Research Article

# REGULATORY REQUIREMENTS FOR THE REGISTRATION OF BIOLOGICS IN U.S

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**ABSTRACT**

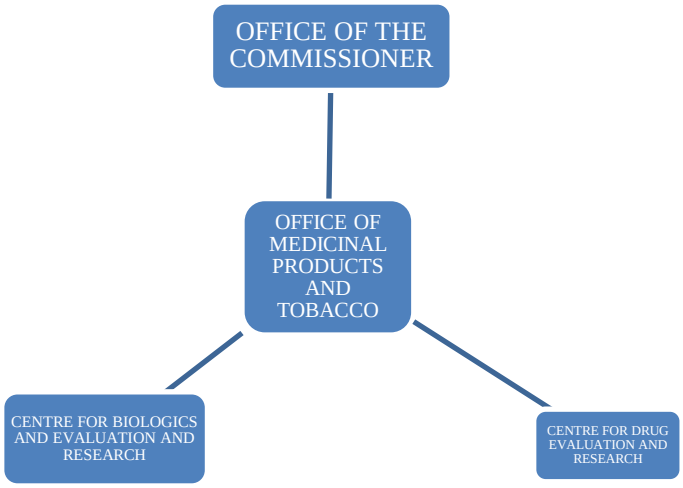
The study highlighted the "Regulatory requirements for registration of Biologics in US" and brief description about the Biologics License Application and its requirements to fill and submit to the USFDA. The requirements to submit to market a new biologic drug follows the CTD format with five modules like Module-1 contains Administrative information, Module-2 contains the overall Quality summary, Module-3 contains Quality information(CMC), Module-4 contains preclinical information and Module-5 contains Clinical information of Biologics. Also provides the Biological Acts, History of Biologics according to US regulations ,the Biologic drugs regulates by the CDER and CBER, combination drugs regulates by both CDER and CBER, the Registration procedure for new biologics, application form (BLA), financial disclosure information of BLA, Patent exclusivity of New Biologics and instructions required for filling of the application form

**Keywords**: BLA, USFDA, CDER, CBER.

## INTRODUCTION

The Food and Drug Administration (FDA or USFDA) is an federal agency of the United States Department of Health and Human Services responsible for protecting and promoting public health through the regulation and supervision of food safety, tobacco products, dietary suppliments, prescription and over-the-counter pharmaceutical drugs (medications), vaccines, Biopharmaceuticlas, blood transfusions, medical devices, electromagnetic radiation emitting devices (ERED),cosmetics, animal foods and feed and veterinary products.[1]

The FDA has seven product and research centers to fulfill FDA's fundamental public health mission: to protect and promote the health of the American people. The Center for Biologics Evaluation and Research (CBER) is one of seven main centers for the U.S. Food and Drug Administration (FDA), which is a part of the U.S. Department of Health and Human Services. CBER is responsible for assuring the safety, purity, potency, and effectiveness of biologics and related products (such as vaccines, live bio therapeutics (probiotics), blood products, and cell, tissue, and gene therapies). Not all biologics are regulated by CBER. Monoclonal antibodies and other therapeutic proteins are regulated by the FDA Center for Drug Evaluation and Research (CDER).Originally, CBER was part of what became the National Institutes of Health, rather than the FDA. The Bureau was transferred from the NIH to the FDA in 1972, where it was renamed Bureau of Biologics and focused on vaccines, serums for allergy shots, and blood products. Later, with the beginning of the biotechnology revolution, it was merged with the FDA's Bureau of Drugs to form the Center for Drugs and Biologics. In 1987, CBER and the Center for Drug Evaluation and Research (CDER) were split into their present form. The two groups were charged with enforcing different laws and had significantly different philosophical and cultural differences. In 2002, the FDA transferred a number of biologically produced therapeutics to CDER. CBER regulates a number of biologics-related products, including blood tests, computer software, and devices related to blood transfusion.




**History of Biologics**

1902: Biologics Control Act
- PHS Hygienic Lab.
- Renamed National Institute of Health (NIH) (1930)
- NIH Div. of Biologics Control (1937)

1937: The NIH is recognized, and responsibility for biologics is transferred to the division of biologics control. In 1944 it is renamed the laboratory of biologics control.

1944: Public Health Service (PHS) Act

1948: The laboratory of biologics control is integrated into the NIH's national Microbial institute .which later becomes the institute of Allergy and infectious diseases.

1955: improperly inactivated polio vaccine
- NIH Div. of Biological Standards
- FDA Bureau of Biologics (1972)

1983: FDA Center for Drugs and Biologics.

1988: Center for Biologics Evaluation and Research (CBER).

2003: Therapeutic Biological products transferred to CDER.[2]

- In 1887, the United States first bacteriological laboratory was established by Joseph Kinyoun at the Marine Health Service Hospital at Staten Island, New York. In 1891, the Laboratory of Hygiene was relocated to Washington, D.C. The Hygienic Laboratory developed procedures for diphtheria antitoxin and provided licensing for biological manufacturers.
- In 1901, the first incident involved the horse named Jim whose tetanus-contaminated serum was used to produce a diphtheria antitoxin that caused the deaths of thirteen children in St. Louis, Missouri.
- In 1902, Congress enacted the Biologics Control Act, also known as the Virus-Toxin Law, which gave the government its first control over the processes used for the production of biological products. The first regulations under this Act became effective on August 21, 1903, and mandated that producers of vaccines be licensed annually for the manufacture and sale of vaccines, serum, and antitoxins. Manufacturing facilities also were required to undergo inspections, and licenses could be revoked or suspended when necessary. Production was to be supervised by a qualified scientist. All product labels were required to include the product name, expiration date, and address and license number of the manufacturer. The Biologics Control Act mandated producers in the United States to be licensed annually for the manufacture and sale of antitoxins, serum, and vaccines.
- In 1930, the Hygienic Laboratory was titled the National Institute of Health.
- In 1937, the Division of Biologics Control was formed within the National Institute of Health.

- In 1944, the Public Health Service Act added licensure of the biologic products themselves in addition to the facilities engaged in their manufacture.
- In 1972, the Division of Biologics was transferred from National Institute of Health to the U.S. Food and Drug Administration and renamed the Bureau of Biologics.
- In 1983, the Bureau of Biologics was merged with the FDA's Bureau of Drugs to form the Center for Drugs and Biologics.
- In 1987, CBER and the CDER were split into two groups. The two groups were charged with enforcing different laws and had significantly different philosophical and cultural differences.
- In 1988, the Bureau of Biologics was transferred to the CBER within the U.S. Food and Drug Administration.
- In 1999, the FDA issued a final rule to implement a single biologics license that combined the two systems, with particular emphasis on analytical characterization. The CBER implements the regulations of the two laws governing biologic products: the FD&C Act and the Public Health Service (PHS) Act. The procedures for the review and monitoring of biologics are almost identical to CDER. In addition to the regulations in 21 CFR Section 202, biologics are also regulated under 21 CFR Section 600 and Section 601.
- In 2002, the FDA transferred a number of biologically produced therapeutics to CDER. CBER regulates a number of biologics-related products, including blood tests, computer software, and devices related to blood transfusion.[3]

**Biologics Definition**

In contrast to chemically synthesized small molecular weight drugs, which have a well-defined structure and can be thoroughly characterized, biological products are generally derived from living material–human, animal, or microorganism–are complex in structure, and thus are usually not fully characterized.

In 1944, the congress revised and recodified the 1902 Act in the Public Health Service Act (PHSA), it clarified that the NDA requirements did not apply to biologics, but it did not elucidate the scope of the biological product definition.

The Section 351 of the Public Health Service (PHS) Act defines a “biological product” as a “virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product… applicable to the prevention, treatment, or cure of a disease or condition of human beings

**Biologic products regulated by CBER**

A biologic will be regulated by the CBER if it is

Cellular products, including products composed of human, bacterial or animal cells (such as pancreatic islet cells for transplantation), or from physical parts of those cells (such as whole cells, cell fragments, or other components intended for use as preventative or therapeutic vaccines).

- Gene therapy products. Human gene therapy/gene transfer is the administration of nucleic acids, viruses, or genetically engineered microorganisms that mediate their effect by transcription and/or translation of the transferred genetic material, and/or by integrating into the host genome. Cells may be modified in these ways ex vivo for subsequent administration to the recipient, or altered in vivo by gene therapy products administered directly to the recipient.
- Vaccines (products intended to induce or increase an antigen specific immune response for prophylactic or therapeutic immunization, regardless of the composition or method of manufacture).
- Allergenic extracts used for the diagnosis and treatment of allergic diseases and allergen patch tests.
- Antitoxins, antivenins, and venoms
- Blood, blood components, plasma derived products (for example, albumin, immunoglobulins, clotting factors, fibrin sealants, proteinase inhibitors), including recombinant and transgenic versions of plasma derivatives, (for example clotting factors), blood substitutes, plasma volume expanders, human or animal polyclonal antibody preparations including radiolabeled or conjugated forms, and certain fibrinolytics such as plasma-derived plasmin, and red cell reagents.

**Combination Products**

The lists above contain some combination products comprised of a biological product component with a device and/or drug component, though such products are not specifically identified. Combination products are assigned to a Center for review and regulation in accordance with the products' primary mode of action. When a product's primary mode of action is attributable to a type of biological product assigned to CDER, the product will be assigned to CDER. Similarly, when a product's primary mode of action is attributable to a type of biological product assigned to CBER, the product will be assigned to CBER.[7]

## METHODOLOGY

The study was organized into 4 steps to achieve the objectives:

1. Type of Study
2. Sources of data
3. The regulatory aspects
4. Study process

### 1. Type of Study

This is a descriptive study, where effort has been made to study and provide recommendations on harmonization of the regulatory framework for the approval of Biologics in United States.

### 2. Sources of Data

In this descriptive study, primary and secondary sources of data have been referred to which include the following:

- Journal Articles published in peer-reviewed publications
- Websites of various regulatory agencies and organizations
- Guidelines and guidance documents issued by the regulatory authorities of the countries included in the study.
- Textbooks
- Records and databases of various regulatory agencies.

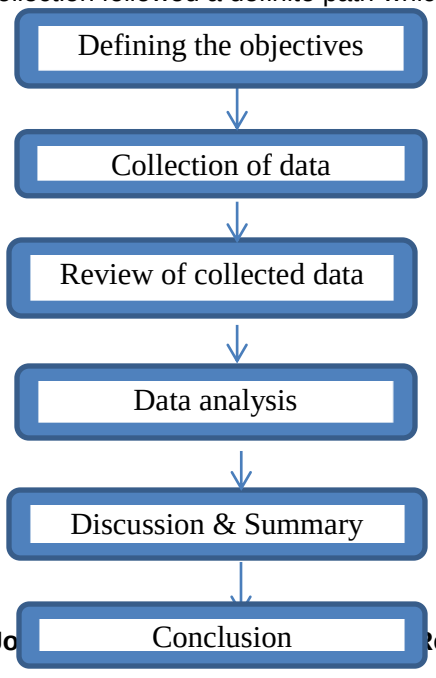
### 3. The regulatory aspects

Thesis part mainly involved 4 phases:

i. Brief description of Biologics.
ii. Description of BLA.
iii. Elements of BLA.
iv. And CTD requirements for registration of Biologics.

### 4. Study process:

The information collection followed a definite path which is outlined below

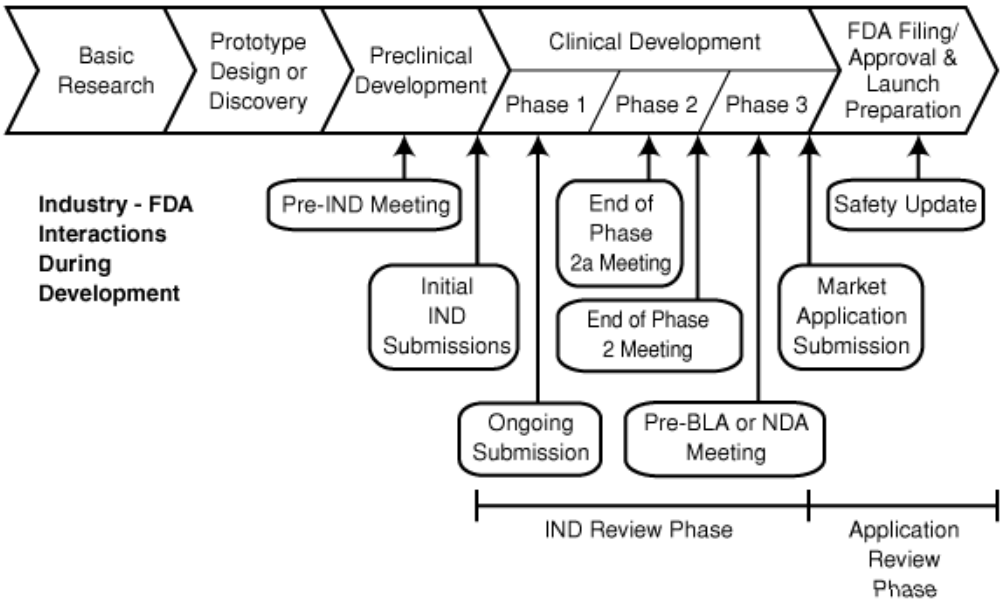


## DISCUSSION

### Registration of Biologics in USA

In the United States, "biological products" are subject to a different premarket pathways and differing intellectual property protections than products regulated only as "drugs". Whereas a biological product must be licensed pursuant to a biologics license application (BLA) showing it is "safe, pure, and potent", the sponsor of a non-biological drug must submit a new drug application (NDA) showing the drug is safe and effective.

The new biological products will receive 12 years of data protection, whereas the new drugs receive up to 5 years of protection. Biologic and drug legislation also provide different schemes for resolving patent issues regarding entry of follow-on products and biosimilars. Before a biologic may be approved and marketed, the biologic must undergo extensive testing and regulatory review in order to determine that the biologic is safe and effective. It is not possible to estimate the time in which preclinical and Phases I, II and III studies will be completed with respect to a given product, although the time period may last many years. Using the U.S. regulatory environment as an example, the stages of this development process are generally as follows.




**Development of stages of Biologics**

### BLA & Regulatory requirements for registration of Biologics in U.S

- Biological license application.
- Checklists of required elements for Biological license application.
- Examination of biologics license application by USFDA.
- Agency review process.
- Complete response letter to the applicant.
- Approval process.
- Post-approval changes.
- Reference product exclusivity for biological products filed under 351(a) of the PHS act.
- Regulatory requirements for registration of biologics according to USFDA.

**1. Biologics license application**

- The Biologics License Application (BLA) is a request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce (21 CFR 601.2). The BLA is regulated under 21 CFR 600 – 680.

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

- Cover letter and application form
- Table of Contents (Index)

- Labeling
- 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

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- Statistical section
- Case Report Tabulations (CRTs)
- Case Report Forms
- Patent Information.
- Patent Certification.
- Establishment Description.
- Debarment Certification.
- Field copy certificate
- User Fee Cover Sheet.
- Other.
- **Cover letter**
- **Application form (Form FDA 356h)**

**3. Examination of biologics license application by USFDA:**

a. Examination
b. Availability of product
c. Manufacturing process
d. Inspection.
e. One biologics license to cover all locations.

**4. Agency review procedures:**

a. Advisory review panels
b. Request for data and views
c. Deliberations of an advisory review panel
- Standards for safety, effectiveness, and labeling

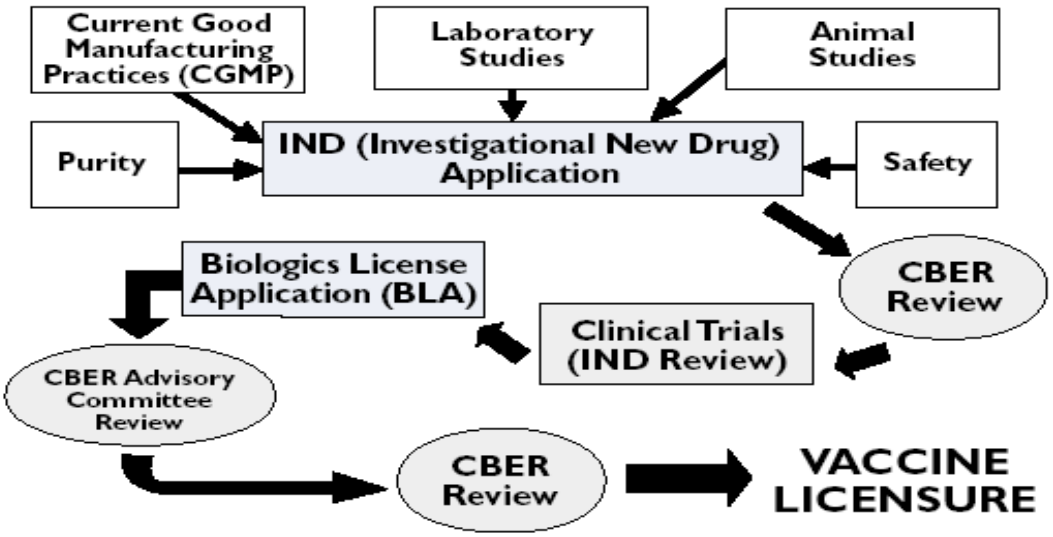
d. Advisory panel report to the commissioner
e. Proposed order
f. Final order
g. Reserved.
h. Reclassification procedure.

**5. Complete response letter to the applicant:**

a. Complete response letter

b. Applicant action
c. Failure to take action

**6. Approval process:**
a. General
b. Reserved
**Biologics approval procedure**
**According to 21 CFR 601.2 section,**
**General:** To obtain a biologics license under section 351 of the Public Health Service Act for any biological product, the manufacturer shall submit an application to the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research, on forms prescribed for such purposes, and shall submit data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed requirements of safety, purity, and potency with respect to each nonclinical laboratory study, either a statement that the study was conducted in compliance with the requirements, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance; statements regarding each clinical investigation involving human subjects contained in the application, that it either was conducted in compliance with the requirements for institutional review or was not subject to such requirements and was conducted in compliance with requirements for informed consent set. A full description of manufacturing methods; data establishing stability of the product through the dating period; sample(s) representative of the product for introduction or delivery for introduction into interstate commerce; summaries of results of tests performed on the lot(s) represented by the submitted sample(s); specimens of the labels, enclosures, and containers, and if applicable, any Medication Guide required proposed to be used for the product; and the address of each location involved in the manufacture of the biological product shall be listed in the biologics license application. The applicant shall also include a financial certification or disclosure statement(s) or both for clinical investigators as required. An application for a biologics license shall not be considered as filed until all pertinent information and data have been received by the Food and Drug Administration. The applicant shall also include either a claim for categorical exclusion or an environmental assessment.




**Post Approval Changes to An Approved Application:**

1. Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes).
2. Changes under §601.12(c) : Changes requiring supplement submission at least 30 days prior to distribution of the product made using the change.
3. Changes under §601.12(d) : Changes to be described in an annual report (minor changes).
4. Changes under §601.12(f) - Labeling change

**Reference product exclusivity for biological products filed under 351(a) of the PHS act:**

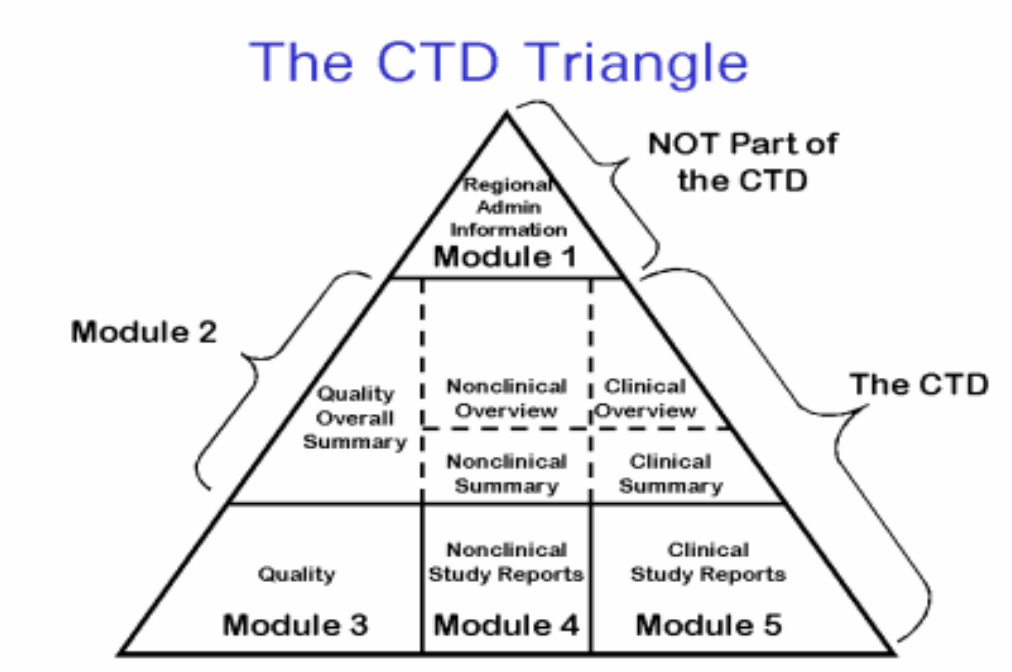
*"Licensor, Predecessor in Interest, or Other Related Entity"*

1. "Modification to the Structure of the Biological Product"
3. "Result[s] in Change in Safety, Purity, or Potency"

9. Regulatory requirements for registration of biologics in US according to USFDA:

The Common Technical Document is divided into five modules:

1. Administrative and prescribing information.
2. Overview and summary.
3. Quality Overall Summary (pharmaceutical documentation).
4. Non clinical Document Safety (toxicology studies).
5. Clinical Document Efficacy (clinical studies).




**Module -1:**

1.FDA form 356h

2.Comprehensive table of contents:

3.Administrative documents

a. Administrative documents
b. Prescribing information
c. Annotated labeling text
d. Labeling comparison

**Module-2:**

Common Technical Document Summaries:

1. Overall CTD table of contents
2. Introduction to the summary documents
3. Overviews and summaries

**Module-3:**

a.Drug substance:

1.Description
2.Characterization

b. Manufacturers
c. Method of manufacture

d. Process control section
e. Reference standard
f. Specifications/Analytical methods
g. Container/Closure system(s)
h. Drug or in vitro substance stability

Drug product:

1.Composition, including components
2.Specifications & Methods for Drug
3.Manufacturer(s)
4.Methods of Manufacture and Packaging
5.Specification & Test Methods for Drug
6.Container/Closure System
7.Microbiology
8.Lyophilization
9.Drug Product Stability
10.Investigational Product/Formulation
11.Environmental Assessment
12.Methods Validation
13.Establishment Description Section

**Module-4:**

Non-clinical studies:

- Relevant species
- Immunogenicity
- Typical preclinical studies
- Study design
- Cross reactivity
- Genotoxicity

**Module-5:**

- Reports of biopharmaceutical studies
- Reports of studies pertinent to pharmacokinetics using human biomaterials
- Reports of human pharmacokinetic studies(PK)
- Population PK study reports
- Reports of human pharmacodynamics (PD) studies
- Reports of efficacy and safety studies

**SUMMARY**

In contrast to chemically synthesized small molecular weight drugs, which have a well-defined structure and can be thoroughly characterized, biological products are generally derived from living material–human, animal, or microorganism–are complex in structure, and thus are usually not fully characterized.

The Biologics License Application (BLA) is a request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce (21 CFR 601.2). The BLA is regulated under 21 CFR 600 – 680. A BLA is submitted by any legal person or entity who is engaged in manufacture or an applicant for a license who takes responsibility for compliance with product and establishment standards.

The CTD is divided into five modules: Module 1: Regional and Administrative Information, Module 2: Quality Overall Summary, Module 3: Quality, Module 4: Non Clinical Study Reports (toxicology studies) and Module 5: Clinical Summary (clinical studies).

The study covered the details about the historical development of Biologics, Biologics regulations by the CDER and CBER, Combinational drugs regulations by the CBER and CDER, the Biologics License Application Form, BLA form, instructions to fill the BLA, elements required for submission of Biologics License Application, fee requirements, financial disclosurement, patent certificate, Debarment certificate, Chemistry, manufacturing and control (CMC), clinical information report, Non-clinical information report, Case Report forms, Patent information, Patent exclusivity, Review procedure of the BLA and examination and response to the applicant by the USFDA. It gives the information about the requirements for the approval procedure, post approval changes like Major, Minor and Moderate changes and Registration of Biologics in the form Of CTD format according to USFDA.

## CONCLUSION

Biologics are natural and very complex drugs used to treat various diseases and disorders. Nowadays Biotechnology also developing to manufacture different kinds of drugs like antibiotics, anticancer drugs. From the thesis I concluded that the way of submission of BLA, Requirements for BLA submission to the FDA, Regulatory requirements for registration of new Biologic according to CTD format like Module-I contain Administrative Information, Module-II contain Overall summary, Module-III contains the Quality summary, Module-IV contains preclinical information and Module-V contains clinical information. And information about the Patent exclusivity of Biologics, approval procedure, post-approval changes after submission of BLA.

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