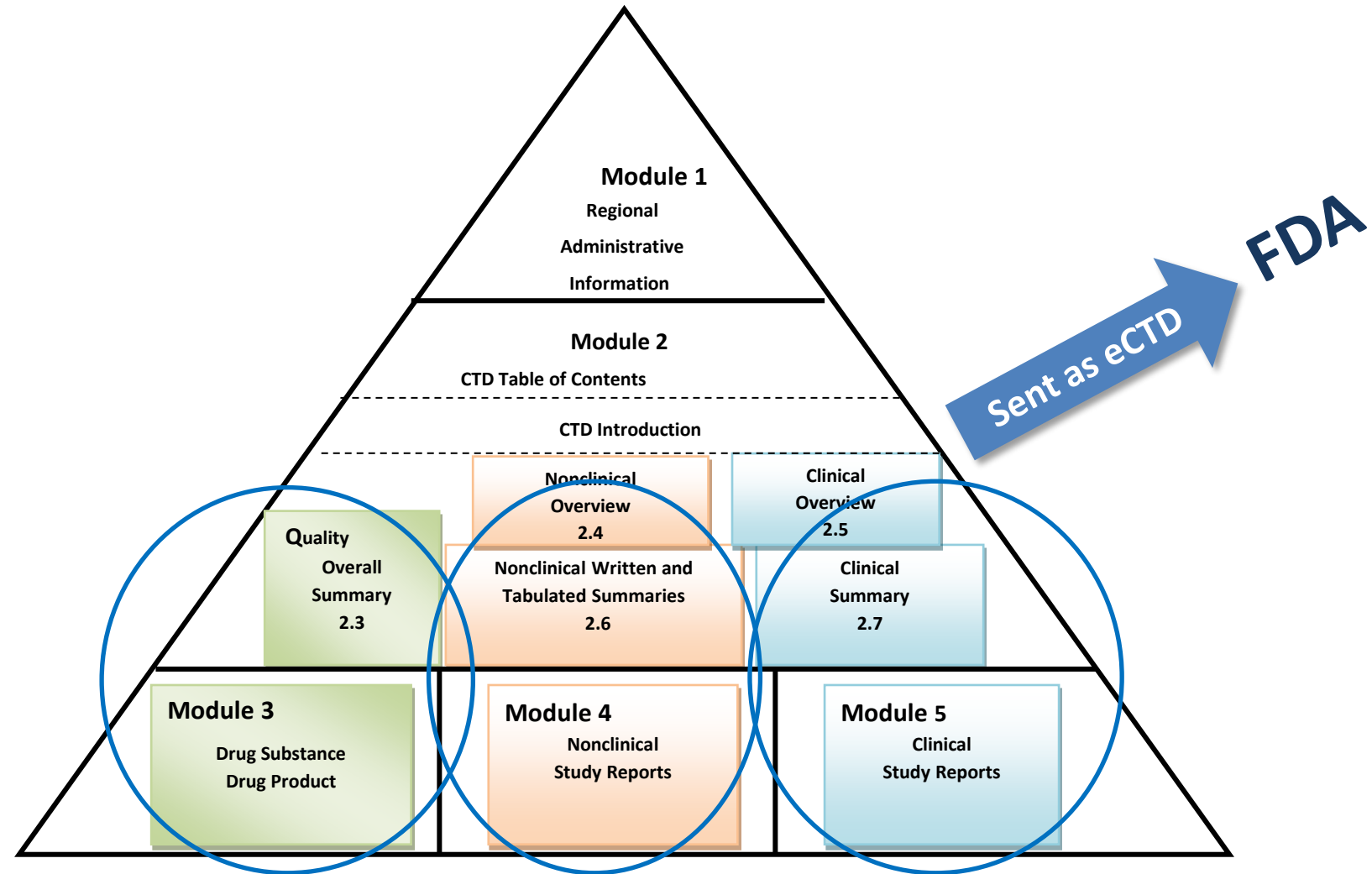


BLA Content and Organization

A LOOK UNDER THE HOOD



ICH Common Technical Document (CTD) Triangle



Major Categories:

CMC: Quality

Non-Clinical: Safety

Clinical: Efficacy

Question #2

If BLA contents were to be submitted to FDA today in paper, how many 3 1/2" binders do you think it would take per BLA copy?

- a. 5
- b. 10
- c. 20
- d. 30
- e. 50



FDA Review Timeline and Milestones

FDA's PDUFA BLA Application Fee

PDUFA VI BLA Fee

- 351(a) BLA Application fee w/ clinical data - \$3,117,218 (FY'22)
 - Paid up front
- Review period for Action
 - 90% of **original** BLAs within 10 months of **initial** filing date
 - 90% of **priority** 351(a) BLAs within 6 months of **day-60** filing date



FDA's BsUFA BLA Application Fee



BsUFA II Biosimilar BLA Fee

- 351(k) BLA Application fee w/ Clinical data - \$1,746,745 (FY'22)
- 351(k) BLA Application fee **w/o** Clinical data - \$873,373 (FY'22)
 - Paid up front
- Review period for Action
 - 90% of **original** 351(k) BLAs within 10 months of day-60 filing date
 - 90% of **resubmitted** 351(k) BLAs within 6 months of receipt

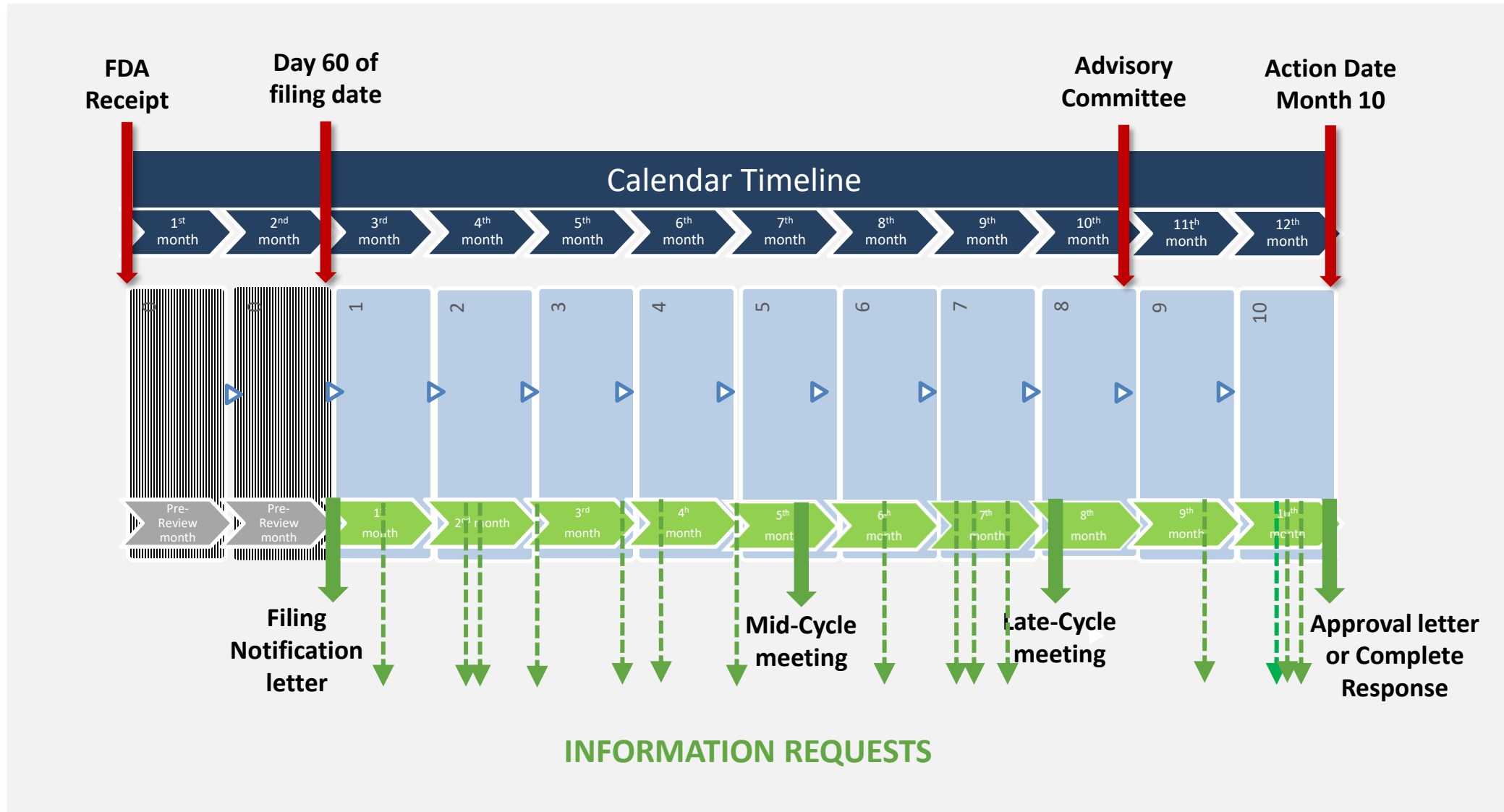
FDA BLA Review Team

Primary Reviewer: Review team member responsible for conducting a scientific review on an assigned section of the application using his/her particular scientific discipline, documents his/her review finding, and recommends the action to be taken on the application. Disciplines usually included on the review team are:

- Clinical (Medical)
- Pharmacology/Toxicology (P/T)
- Product Quality (formerly CMC)
- Biometrics (Statistical)
- Clinical Pharmacology
- Clinical Microbiology (for antimicrobial products)
- Study Endpoints and Labeling Development (SEALD)
- Pediatric and Maternal Health Staff (Pediatric Review Committee or PeRC)
- QT-IRT
- Medication Error (for proprietary name)
- Risk Management Analyst for Risk Evaluation and Mitigation Strategies (REMS) submissions*
- Office of Scientific Investigations (OSI) Bioresearch Monitoring (BIMO) Program
- Office of Compliance's Office of Manufacturing Product Quality (OMPQ)
- Office of Prescription Drug Promotion (OPDP) labeling
- Controlled Substances
- Patient Labeling (DMPP)
- Other disciplines that are required on a less frequent, case-by-case basis



FDA Standard BLA Review Timeline



NME or NBE Review Timeline

Major changes under PDUFA V

Review cycle of 10 months
doesn't begin until after
initial day 60 application
Completeness assessment

New sponsor
mid-cycle
meeting

Likely need for
Advisory Committee
meeting

New sponsor late-
cycle meeting

Review cycle of
12 calendar
months



FDA Refuse-to-File

Possible Reasons for Refuse-to-File (RTF):

- Materially lacking or inadequately organized
- Inadequate content, presentation, or organization within required technical sections and integrated summaries
- Significant electronic submission issues
- Missing evidence of effectiveness
- Missing critical data, information, or analyses
- (Not easily correctable deficiencies)



Applicant's RTF Choices

- Amend BLA and resubmit
- Request informal agency conference within 30 days
 - Pathways after meeting:
 - CDER/CBER decides to reverse RTF decision
 - Sponsor request that FDA file and review BLA with or without amendment to correct deficiencies:
 - FDA will then file BLA under protest
 - PDUFA filing date – 60 days after meeting date
 - Sponsor amends BLA and resubmit: new clock and PDUFA fee, FDA to review for file ability
- Regardless of path forward, lost time and money (25% of BLA fees)

Pre-Approval Inspections

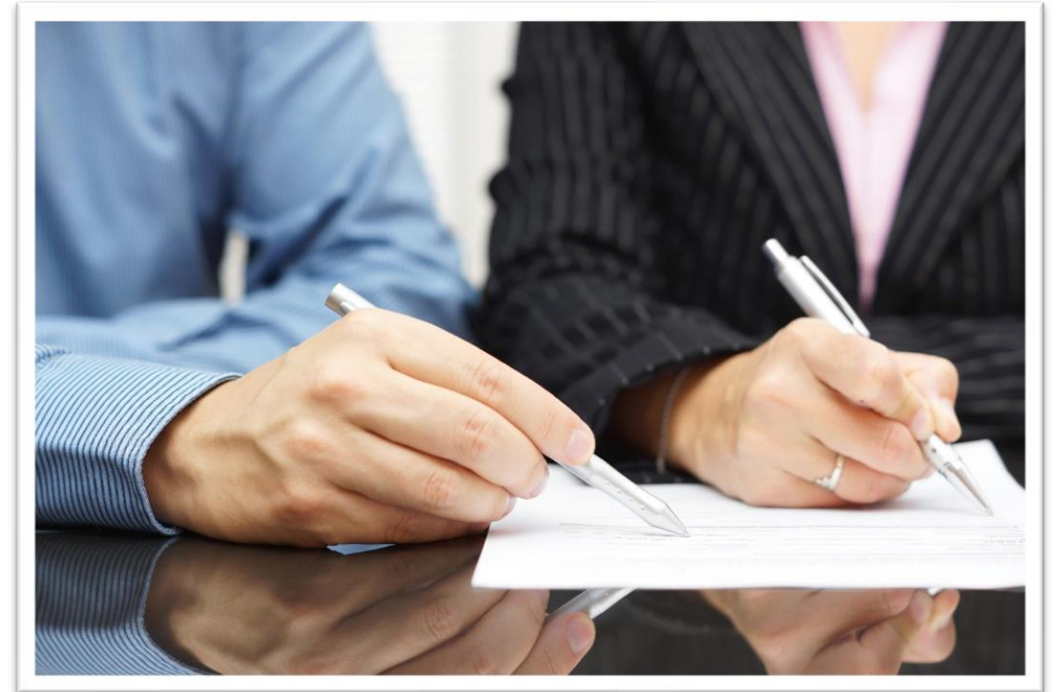


- FDA Pre-Approval Inspections (PAI) for Compliance to GXP:
 - Likely most GMP manufacturing facilities (internal and 3rd party), unless specific sites have favorable FDA inspection history (risk-based)
 - GCP inspection likely of sponsor then high-risk clinical site(s), and/or CRO
 - Potential GLP inspection(s), if necessary
- All sites need to be inspection-ready at time of submission
- On-site inspections typically occur within 2-5 months of submission

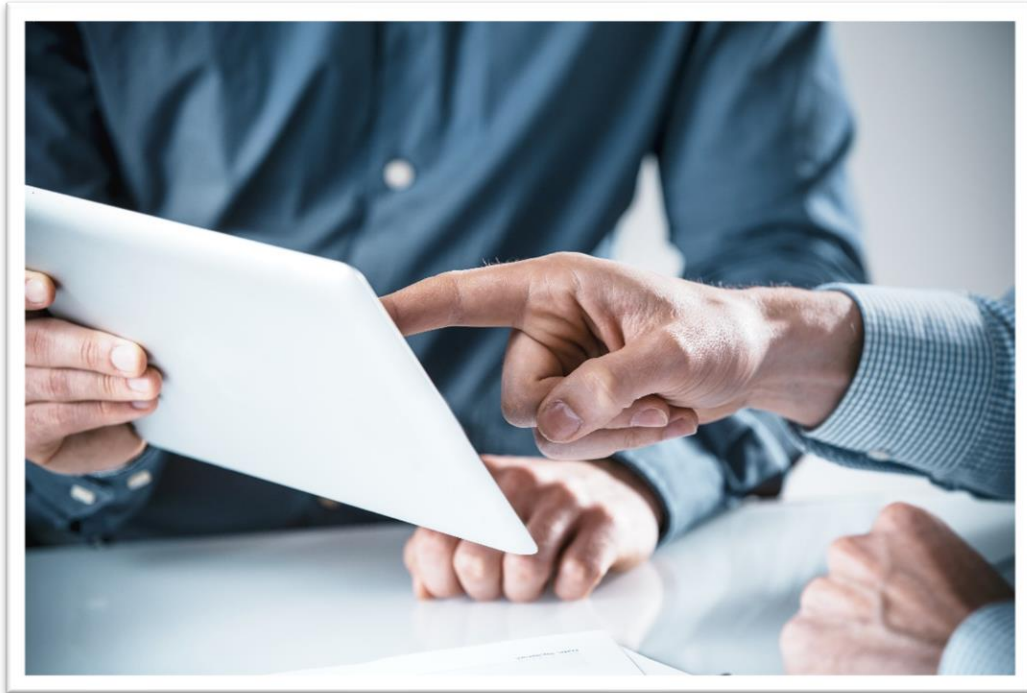
Mid Cycle Meeting (if needed)

Provides mid-cycle updates, including:

- Any significant issues identified by review team to date
- Any new information requests
- Information regarding major safety concerns
- Preliminary review team thinking regarding risk management such as REMS, post-approval safety studies
- Proposed date(s) for the late-cycle meeting
- Updates regarding plans for the AC meeting (if an AC meeting is anticipated)
- Other projected milestones dates for remainder of review cycle



Advisory Committee (if needed)



Advisory Committee meeting may be held for one or more of following reasons (not exhaustive list):

- Application is NME or original BLA
- Clinical trial design used novel clinical or surrogate endpoints
- Significant issues regarding safety and/or effectiveness of drug or biologic
- Application raises significant public health questions regarding role of drug or biologic in treatment or prevention of disease

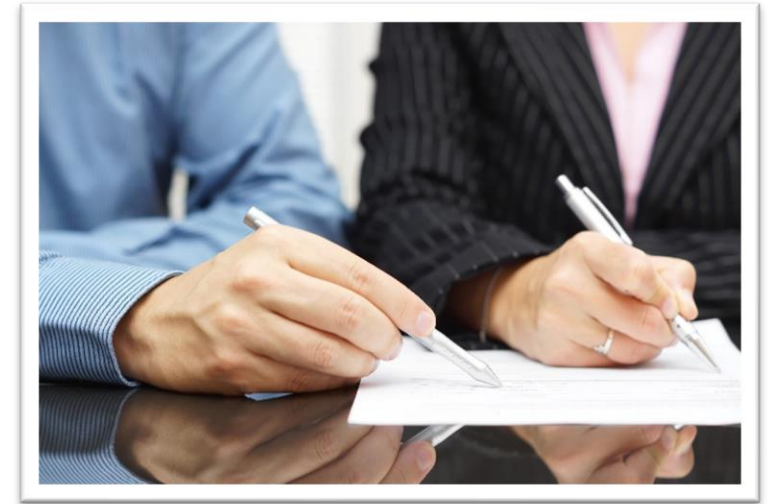
Advisory Committee

- Seeks outside opinions by patients, laypersons, clinicians, competitors, practicing physicians, etc. of product's proposed approval based on safety and efficacy data in FDA's meeting package
- Logistically:
 - FDA presents summary of its findings and its concerns for approval (Simple Questions)
 - Sponsor's rebuttal of FDA position
 - Closed and open parts of meeting
 - Outside opinions (competitors, 3rd party advocates, patients, physicians, etc.)
 - FDA Advisory Committee votes on proposed safety and efficacy questions proposed by FDA



Late Cycle Review (if needed)

- Meeting intended to share information, identify deficiencies, plan for AC in order to avoid redundancy, and plan rest of review
- Will occur not less than 12 calendar days before date of AC meeting
- May include:
 - Major deficiencies identified to date
 - Issues to be discussed at the AC meeting (if planned)
 - Current assessment of need for REMS or other risk management actions
 - Information requests from review team to applicant
 - Additional data or analyses applicant may wish to submit
 - Major labeling issues, if appropriate (do not discuss line-by-line labeling)



Other Interactions with FDA

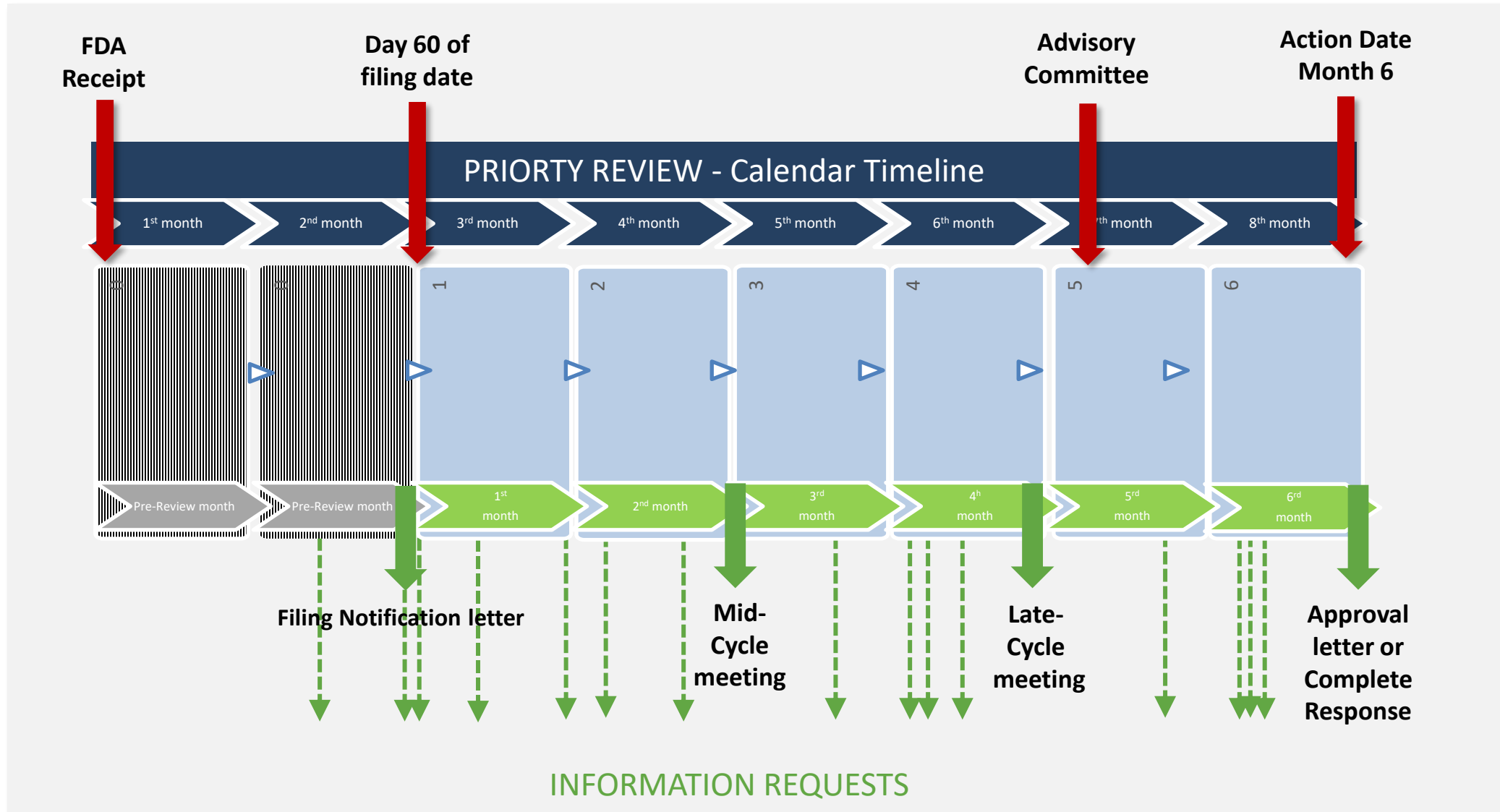
Multiple FDA Information Requests

- May involve detailed CMC, non-clinical, clinical and labeling questions
- May request data, rationale, new studies, etc.
- Can have very short response periods
- Ultimately may extend review period

Unsolicited BLA amendments may extend Action Date

- Applications expected to be complete at time of submission
- Unsolicited amendments expected to be rare and not to contain major new information or analyses

Priority Review Timeline



Priority BLA – Compressed Review

FDA's Expectations of Sponsor

- Discuss expedited programs with FDA during clinical development
- Expect timely and frequent interactions with FDA regarding planned submission
- Submit complete lists of clinical and manufacturing sites ahead of submission
- Facilities be truly ready for inspection at time of submission
- Respond to information requests in timely and complete manner
- Do not submit unsolicited amendments
- Pre-BLA communication of proposed labeling and PMRs/PMCs



FDA Decision on Action Date

FDA approval letter

or

Complete Response Letter (CRL)

Post Approval Commitments

Possible Clinical / Non-clinical commitment

- Post Marketing Commitment (PMC)
- Post Marketing Regulations (PMR)
- Risk Evaluation and Mitigation Strategy (REMS)
 - Should be discussed in pre-BLA FDA interactions

Quality

- Likely to have post approval commitments
- Usually resulting from FDA review of BLA



PMR/PMC

Non-clinical studies or clinical trials to be conducted after approval

- Required by regulation or statute (PMR)
 - For accelerated approval, clinical benefit studies
 - Pediatric studies, if applicable
- Condition of approval (PMC)
 - Phase IV Safety or subpopulation studies
- FDA maintains public website on open PMR/PMC commitments (<https://www.accessdata.fda.gov/Scripts/cder/pmc/index.cfm>)

The screenshot shows the FDA website's "Postmarket Requirements and Commitments" search page. The page header includes the U.S. Department of Health and Human Services logo, the FDA logo, and the text "U.S. FOOD & DRUG ADMINISTRATION". A search bar is located in the top right corner. Below the header is a navigation menu with links for Home, Food, Drugs, Medical Devices, Radiation-Emitting Products, Vaccines, Blood & Biologics, Animal & Veterinary, Cosmetics, and Tobacco Products. The main content area features a breadcrumb trail: Home > Drug Databases > PMC Home. The title "Postmarket Requirements and Commitments" is prominently displayed. Below the title are social media sharing options for Facebook, Twitter, LinkedIn, Pinterest, Email, and Print. A link to "Introduction | FAQ" is provided. The main text explains that postmarket requirement and commitment studies and clinical trials occur after a drug or biological product has been approved by FDA. It references a "Report to Congress: Reports on Postmarketing Studies [FDAMA 130]" and a "Guidance for Industry (PDF - 456KB)". A separate website for "post approval studies for medical devices" is also mentioned. The search form includes the following fields and options:

- Center:** Radio buttons for "Both CBER and CDER" (selected), "CBER", and "CDER".
- Applicant:** Text input field with the placeholder "Enter at least 3 characters".
- Product:** Text input field with the placeholder "Enter at least 3 characters".
- NDA/ANDA/BLA Number:** Text input field with the placeholder "Enter at least 3 numbers".
- Requirement/Commitment Status:** A dropdown menu currently set to "All Statuses", with a link to "Status Definitions".
- Required Under:** A checkbox for "Accelerated Approval".

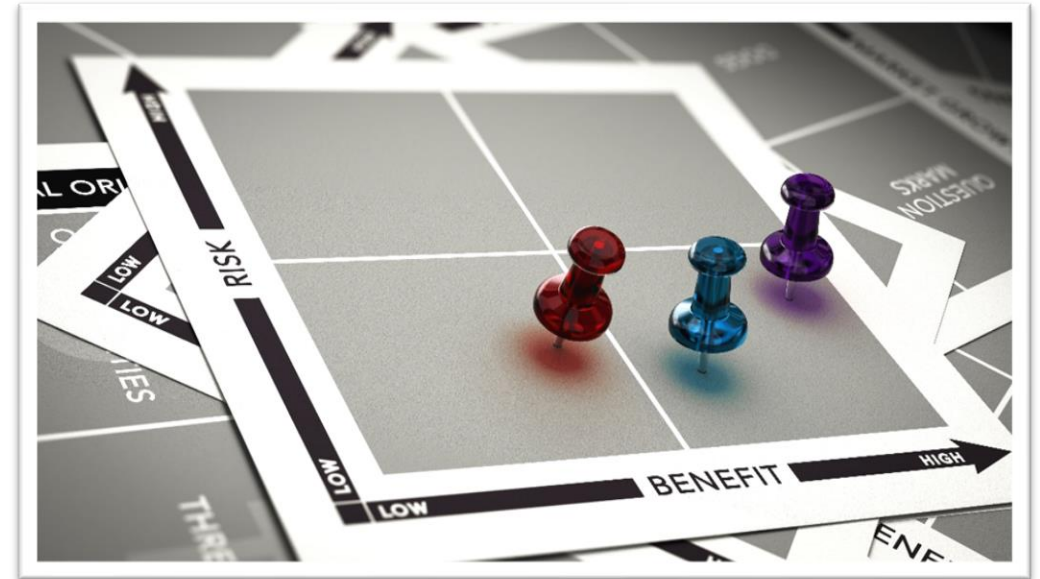
Examples of PMCs



- **Drug interaction studies** – studies of possible modification of effect when administered with another drug
- **Safety studies** - assess safety in larger populations over broader time frames, beyond that of Phase 3 studies
- **Safety studies** - completion of clinical trials in progress at time of approval
- **Randomized clinical trials** – studies of efficacy and safety of drug within sub-groups within larger population such as:
 - Pregnant women, children, geriatric (elderly) patients
 - Patients with specific disease characteristics, such as liver (hepatic) impairment or kidney (renal) impairment

REMS (Risk Evaluation Mitigation Strategy)

- Addresses safety measures beyond professional labeling needed to ensure benefits outweigh risks
- Some products not approvable without REMS
- Sponsors develop REMS, FDA reviews and approves
 - Should be discussed in pre-BLA FDA interactions
 - Proposed REMS plans may be included in BLA submission
- REMS has specific safety measures unique to safety risks associated with specific drug or class of drugs
- Healthcare professionals and distributors may need to follow specific safety procedures prior to prescribing, shipping, or dispensing drug
- As of Sep 2021, there are 61 approved REMS*



Risk and Possible Mitigation

Adverse Event

- Serious Infection

- Severe allergic reaction

- Liver damage

- Severe birth defects

Possible REMS Action

- Patient education of initial warning signs of infection

- Healthcare professional must be certified to administrate product

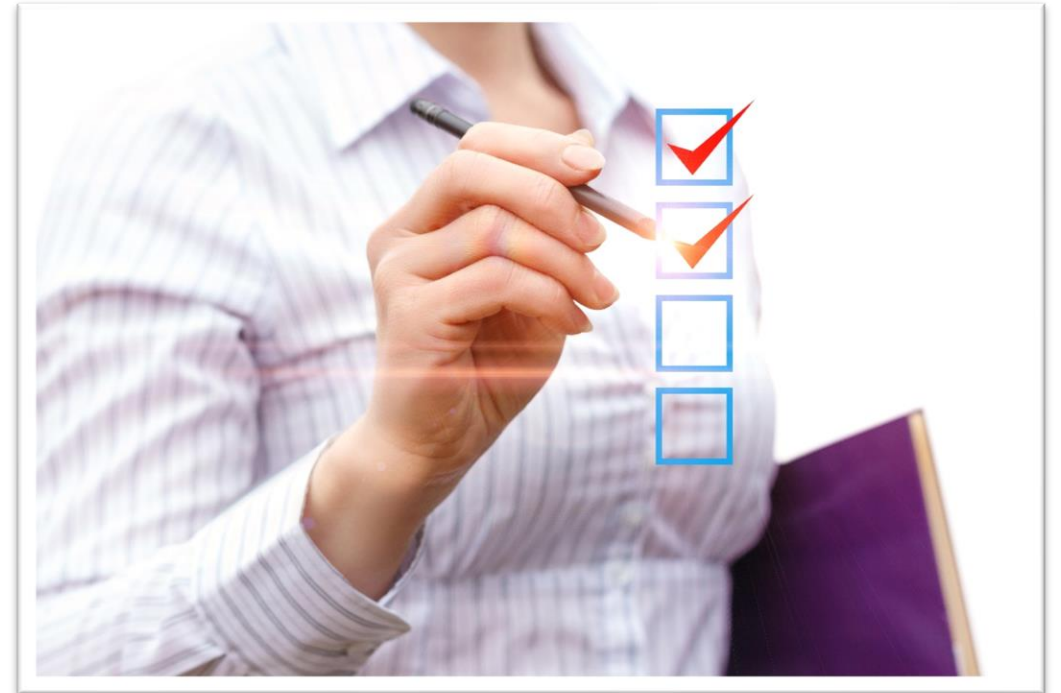
- Liver function monitoring while patient is taking drug

- Negative pregnancy test prior to dispensing each prescription

Possible Elements of REMS

May contain one or more elements:

- Medication Guide
- Patient package insert
- Communication plan to Health Care Practitioner
- Elements to assure safe use (ETASU)
- Timetable for submission of assessments of strategy (required)



Question #3

There are REMS programs for drugs such as DEA schedule 2 opioid analgesic, peanut allergy powder, and fentanyl. Biological drugs are less likely to require a REMS program. Can anyone name one of them?

?

Other Approaches

Product Specific Contents:

- Vaccines
- Blood & Blood Products
- Allergenics
- Cellular & Gene Therapy Products
- Xenotransplantation



THANK YOU

Andy Papas, MBA, PhD

VP Regulatory Affairs

apapas@nsf.org

Skype: Apapas_nsf



Additional Information

CBER BLA for Non-User Fee Products

- Products exempted from PDUFA include:
 - Whole blood or a blood component for transfusion
 - Bovine blood product for topical application licensed before September 1, 1992
 - Allergenic extracts
 - Cord blood and peripheral blood stem cells separated from whole blood by physical or mechanical means for transfusion
 - In vitro diagnostic biologic product licensed under section 351 of the PHS Act (These BLAs are subject to MDUFA)
 - Biological product licensed for further manufacturing use only
- These non-user fee products subject to procedures of CBER's Managed Review Process, not PDUFA/BsUFA program