Review Article

# Preparation of Biologics License Application (BLA) for USFDA: An Overview

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**Received:** 08-01-2023; **Revised:** 24-03-2023; **Accepted:** 30-03-2023; **Published on:** 15-04-2023.

**ABSTRACT**

A Biologics License Application (BLA) is submitted by a manufacturer of vaccines, blood and blood components, somatic cells, gene therapy and other biological drug products to get marketing permission from regulatory authority of the intended market. Application can be submitted by an applicant (manufacturer) and must contain the data derived from non-clinical laboratory studies and clinical studies which demonstrate that the manufactured product meets prescribed requirements of safety, purity and potency. Among further things like safety and purity assessments must consider the storage and testing of cell substrates that are often used to manufacture biologics. The Center for Biologics Evaluation and Research (CBER), the Center within FDA, regulates and evaluates the application as per the Federal Food, Drug and Cosmetic Act 1938. Distribution or sell of biologic products in US is regulated under 21 CFR 600-680. This review article will give an overview of the process of submission and approval of BLA by the CBER, USFDA.

**Keywords:** Biologics License Application (BLA), Center for Biologics Evaluation and Research (CBER), Biological drug products, Federal Food, Drug and Cosmetic Act 1938,21 CFR.

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**DOI:**
10.47583/ijpsrr.2023.v79i02.022

**DOI link:** http://dx.doi.org/10.47583/ijpsrr.2023.v79i02.022

## INTRODUCTION

### Brief information about Drugs and Biologics:

**Drugs:** A drug is typically manufactured through chemical synthesis, which means that it is made by combining specific chemical ingredients in an ordered process. Drugs generally have well-defined chemical structures, and a finished drug can usually be analyzed to determine all its various components. Drug manufacturer can change the manufacturing process extensively and analyze the finished product to establish that it is the same as before the manufacturing change[1].

### Center for evaluation of the Drug Product:

The Center for Drug Evaluation and Research (CDER) performs an essential public health task by making sure that safe and effective drugs are available to improve the health of people in the United States[2].

### Biologics:

A biologic is manufactured in a living system such as a microorganism, or plant or animal cells. Most biologics are very large, complex molecules or mixtures of molecules. Many biologics are produced using recombinant DNA technology. It is difficult, and sometimes impossible, to characterize a complex biologic by testing methods available in the laboratory, and some of the components of a finished biologic may be unknown. Therefore, for biologics, "the product is the process." Because the finished product cannot be fully characterized in the laboratory, manufacturers must ensure product consistency, quality, and purity by ensuring that the manufacturing process remains substantially the same over time[1].

### Biological Product:

Biological products are regulated by the Food and Drug Administration (FDA) and are used to diagnose, prevention, treatment, and cure of the diseases and medical conditions. Biological products are a diverse category of products and are generally large, complex molecules. These products may be produced through biotechnology in a living system, such as a microorganism, plant cell, or animal cell, and are often more difficult to characterize than small molecule drugs. There are many types of biological products approved for use in the United States, including therapeutic proteins, monoclonal antibodies and vaccines[3].

### Current Statistical Market of Biologics and Biological Products:

***The global biologics market was estimated at US$ 366.43 billion in 2021 and it is expected to hit over US$ 719.84 billion by 2030 with a noteworthy CAGR of 7.8% from 2022 to 2030[4].***

The application procedure for biological products in detail is discussed in the following section.

**Biologics License Application (BLA):**

The BLA is regulated under 21 CFR 600 – 680.The biologics license application is a request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce (21 CFR 601.2). A Biologics License Application generally applies to vaccines and other allergenic drug products and genetic therapies[5].

Issuance of the license is a determination that the product, the manufacturing process, and the manufacturing facilities meet applicable requirements to ensure the continued safety, purity and potency of the product. Among other things, safety and purity assessments must consider the storage and testing of cell substrates that are often used to manufacture biologics[6].

It is usually submitted after an Investigational New Drug (IND) and after the appropriate clinical studies has been conducted[7].

**21 CFR Part 600 - 680:**

USFDA have given the guidelines for the regulation of the biological products for the approval in the USA and they have provided the regulations in the 21 CFR Part 600-680[8]. These parts are mentioned in the **Table 1**.

**Table 1:** 21 CFR Part 600-680

| Food and Drugs | Parts |
|---|---|
| **Food and Drug Administration, Department of Health and Human Services** | **1-1299** |
| **Subchapter F: Biologics** | **600-680** |
| **Part 600: Biological Products: General** | **600.2-600.90** |
| Subpart A: General Provisions | 600.2-600.3 |
| Subpart B: Establishment Standards | 600.10-600.15 |
| Subpart-C: Establishment Inspection | 600.20-600.22 |
| Subpart D: Reporting of Adverse Experiences | 600.80-600.90 |
| **Part 601: Licensing** | **601.2-601.95** |
| **Part 606: Current Good Manufacturing Practices for Blood and Blood Components** | **606.1-606.171** |
| **Part 607: Establishment Registration and Product Listing for Manufacturers of Human Blood and Blood Products and Licensed Devices** | **607.1-607.80** |
| Subpart A: General Provisions | 607.1-607.8 |
| Subpart B: Procedures for Domestic Product Establishments | 607.20-607.39 |
| Subpart C: Procedures for Foreign Product Establishments | 607.40 |
| Subpart D: Exemptions | 607.65 |
| Subpart E: Establishment Registration and Product Listing of Licensed Devices | 607.80 |
| **Part 610: General Biological Products Standards** | **610.1-610.68** |
| **Part 630: Requirements for Blood and Blood Components intended for further Manufacturing Use** | **630.1-630.40** |
| Subpart A: General Provisions | 630.1-630.3 |
| Subpart B: Donor Eligibility Requirements | 630.5-630.35 |
| Subpart C: Donor Notification | 630.40 |
| **Part 640: Additional Standards for Human Blood and Blood Products** | **640.1-640.130** |
| **Part 660: Additional Standards for Diagnostic Substances for Laboratory Tests** | **660.1-660.55** |
| **Part 680: Additional Standards for Miscellaneous Products** | **680.1-680.3** |
| Allergenic Products | 680.1 |
| Manufacture of Allergenic Products | 680.2 |
| Tests | 680.3 |

**Center for Evaluation of Biological Products:**

***Center for Biologics Evaluation and Research (CBER):***

CBER is the Center within FDA that regulates biological products for human use under applicable federal laws, including the Public Health Service Act and the Federal Food, Drug and Cosmetic Act. CBER protects and advances the public health by ensuring that biological products are safe and effective and available to those who need them. CBER also provides the public with information to promote the safe and appropriate use of biological products[9].

Vision of the Center for Biologics Evaluation and Research (CBER) is uses sound science and regulatory expertise to is to protect and improve public and individual health in the United States and, where feasible, globally; facilitate the development, approval of, and access to safe and effective products and promising new technologies and strengthen CBER as a preeminent regulatory organization for biologics[10].

The mission of the Center for Biologics Evaluation and Research (CBER) is to ensure the safety, purity, potency, and effectiveness of biological products including vaccines, allergenic, blood and blood products, and cells, tissues, and gene therapies for the prevention, diagnosis, and treatment of human diseases, conditions, or injury[10].

**Requirements for Biologics License Application:**

Biologics are evaluated for market by the FDA through the filing of a Biologic License Application (BLA). A BLA, although similar to a New Drug Application (NDA), has its own set of intricate requirements. It is difficult to know whether an applicant has included all of the information required, and provided that information in an acceptable format, under the applicable regulations[11].

While there are many components of a BLA submission, the primary requirements are specified in Form FDA 356h – Application to Market a New or Abbreviated New Drug or Biologic for Human Use[12].

The checklist shown in **Figure 1** is intended to act as a general guide and reminder of the types of information which must be included in a BLA, however, applicants must be aware that unique and specific information will be required depending on the type of BLA (e.g., blood, vaccines)[11].

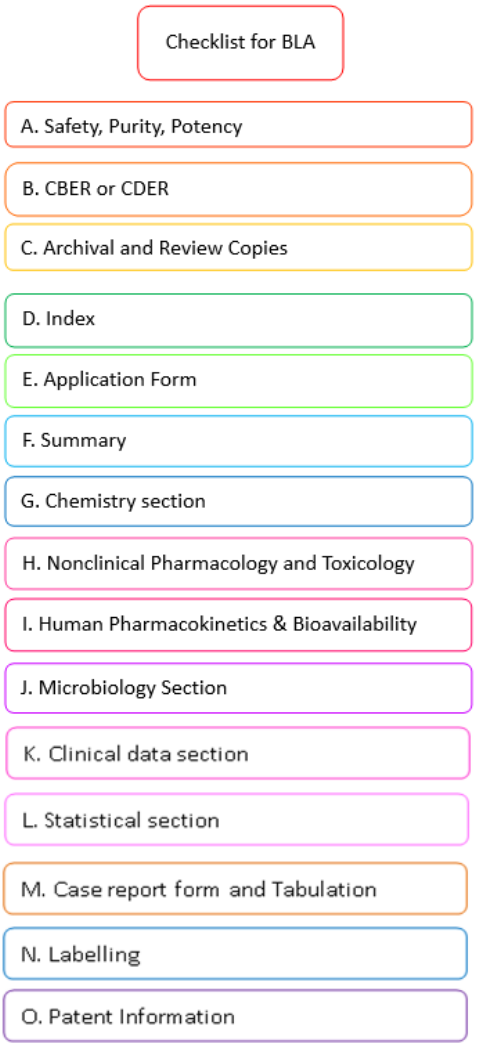


**Figure 1:** Checklist for Biologics License Application

**A. Safety, Purity and Potency:** An applicant (and, by logical extension, the application) must demonstrate:

(i) The product is safe, pure and potent or not

(ii) The facilities for production meet the standards designed to assure that it continues to be safe, pure and potent.

**B. CBER or CDER:**

An applicant must determine which division of the FDA to submit its application, as the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER) share responsibility for BLA.

CBER regulates: (i) Allergenic; (ii) Blood and blood components, including pharmaceutical products made from blood; (iii) Devices (used to safeguard blood, blood components and cellular products from HIV, hepatitis, syphilis and other infectious agents.

CDER regulates: (i) Monoclonal antibodies for in vivo use; (ii) Proteins intended for therapeutic use that are extracted from plants, animals or microorganisms, including recombinant versions of these products.

**C. Archival and Review Copies:**

Federal regulations require the submission of two copies of a BLA which is primarily are archival and review copies

The archival copy is a complete copy of an application submission and must be bound in a BLUE cover jacket. The archival copy should include a cover letter to:

(i) Confirm any agreements or understandings between the FDA and the applicant;

(ii) Identify a contact person regarding the application;

(iii) Identify the reviewing division of the FDA and the HFD number

The review copy is divided into six technical sections ("review sections") and should be submitted with each review section separately bound in a specific color which is given as follow:

(i) Chemistry, Manufacturing and Controls (CMC)- RED

(ii) Nonclinical Pharmacology and Toxicology – YELLOW

(iii) Human Pharmacokinetics and Bioavailability – ORANGE

(iv) Microbiology (if required) - WHITE

(v) Clinical Data - LIGHT BROWN

(vi) Statistical - GREEN.

Each review section should contain the following documents:

(i) A copy of the cover letter attached to the archival copy

(ii) A completed application form FDA 356h

(iii) A copy of the summary

(iv) A copy of the general index of the entire application

(v) An index specific to that particular review section;

(vi) Letters of reference or authorization, if appropriate

(vii) Patent information.

**D. Application form:**

Every application must be accompanied by a completed application form FDA 356h.

The application form should be signed by the applicant, or the applicant's attorney, agent or other authorized official.

If the person signing the application form does not reside or have a place of business within the U.S., the application must contain the name and address of, and be countersigned by, an attorney, agent or other authorized

official who resides or maintains a place of business within the U.S.

The application form along with the cover letter, letters of authorization (if any), Index and Summary should be packaged together and bound in a single volume.

**E. Index:**

An application must contain an index of all the elements of the application.

For each element of the application, the index must identify the volume and page number. Each review section must contain an index specific to that review section.

**F. Summary:**

An application must contain a summary, usually between 50 to 200 pages in length integrating all of the information in the application and providing a general understanding of the drug and its application.

The summary must present the most important information about the biologic and the conclusions to be drawn from this information, a factual summary of safety and effectiveness data and a neutral analysis of this data, an annotated copy of the proposed labeling, a discussion of the product's benefits and risks.

**G. Chemistry section:**

Chemistry, Manufacturing and Controls Section (CMC) - An application must present chemistry, manufacturing and control information for both the drug substance and the drug product (the finished dosage form of the product).

**The CMC for Drug substance –** It should include the following information:

(i) Description and characterization; (ii) Manufacturer; (iii) Method of manufacture; (iv) process controls (iv) Container and closure system; and (v) Drug substance stability.

**Method of Manufacture -** Information on the method of manufacture should include:

(i) Raw materials (a list of all materials used in the manufacture of the drug substance, and their test and specifications)

(ii) Flow charts (a complete visual representation of the manufacturing process)

(iii) Detailed description of the drug substance.

**Process Controls -** Information on process controls should include:

(i) In-process controls (description of the sampling procedures and the test methods used)

(ii) Process validation (summary report, including protocols and results, for each validation study of each critical process or factor that affects drug substance)

**H. Nonclinical Pharmacology and Toxicology:**

An application should list all nonclinical studies, with volume and page numbers, in the application's table of contents and replicated at the beginning of this review section.

A recommended order for submission of various types of studies is:

(i) Pharmacology Studies

(ii) Acute Toxicity Studies

(iii) Multiple dose Toxicity Studies

(iv) Special Toxicity Studies

(v) Reproduction Studies

(vi) Mutagenicity Studies

**I. Microbiology section:** This section should include the following information:

(i) Mechanism of action

(ii) Pharmacokinetics

(iii) Antimicrobial activity

(iv)Enzyme hydrolysis rates

(v) Miscellaneous studies

**J. Clinical data section:** The application should generally describe the clinical investigations of the drug, including the following:

(i) A description and analysis of each clinical pharmacology study of the drug.

(ii) A description and analysis of each controlled clinical study pertinent to a proposed use of the drug, including the protocol and a description of the statistical analyses used to evaluate the study.

(iii) A description of each uncontrolled clinical study, a summary of the results and brief statement explaining why the study is classified as uncontrolled.

(iv)An integrated summary of the benefits and risks of the drug

(v) A statement with respect to each clinical study involving human subjects that it either was conducted in compliance with the institutional review board regulations, or was not subject to the regulations, and that it was conducted in compliance with the informed consent regulations.

**K) Case Report Forms and Tabulations:** An applicant should submit case reports for:

(i) All patients who died during a clinical study.

(ii) Patients who did not complete a study because of any adverse event, whether or not the adverse event is considered drug related by the investigator or sponsor, including patients receiving reference drugs or placebo.

**L. Labeling:** The labeling should include the following information:

(i) Proper name of the product

(ii) Name, address and license number of the manufacturer

(iii) Lot number or other lot identification

(iv) Expiry date of the product

(v) The statement "$R_X$ only" for prescription ofbiological

(vi) Must include the preservative used with its concentration

(vii) Recommended storage temperature should be mentioned on the label

**M. Patent Information:** An applicant must submit basic information about each patent, including the following:

(i) Patent number and the date on which the patent will expire

(ii) Type of patent

(iii) Name of patent owner

(iv) If the patent owner or applicant does not have a place of business within the U.S., the name of the agent of the patent owner or applicant who resides or maintains a place of business within the U.S. authorized to receive notice of patent certification.

**Biologics License Application Process:**

Vaccines and biologics follow the same general pathway as for drugs.

Sponsor shall submit all the non-clinical data in case of IND to FDA, FDA inaction in 30days to triggers the study under the IND to proceed.

The sponsor can initiate the clinical trials and process and review remains the same as of small molecules.

For every phase of a clinical trial, the sponsor has to review and continue to the next phase of the trial.

Once the clinical trial data is ready, the sponsor has to perform a pre-approval meeting.

After a sponsor submits a BLA to the FDA, they assemble a review team and then evaluates, within the first 60 days after submission, whether it can file the application or refuse.

For Biologics License Application the manufacturer shall submit an application to the Director, Center for Biologics Evaluation and Research (CBER) of FDA on forms prescribed for such purposes, and shall submit data derived from nonclinical studies and clinical studies to prove safety, purity, and potency of the biological Product.

USFDA also inspect the manufacturing process of the biological product[13]. Approval process of Biologics License Application is shown in **Figure 2.**

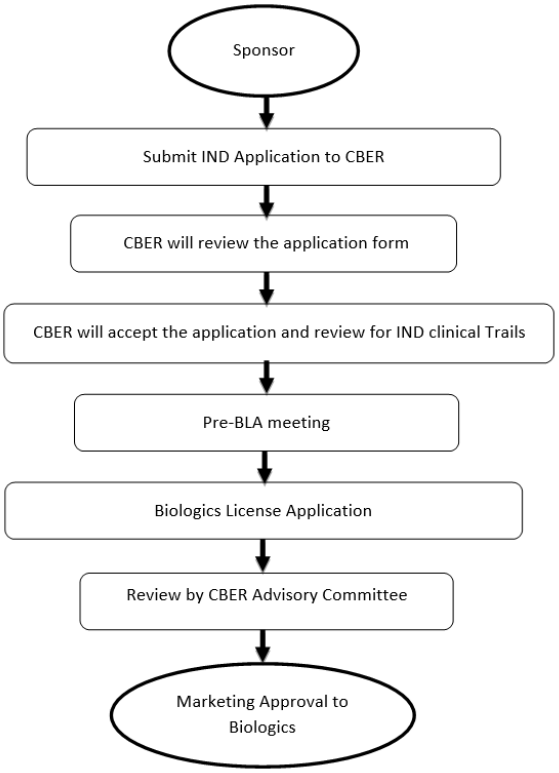


**Figure 2:** Biologics License Approval Process[14]

## CONCLUSION

The biologics license Application is submitted to the US Food and Drug Administration (FDA)to *request marketing approval of a new biologic medicinal product in the USA*. The Biologics License Application (BLA) is the submission of the documentation that demonstrates the safety, efficacyand potency ofthe biologic for which a marketing application is required. In addition to safety and efficacy data, information regarding the chemistry, manufacturing, and control (CMC) is also submitted.

**Acknowledgement:**

The authors are very much thankful to Principal, SNJBs Shriman Sureshdada Jain College of Pharmacy, Chandwad, for providing library and internet facility.

**Conflict of interest:**

There is no conflict of interest regarding the publication of this article

**Abbreviations:**

1. BLA: Biologics License Application.
2. NDA: New Drug Applications.
3. CFR: Code of Federal Regulation
4. IND: Investigational New Drug
5. NDA: New Drug Application

6. USD: United States Dollar
7. CBER: Center for Biologics Evaluation and Research.
8. CDER: Center for Drug Evaluation and Research.
9. FDA: Food and Drug Administration.
10. CMC: Chemistry, Manufacturing and Control

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**Source of Support:** The author(s) received no financial support for the research, authorship, and/or publication of this article.

**Conflict of Interest:** The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.