The Biologic License Application (BLA) Process

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ACI's FDA Boot Camp

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Outline of Topics

- What is a BLA?
- Products that Require a BLA
- BLA Contents
- BLA Review Timeline
- NDA Approval vs. BLA Licensure
- Abbreviated BLA for Biosimilars

What is a BLA?

- The Biologics License Applications (BLA) pathway was created by section 351 of the Public Health Service Act (PHSA) — 42 U.S.C. § 262.
  - FDA provided detailed regulatory requirements in 21 C.F.R. § § 600-680.

- A BLA is "**a request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce**." (21 C.F.R. § 601.2)

- Biological products are a **subset of drugs**; therefore both are regulated under provisions of the Food, Drug, and Cosmetic Act (FD&C Act). However, the applicable premarket review for biological products is licensure under section 351 of the PHSA, instead of approval under section 505 of the FD&C Act.

Products that Require a BLA

- A BLA license is required for every "**biological product**" prior to introduction into commerce. The term includes the following:
  - *virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings*. (42 U.S.C. § 262(i))

- FDA regulations and policies have established that biological products include blood-derived products, vaccines, in vivo diagnostic allergenic products, immunoglobulin products, products containing cells or microorganisms, and most protein products.

- However, some therapeutic protein products, including insulin, glucagon, and human growth hormone, are approved under section 505 of the FD&C Act rather a BLA.

Contents of a BLA

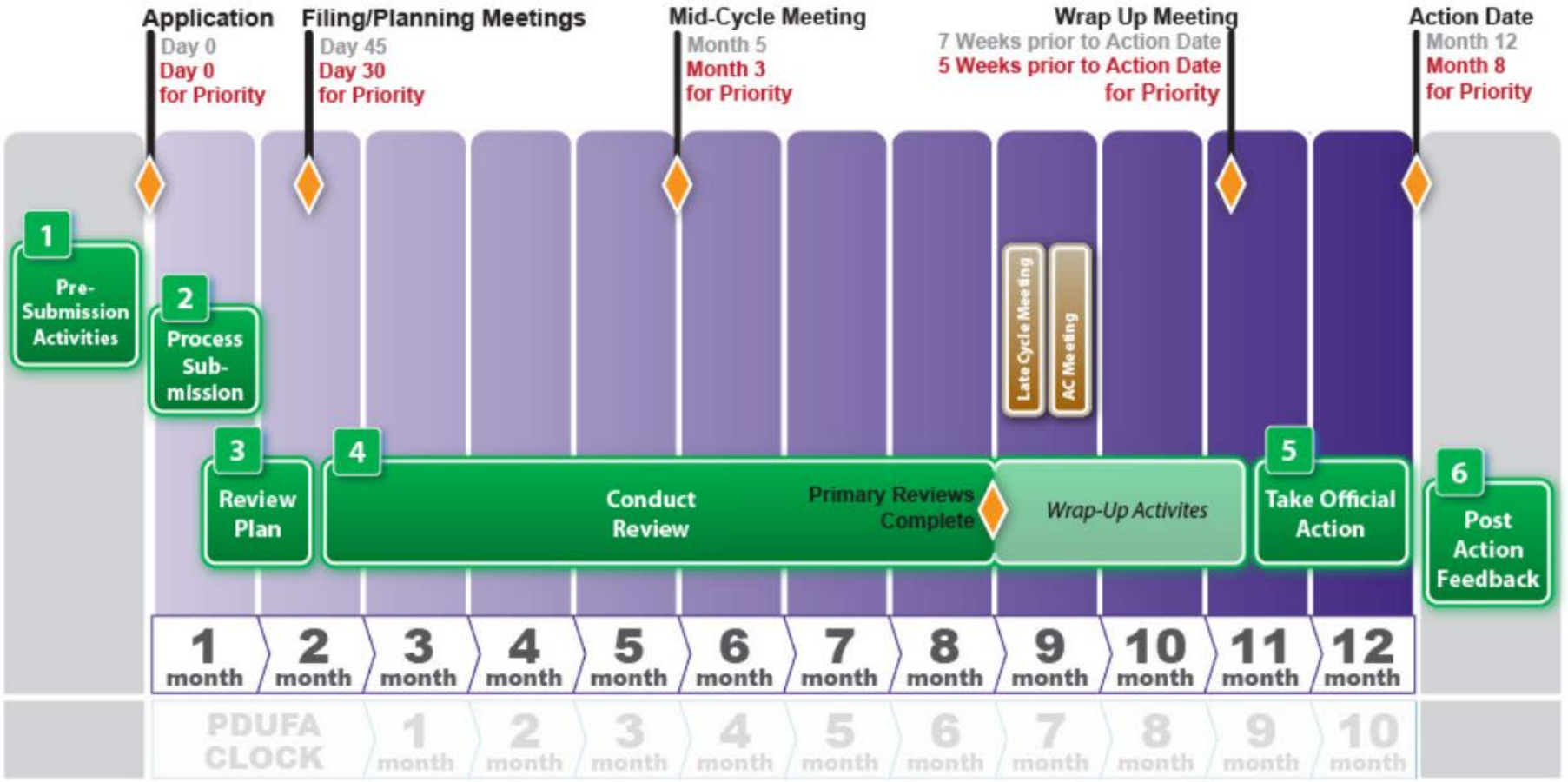
- A BLA must contain the following information:
  - Form FDA 356h (cover sheet)
  - Applicant information
  - Product/manufacturing information
    - Source material / raw materials
    - Manufacturing process and controls
    - Formulation
    - Facility information
    - Contamination / cross-contamination information
    - Environmental assessment or categorical exclusion
  - Safety, efficacy and use
    - Pre-clinical studies
    - Clinical studies
    - Labeling

BLA Review Timeline

- Under the current Prescription Drug User Fee Agreement (PDUFA), FDA agreed to review the majority (90%) of BLAs in 10 months of the 60 day filing date. For priority submissions, the deadline is 6 months of the 60 day filing date.

- In practice, the deadline produces a decision within about a year of the submission of the application.

BLA Review Timeline



BLA Review Timeline

- **Pre-submission meeting between the applicant and FDA**
  - Purpose: discuss the planned content of the BLA with the appropriate FDA review division.
  - Timing: at least 2 months prior to the planned submission of the application.
  - At the meeting, FDA and the applicant may agree on delayed submission of some application components.

- **Application submission**
  - FDA expects the application to be complete at submission, based on the pre-submission meeting.

BLA Review Timeline

- **Day 74 Letter**
  - Purpose: Highlight filing review issues.
  - Timing: within 74 calendar days from the date of FDA's receipt of the original submission.
  - Includes preliminary plans on whether to hold an Advisory Committee (AdComm) meeting to discuss the application.

BLA Review Timeline

- **Mid-cycle and other communication**
  - Purpose:
    - Mid-cycle communication provides the applicant with an update regarding the status of the review.
    - Information Request (IR) Letters request additional information as needed from the applicant.
    - Discipline Review (DR) Letters convey thoughts on possible deficiencies to an applicant, as each discipline finishes the review of the application.
  - Timing:
    - Generally, FDA contacts the applicant within 2 weeks following FDA's internal mid-cycle review meeting.
    - IR and DR Letters are sent out as needed.
  - For the mid-cycle communication, members of the FDA review team call the applicant to provide an update on the status of the review of the application.

BLA Review Timeline

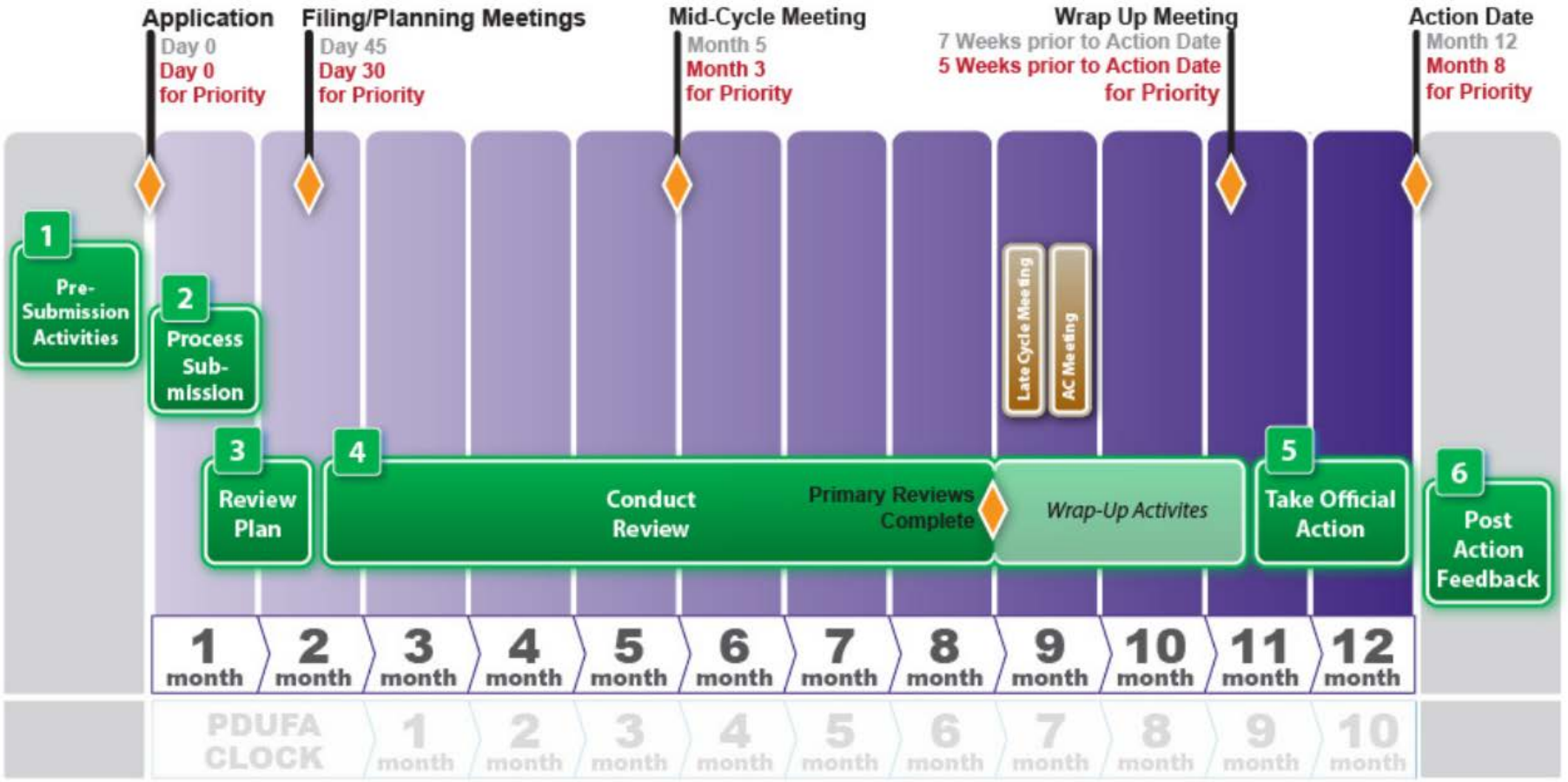
- **Late-cycle meeting**
  - Purpose:
    - Discuss the status of the review of the application late in the review cycle.
    - If an AdComm meeting is convened, FDA will provide a background package for the meeting.
  - Timing:
    - Generally, 3 months prior to the PDUFA goal date.
    - If an AdComm meeting is convened, the late-cycle meeting will occur at least 12 calendar days prior to the Committee's meeting.
  - Includes an assessment of the need for a Risk Evaluation and Mitigation Strategies (REMS) plan for the product.

BLA Review Timeline

- **Wrap-up Meeting**
  - Purpose:
    - Internal meeting by FDA to facilitate the development of a comprehensive understanding of the safety, efficacy, and quality of the proposed product and a preliminary decision on the regulatory action.
  - Timing:
    - About 8 months following submission.
  - FDA discusses a plan for resolution of outstanding issues, which may be resolved internally or with the applicant.

- **FDA Official Action**

BLA Review Timeline



NDA Approval vs. BLA Licensure

- Small-molecule drugs and certain therapeutic proteins must be approved through the New Drug Application (NDA) process, under section 505 of the FD&C Act.

- The **BLA review process is largely similar to the NDA review process**:
  - Same PDUFA timeline
  - Same regulations for Investigational New Drugs (INDs), Accelerated Approval, Fast Track designation, and orphan drug designation
  - Same pediatric study requirements
  - (post approval) Same regulations with regard to labeling and advertising

NDA Approval vs. BLA Licensure

- Several features are **unique to BLAs**:
  - The **generic drug provisions** in the FD&C Act **do not apply to BLAs**.
  - Product and facility must meet "**product standards**," which include a facility inspection and method validation.
  - FDA requires the submission of **specific information** for most types of biological products.
  - Closer scrutiny of the **manufacturing process and facilities**
    - Changes in the manufacturing process, equipment, or facilities may require additional clinical studies to demonstrate the product's continued safety, identity, and potency.

NDA Approval vs. BLA Licensure

- A subset of biological products are reviewed by the Center for Drug Evaluation and Research (CDER), whereas all others are reviewed by the Center for Biologics Evaluation and Research (CBER).
- CDER reviews the following:
  - Monoclonal antibodies for in vivo use
  - Proteins intended for therapeutic use
  - Immunomodulators
  - Growth factors, cytokines, and monoclonal antibodies intended to alter the production of hematopoietic cells in vivo.
- All biological products require an approved BLA to be marketed in the U.S.

Regulatory Pathway for Biosimilars

- Biologics Price Competition and Innovation Act (BPCIA) enacted March 23, 2010 as part of Patient Protection and Affordable Health Care Act
  - Adds new section 351(k) of Public Health Services Act to create abbreviated approval pathway for biological products that are “biosimilar” or “interchangeable” with an FDA-approved biological product
  - Also amends 35 U.S.C. § 271 (patent infringement) and 28 U.S.C. § 2001(declaratory judgment)

BPCIA Applicability

- Applies to licensure of a “biological product”:
  - virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or
  - ***protein*** (except any chemically synthesized polypeptide)
  - applicable to the prevention, treatment, or cure of a disease or condition of human beings

BPCIA Applicability

- Application must show that biological product is "biosimilar to a "reference product"
- "Reference product" for purposes of BPCIA is a single biological product licensed under PHS Act, i.e., under a BLA

Definition of Biosimilar

- Must be “highly similar” to the reference product
  - “No clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency of the product”
  - Could include differences in expected range of safety, purity and potency
  - Slight differences in rates of adverse events ordinarily will not be considered clinically meaningful

Definition of Biosimilar (cont.)

- Must have same condition of use in labeling as approved for reference product
- Must utilize same mechanism of action for use listed in labeling
- Must have same route of administration, dosage form, and strength as reference product
- Must be based on data from a clinical study, subject to waiver by the Secretary
  - At least one clinical study will be expected (immunogenicity/PK-PD)
  - Comparative PK-PD studies viewed as key to demonstrating biosimilarity

Approval as Interchangeable Biosimilar

Heightened Requirements:

- "Biosimilar" to reference product, plus:
- Expected to produce the same clinical result in any given patient
- No risk in switching between reference product and biosimilar

Advantages of Interchangeability:

- If conditions met, biosimilar may be substituted for reference product without intervention of prescribing physician
- First interchangeable biosimilar has some market exclusivity before FDA can approve second interchangeable product

Key Issues

- Definition of “Biosimilar”
- Interchangeability
- Clinical Studies
- Naming of Biosimilars
- Innovator Data Exclusivity
- Biosimilar Market Exclusivity
- Resolution of Patent Disputes

Thank you!

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