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# Overview Biological License Application

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**Abstract**: *Biological products are highly evolving products its respects years. Thus biological products needs to be regulated. In USA biological products are approved and regulated by food and drug administration (FDA). To get approval of biologicals in USA, biologics license application is used BLA ensures that safe and effective products are approved in the market. Bio-similar are the product which differ from original FDA approved biological drug while still being very close to it.*
*The BLA application can either be full BLA (351 a) or it can be used for the bio-similar i.e. (351 k). In USA the biologics and bio-similar are included in the public health service act which has certain rules and regulations for approval of biologics. Thus review collectively gives us the idea about biologic license application and also its requirements and forms which are needed while approval of products.*

**Keywords**: Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Public Health Service, Public Health Service, Food and Drug Administration, Common Technical Document, New Drug Application

## I. INTRODUCTION

A **biologics license application** (**BLA**) is defined by the U.S. Food and Drug Administration (FDA) as follows:
The application for a biologics license is a request for authorization to deliver a biologic product for introduction into interstate commerce (21 CFR 601.2). Regulations for the BLA are found in 21 CFR 600–680. Any legal person or business involved in manufacturing or a license applicant who accepts responsibility for adhering to establishment and product standards must submit a BLA. The prerequisites for a BLA are outlined in Form 356h. This comprises:

- Applicant information
- Product/manufacturing information
- Pre-clinical studies
- Clinical studies
- Labeling

The Center for Drug Evaluation and Research (CDER) oversees some biological products, while the Center for Biologics Evaluation and Research oversees others (CBER). **(1)**
The Public Health Service Act's provisions allow for the approval of biological goods for marketing (PHSA). A company must have a license for the product in order to manufacture biologics for interstate commerce, according to the statute. A biologic licensing application is a document that includes particular details on the biologic product's production procedures, chemistry, pharmacology, and medicinal effects. The application is granted and a license is issued allowing the company to commercialize the product if the information provided complies with FDA criteria. A BLA is thus a request for authorization to commercialize and launch an innovative biologic medicine in the US. Any legal person or business involved in manufacturing or a license applicant who accepts responsibility for adhering to establishment and product standards must submit a BLA.
There are **two pathways** of BLA.

1) 351 (a) : the full BLA
2) 351 (k) : the biosimilar BLA (ppt)

**351(a) :**
The Public Health Service (PHS) act's typical route for approving biologics and innovator biologics is 351(a). According to section 351(a), the submitted application must include all relevant data pertaining to a biological product's

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efficacy and safety. Due to its independence from any other biological product, it is also referred to as a "stand alone" application.

It is the biologics' initial approval process. It is the procedure for approving novel biologics.

It is sometimes referred to as the conventional route for approving novel biopharmaceuticals.

**351(k) :**

It is an application for a biologics license through the USFDA. Manufacturers submit the application to have a product that is "very similar" to an FDA-approved reference product examined as a biosimilar or interchangeable.

The USFDA's 351(k) application process is used to apply for biologics licenses. Manufacturers submit the application to have a product that is "very similar" to an FDA-approved reference product examined as a biosimilar or interchangeable. According to the PHS Act, a 351(K) application must explain how the biosimilarity is entirely supported by evidence from animal studies, clinical trials, and analytical investigations. The FDA will, however, further determine which of the subsequent studies must be incorporated into the application:

1. **Analytical Studies** – To prove similarity between the biological product and the reference product, even if there are slight variations in the clinically inactive substances
2. **Animal Studies** – includes a toxicity assessment
3. **Clinical Studies** – In order to guarantee product safety under use conditions, it also comprises evaluation of immunogenicity and pharmacokinetics (PK) or pharmacodynamics (PD). **(2)**

***BIOSIMILARS-*** A biosimilar medication, as the name suggests, differs from an original, FDA-approved biologic drug while still being very close to it. A parent biologic drug, often known as a reference biologic, is the original medication. For patients with some of the most challenging diseases to manage, such cancer, rheumatoid arthritis, and psoriasis, biosimilars are safe, efficient medications. These crucial treatment alternatives boost patient accessibility and may result in billions of dollars in cost savings for the healthcare system. **(ppt)**

**Biosimilars are not generics "A biosimilar can have minor differences compared to its parent biologic".**

Because biosimilar molecules differ structurally from their original counterparts, biosimilar drug products are not regarded as being chemically equivalent to those original medications. The sponsors of 351(k) applications must include analytical characterization, pharmacokinetic and pharmacodynamic profiles, and comparative clinical trials in order to remove any remaining uncertainty before biosimilars can be approved. The sponsor must submit analytical studies demonstrating similarity to the reference product, animal studies (including toxicity assessment), and one or more studies in at least one clinical indication for use to prove the purity, potency, and safety of the proposed biosimilar in order to prove that it is highly similar to a licenced reference product. (4)

It comprises vaccines, blood and blood components, allergens, somatic cells, gene therapies, tissues, and recombinant therapeutic proteins. A biosimilar product is a medication that is similar to a biologic medication that has previously been approved. The components of biologics and their biosimilars, which can include carbohydrates, proteins, nucleic acids, or intricate mixtures of these elements, are derived from natural sources (human, animal, or microbe). They might even be live things in some cases, like tissues and cells.

Under the Public Health Service (PHS) Act, biologics and biosimilars are evaluated and approved. The FDA demands that a biosimilar be very similar to the reference product, but not identical, as opposed to generic drugs. A biosimilar must also show that there are no clinically significant changes between it and the reference product in terms of effectiveness, safety, and potency. The 351(k) method is seen as being "abbreviated" since the Agency typically requires less safety and efficacy data to approve a biosimilar than to approve the original biologic.

Biosimilar Sponsors are required to prove biosimilarity, primarily through nonclinical studies, using a strategy that looks at the structure and functionality of the biosimilar molecule. A biologic cannot be created by merely adding chemicals like amino acids to a pot and stirring it; rather, each biologic has a distinct and complicated molecular structure. To create the proper molecular structure, each molecule needs to be positioned exactly where it needs to be. **(5)**

**General Requirement of 351(k) Pathway**

The application must include the following information:

- Demonstration of the product-in-review to be biosimilar to a reference product

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- Usage of same mechanism(s) of action for the intended condition(s) of use, limiting to the mechanisms of the reference product
- Previously approved condition(s) of use for labelling
- Route of administration, dosage form and strength as per the reference product
- Details regarding the manufacturing of the product to ensure the safety and efficiency of the manufacturing plant and process. (**2**)

**Content and Organization of a BLA :**

1. Form 356h
2. Chemistry
3. Non-Clinical and Clinical
4. Electronic Common Technical Document (eCTD)
5. Prescribing Information
6. Master Files (ppt)

**Checklist of required elements for biologics license application:**

- Cover letter and application form
- Table of Contents (Index)
- Labelling
- Summary
- Chemistry, Manufacturing and Controls (CMC)
- Nonclinical Pharmacology and Toxicology
- Human Pharmacology and Bioavailability/Bioequivalence
- Clinical Microbiology
- Clinical data section
- Safety Update reports
- Statistical section
- Case Report Tabulations (CRTs)
- Case Report Forms
- Patent Information.
- Patent Certification
- Establishment Description
- Debarment Certification.
- Field copy certificate
- User Fee Cover Sheet
- Cover letter
- Application form (Form FDA 356h). (**ppt**)

**Biologic license application process**

A BLA is submitted following the approval of an investigational new medication. The FDA will respond in 74 days if the Form 356h is incomplete. According to a BLA, the substance is "safe, pure, and potent," the production sites can be inspected, and the license number is printed on each product container.

Annual reports, adverse event reports, manufacturing adjustments, and labelling changes must be filed after approval. (**1**)

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The Food and Drug Administration (FDA) must be notified via a Biologics License Application (BLA) before a biologic product can be distributed among the states. It is governed by 21 CFR 600–680. An applicant who is in charge of the product's safety and effectiveness may file a BLA. (**9**)

**Apply for a Biologics License Application**

A biologics license application can be made by anyone who is involved in the production of biologics or who is in charge of ensuring that a biologic complies with regulatory requirements. Before submitting the application, applicants should choose a review committee and schedule a meeting with the Food and Drug Administration (FDA).

They ought to arrange a bioresearch monitoring examination as well. They should take the advisory committee's needs and schedule into account when deciding when to submit. In some circumstances, the manufacturer may also want to think about whether they want to meet with the FDA to discuss the validation plan before they submit the application or submit a validation plan for evaluation by the FDA.

**Submit a Form FDA 356h**

The Center for Biologics Evaluation and Research (CBER), a component of the FDA that specialises in biologics, is where applicants must then deliver a Form FDA 356h.

Submissions may be made electronically or on paper. However, just like with New Drug Applications (NDA), a biologics licensing application can be submitted via an electronic Common Technical Document (eCTD).

An application to commercialize a brand-new pharmaceutical, biologic, or antibiotic for human use is known as a Form FDA 356h.

**The Form FDA 356h contains the following information:-**

- A summary of information submitted as part of the application.
- Information on the applicant submitting the biologics license application.
- A preclinical data section.
- A clinical data section that includes safety and efficacy data on the product.
- Draft labeling of the product to be licensed.
- Information on the manufacturing, chemistry, and controls of the product.
- A data summary of validation of important processes and assays involved in the manufacture of the product.
- A description of the facility where the product is manufactured.
- Case report form tabulations on the manufacturer's clinical experience with the product.
- Case report forms and serious event narratives.

Copies of significant standard operating procedures relevant to the manufacture of the medicine should also be included in the information on the chemistry, manufacturing, and controls. Manufacturers may occasionally be asked to provide information on their readiness for an FDA inspection.

**Await FDA Review**

The FDA will examine the biologics licencing application after receiving it to see if it is complete.

- The validation data and the standard operating procedures are also included in this initial evaluation. Then, a filing meeting will be held to identify any issues that might lead to the issuing of a Refuse to File (RTF), such as missing data or manufacturing details.
- The FDA will consider what information needs to be submitted by the manufacturer within 74 days if they have not provided all the necessary information. Based on their conclusions, they will subsequently issue a filing letter or a Refuse to File (RTF). (**Ppt)**

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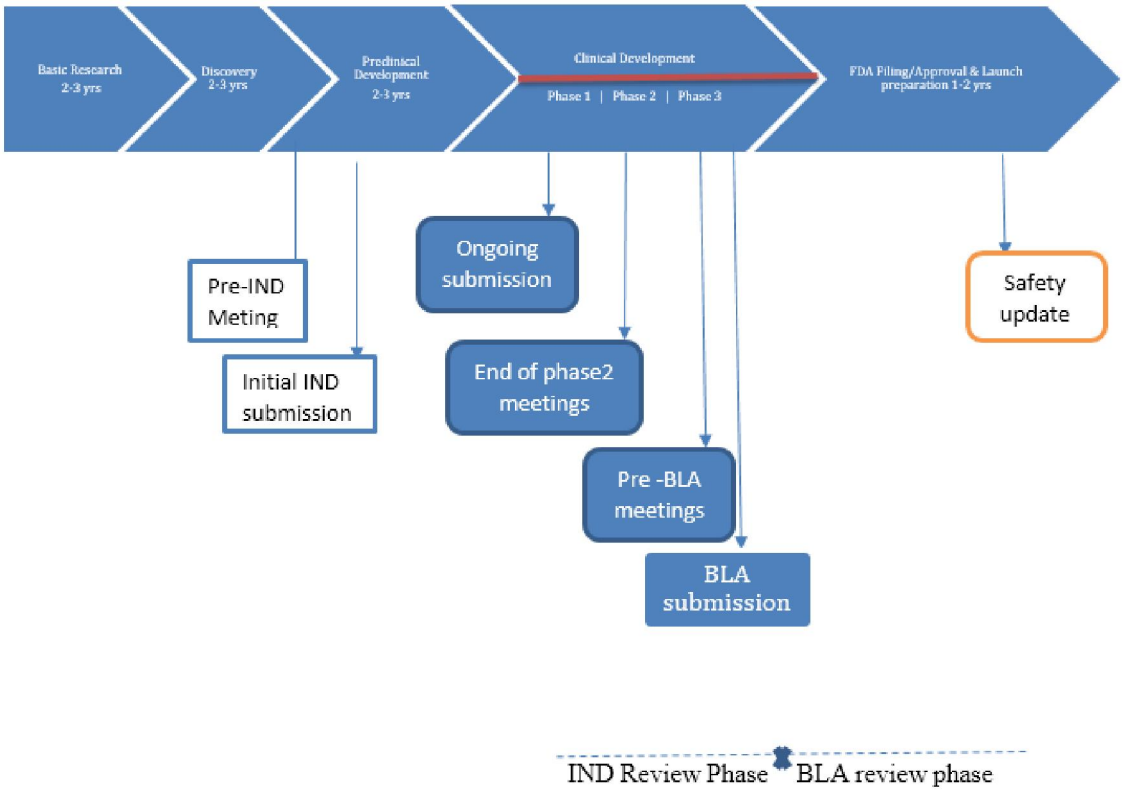
**BLA Review Timeline**




**Types of Meetings:**

There are three categories of meetings between sponsors or applicants for PDUFA products and CDER or CBER staff: Type A; Type B; and Type C. Each type of meeting will be subject to different procedures, as described below.

- Type A: for stalled development or to address an important safety issue
- Type B: Specific developmental meetings such as pre-BLA meetings.
- Type C: other meetings

**Type A Meeting-**

A Type A meeting is one that is immediately required for a drug development programme that has stalled to move forward (i.e., a critical path meeting). Type A meetings are often designated for discussions on clinical holds, dispute resolution, and special protocol assessments that sponsors request following the FDA's evaluation of protocols in assessment letters. Within 30 days of the FDA receiving a written request for a meeting from a sponsor or applicant for a PDUFA product, 2 Type A meetings should be planned. If the sponsor or applicant seeks a meeting date that is more than 30 days from the time the agency receives the request, the request will not be granted. **(6)**

**Type B Meeting-**

Pre-IND meetings (21 CFR 312.82), some end-of-Phase 1 meetings (21 CFR 312.82), end-of-Phase 2/pre-Phase 3 meetings (21 CFR 312.47), and pre-NDA/BLA meetings are all examples of Type B meetings (21 CFR 312.47).

Requests for Type B meetings will be honoured by FDA, excepting extremely rare situations (e.g., submitted information or data are inadequate for meaningful Agency comment). Meetings of Type B should be planned to take

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place within 60 days of the Agency receiving the written request. The meeting should be scheduled to take place no later than 14 days after the date requested if the sponsor or applicant requests a date for the meeting that is more than 60 days from the time the Agency receives the request.

Each requestor should make an effort to foresee future demands and, to the degree possible, combine drug development challenges in order to enhance efficient organisation of formal meetings. Because of this consolidation, FDA anticipates granting just one Type B meeting for each potential application (such as an NDA or BLA) or combination of closely related products (e.g., same active ingredient but different dosage forms being developed concurrently). When holding separate meetings to address unrelated topics would be advantageous, the Agency may approve more than one of each Type B meeting. Some of the Type B sessions may need to be repeated in order to develop a medication simultaneously for related and unrelated claims.**(6)**

**Pre- BLA (Type B) meetings for Original Submissions and Efficacy Supplements**

A pre-BLA meeting's main goal is to go over the planned information for the marketing application. This gathering offers the chance to:

• inform the review team of any significant unsolved concerns from the development programme;
• list any studies the applicant intends to use as support for the product's efficacy;
• determine the status of ongoing or required studies suitable for evaluating paediatric safety and efficacy,
• provide FDA reviewers with information about the general data that must be included in the marketing application,
• Talk about the best strategy for presenting and arranging data in the marketing application, as well as relevant statistical analysis techniques.
• talk about the commercial production process and product comparability in relation to CMC preparation for a BLA (if applicable)

**Submission of Pre-BLA (Type B) meeting requests to OTAT**

The meeting request should be submitted by the sponsor as a modification to the current IND. The meeting request should include a list of the meeting's precise goals as well as a list of questions (divided into categories like Chemistry, Manufacturing, and Controls (CMC), Pharmacology/Toxicology, Clinical, and Statistical) organised by field of study.

It would be very appreciated if you could send polite emails to the Regulatory Project Manager (RPM) for the IND and OTATRPMS@fda.hhs.gov about adding the meeting request to the file.

After receiving a meeting request, OTAT doesn't send an email or letter to confirm receipt of it. The meeting date, if approved, or the grounds for denial will be sent by OTAT together with the decision to accept or deny the meeting request according to the timelines outlined in the Table. ( **7**)

**pre-IND meeting**

Prior to submitting an IND, the FDA permits one pre-IND meeting to address any queries or worries about the clinical trial methodology. Any subject, including general product development, manufacturing details, nonclinical testing, protocol design, and other regulatory issues, may be covered during this discussion. Meeting with the FDA has been shown to shorten the time needed for medication development. The investigator will not be charged for attending this conference.

A meeting request letter to the FDA that includes a succinct product description, proposed regulatory pathway, proposed indication(s) or context of product development, objectives and anticipated outcomes, proposed agenda, preliminary questions, sponsor attendees, proposed meeting format, and meeting dates is the first step in the pre-IND meeting request process. A teleconference or in-person meeting can run up to an hour. Instead of a meeting, sponsors can merely require written responses. The FDA will reply with the meeting type and date that have been approved. The study team will then need to deliver a briefing packet with the finalised study questions and information 30 days before the conference. About two days before to the meeting, the FDA will send preliminary comments, giving you time to study them before speaking with them. The meeting may be cancelled if the sponsor decides the initial comments are

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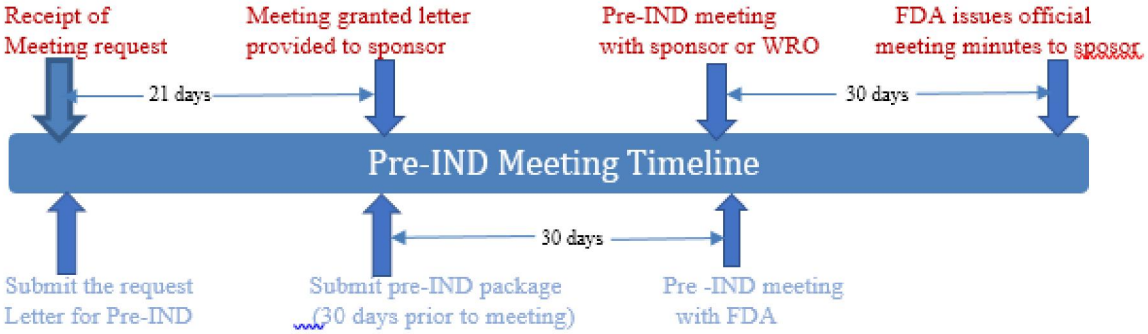
sufficient. Any unanswered questions should be the main topic of discussion at the meeting. The pre-IND meeting is the only time that additional inquiries or suggestions may be made.




WRO = Written Responses Only

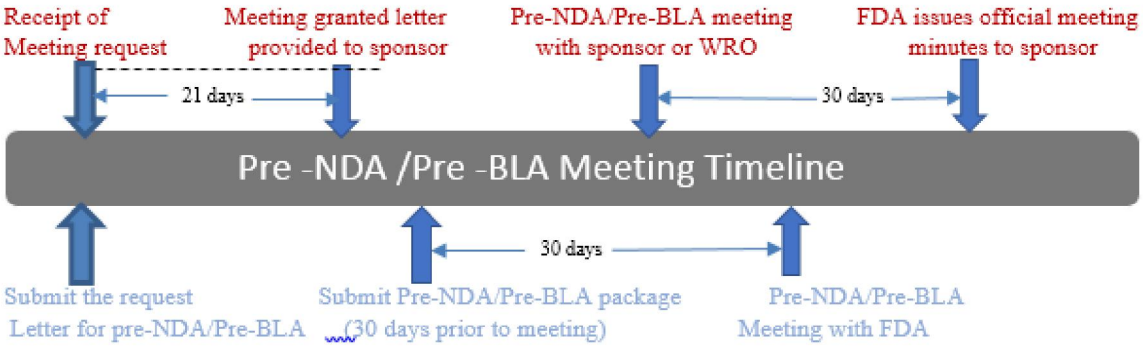
FDA Responsibilities
Sponsor Responsibilities

**pre-NDA/pre-BLA**

The sponsor and FDA must meet before submitting a New Drug Application (NDA) or a Biologics License Application (BLA) in order to ensure that the application is well-structured and easy to examine. This covers a discussion of the structure and content of the anticipated application, as well as the data presentation, dataset structure, acceptability of the data for submission, and the anticipated application submission date. The meeting should normally take place no less than 60 days before the anticipated submission of the marketing application in order to give adequate time for a meaningful response to FDA feedback.

The pre-NDA/pre-BLA phase of development may involve queries about the submission's formatting, such as regulatory requirements, the submission's structure, the electronic common technical document (eCTD), and inquiries about the effectiveness evidence from the Phase 3 study. The pre-NDA/pre-BLA meeting aids in deciding whether unresolved issues call for more information or further studies/trials that could affect the ability to submit the subsequent submission.

Unresolved issues, trials to support quality, safety, and efficacy, paediatric studies, data summary, data format, and presentation, drug name review, new molecular entities (NMEs), early discussions of risk management plans, post-marketing studies or trials, quality information and inspection considerations, outline of data to be submitted for abuse potential assessment, and drug scheduling are a few examples of pre-NDA/pre-BLA meeting topics.

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**Type C Meeting**

Any discussion between the FDA and a sponsor or applicant addressing the development and review of a product in a human drug application, as defined in section 735(1) of the Act, that is neither a Type A or Type B meeting is referred to as a Type C meeting**.**

The majority of meetings about advertising and promotional labelling for approved drug products, with the exception of meetings about launch activities and materials and post-marketing safety evaluation meetings, are not Type C meetings and are not covered in this guidance document. These meetings are not related to the review of human drug applications for PDUFA products. Meetings of this type should be planned to take place no later than 75 days after the Agency receives a written request for one.

The meeting should be scheduled to take place no later than 14 days after the date requested if the sponsor or applicant requests a date for the meeting that is more than 75 days from the time the Agency receives the request. **(6)**

## II. CONCLUSION

A Biologics License Application (BLA) is crucial for biologics and biosimilars. It ensures safety, purity, and potency. There are two pathways: 351(a) for innovators and 351(k) for biosimilars. The FDA reviews BLAs to determine if products meet regulatory standards.BLA submission requires extensive data, including clinical trials. The FDA evaluates manufacturing, labeling, and product quality. A BLA is necessary for marketing approval in the US. Biosimilars require comparative studies to reference products. The FDA assesses biosimilarity based on analytical, animal, and clinical data.BLA approval enables biologics and biosimilars to reach patients. The process involves pre-IND meetings, IND submissions, and FDA review. Manufacturers must demonstrate product safety and efficacy. The BLA process is complex and requires careful planning.FDA approval is essential for biologics and biosimilars to be marketed. The BLA process ensures public health protection. It enables innovation and access to life-saving treatments. The FDA's rigorous review process ensures product quality.BLA approval is a significant milestone for biologics and biosimilars.

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