

Regulatory Requirements for Registration of Biologics in US

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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, Biologics, 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 supplements, prescription and over-the-counter pharmaceutical drugs (medications), vaccines, Biopharmaceuticals, 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 biotherapeutics (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).

1.1 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 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.
- ❖ 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

1.2 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 rectified 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.”⁴

In 1986, the FDA issued a policy statement stating that it would determine whether biotechnology products constituted biologics “based on the intended use of each product on a case-by-case basis. Thus, the FDA continued to make product-specific determinations informed by history and precedent, and different units of the FDA had to agree on the approval pathway for a given product.

In 1991, CDER and CBER executed an interceptor agreement (ICA) that attempted to clarify the governing authorities for products derived from living material. The agreement provided that the following products, among others, were subject to license under the PHSA: vaccines, proteins, peptides and carbohydrates produced by cell culture (other than hormones and products previously derived from

human or animal tissue and approved as drugs): proteins made in transgenic animals: blood and blood products: and allergenic products.

In February 2012, the FDA issued draft guidance aimed at implementing recent legislation that added “protein (except any chemically synthesized polypeptide)” to the biological product definition. In draft guidance, the FDA proposed a bright-line rule distinguishing proteins from “peptide” and chemically synthesized polypeptide(s) that the FDA proposes to approve under the FDCA. The agency proposed to define “protein” as “any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acid sizeZ.”

Biological products subject to the PHS Act also meet the definition of drugs under the Federal Food, Drug and Cosmetic Act (FDC Act). Note that hormones such as insulin, glucagon, and human growth hormone are regulated as drugs under the FDC Act, not biological products under the PHS Act. Both the FDA’s Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) have regulatory responsibility for therapeutic biological products, including premarket review and oversight.⁶

1.3 Biologic products regulated by CDER

A biologic will be regulated by the CDER if it is:

- Monoclonal antibodies for in vivo use.
- Proteins intended for therapeutic use, including cytokines (e.g. interferon’s), enzymes (e.g. thrombolytics), and other novel proteins, except for those that are specifically assigned to CBER (e.g., vaccines and blood products). This category includes therapeutic proteins derived from plants, animals, or microorganisms, and recombinant versions of these products.
- Immunomodulators (non-vaccine and non-allergenic products intended to treat disease by inhibiting or modifying a pre-existing immune response).
- Growth factors, cytokines, and monoclonal antibodies intended to mobilize, stimulate, decrease or otherwise alter the production of hematopoietic cells in vivo.

1.4 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.
- Allergenic extracts used for the diagnosis and treatment of allergic diseases and allergen patch tests.
- Antitoxins, antivenoms, and venoms
- Blood, blood components, plasma derived products (for example, albumin, immunoglobulin’s, clotting factors, fibrin sealants, protein inhibitors), including recombinant and transgenic versions of plasma derivatives, (for example clotting factors), blood substitutes, plasma volume expanders.

AIM & OBJECTIVE

Aim:

The aim of the project is to highlight the “Regulatory Requirements for the Registration of Biologics in U.S”.

Objectives

The objective of dissertation work is to know the:

- Basic understanding on the “Regulatory requirements for registration of biologics in U.S”.
- Presentation of application forms, its requirements and guidance to fill and apply for new Biologics in U.S.
- CTD requirements for registration of Biologics.

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.

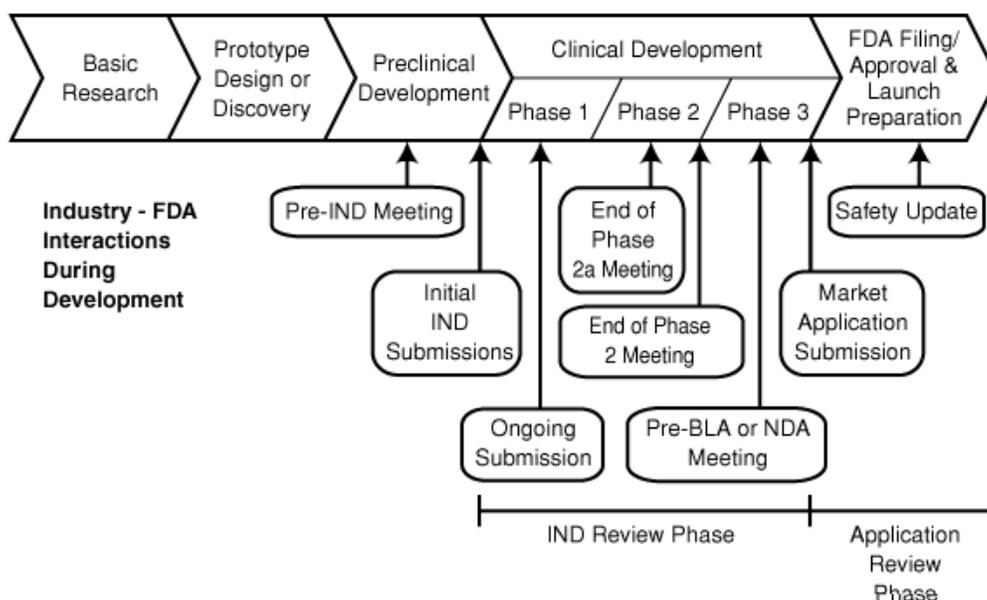


Fig. 3: Development of stages of Biologics

• Preclinical Research (approximately 1 to 3.5 years)

- In vitro (“test tube”) and animal studies must be conducted in accordance with GLP to establish the relative toxicity of the drug or biologic over a wide range of doses and to detect any potential to cause a variety of adverse conditions or diseases, including birth defects or cancer. If results warrant continuing development of the drug or biologic, the results of the studies are submitted to the FDA by the manufacturer as part of an Investigational New Drug Application (“IND”), which must be reviewed by the FDA before proposed clinical testing can begin. An IND must include, among other things, preclinical data, chemistry, manufacturing and control information, and an investigational plan, and must become effective before such trials may begin. An IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, raises concerns or questions relating to one or more proposed clinical trials.

• Clinical Trials (approximately 3.5 to 6 years):

- **Phase I:** consists of basic safety and pharmacology testing in approximately 20 to 80 human subjects, usually healthy volunteers or stable patients, and includes studies to evaluate the metabolic

and pharmacologic action of the product in humans, how the drug or biologic works, how it is affected by other drugs, how it is tolerated and absorbed, where it goes in the body, how long it remains active, and how it is broken down and eliminated from the body.

- **Phase II** includes basic efficacy (effectiveness) and dose-range testing in a limited patient population (usually 100 to 200 patients) afflicted with a specific disease or condition for which the product is intended for use, further safety testing, evaluation of effectiveness, and determination of optimal dose levels, dose schedules, and routes of administration. If Phase II studies yield satisfactory results and no hold is placed on further studies by the FDA, Phase III studies can be commenced.
- **Phase III** includes larger scale, multi-center, comparative clinical trials conducted with patients afflicted by a target disease, in order to provide enough data for a valid statistical test of safety and effectiveness required by the FDA and others, and to provide an adequate basis for product labeling. When results from Phase II or Phase III show special promise in the treatment of a serious or immediately life-threatening disease or condition for which existing therapeutic options are nonexistent, limited, or of minimal value, the FDA may allow the sponsor to make the new drug available to a larger number of patients through the regulated mechanism of a Treatment Investigational New Drug Application (“IND”) during Phase II, Phase III, or after all clinical trials have been completed. Although INDs may enroll and collect a substantial amount of data from tens of thousands of patients, they are not granted in all cases.

Upon completion of Phase III trials, the sponsor assembles the statistically analyzed data from all phases of development, along with the chemistry and manufacturing and pre-clinical data and the proposed labeling, among other things, into a single large document, the BLA.

Biological License Application (BLA)

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. Form 356h specifies the requirements for a BLA.

This includes:

- Applicant information
- Product/Manufacturing information
- Pre-clinical studies
- Clinical studies
- Labeling.¹⁷

FDA Review of BLA

The FDA carefully scrutinizes data from all phases of development (including an IND) to confirm that the manufacturer has complied with regulations and that the biologic is safe and effective for the specific use (or “indication”) under study. The FDA may refuse to accept the BLA for filing and substantive review if certain administrative and content criteria are not satisfied. Even after accepting the submission for review, the FDA may also require additional testing or information before approval of BLA. The FDA must deny approval of a BLA if applicable regulatory requirements are not ultimately satisfied.

FDA Review Procedures

For purposes of reviewing biological products that have been licensed to determine that they are safe and effective and not misbranded, the following regulations shall apply. Prior administrative action exempting biological products from the provisions of the Federal Food, Drug, and Cosmetic Act is superseded to the extent that these regulations result in imposing requirements pursuant to provisions therein for a designated biological product or category of products (19).

Advisory review panels

The Commissioner of Food and Drugs shall appoint advisory review panels:

- To evaluate the safety and effectiveness of biological products for which a license has been issued pursuant to section 351 of the Public Health Service Act,
- To review the labeling of such biological products and
- To advise which biological products under review are safe, effective, and not misbranded.

An advisory review panel will be established for each designated category of biological product. The members of a panel will be qualified experts, appointed by the Commissioner, and will include persons from lists submitted by organizations representing professional, consumer, and industry interests. Such persons will represent a wide divergence of responsible medical and scientific opinion. The Commissioner shall designate the chairman of each panel, and summary minutes of all meetings shall be made.

Request for data and views

- The Commissioner of Food and Drugs will publish a notice in the Federal Register requesting interested persons to submit, for review and evaluation by an advisory review panel, published and unpublished data and information pertinent to a designated category of biological products.
- For paper submission, 12 copies of the submission on any marketed biological product within the class shall be submitted, preferably bound, indexed, and on standard sized paper, approximately 8 1/2 inches. The time allotted for submissions will be 60 days, unless otherwise indicated in the specific notice requesting data and views for a particular category of biological products.
- When requested, abbreviated submissions should be sent. All submissions shall be in the following format, indicating “none” or “not applicable” where appropriate, unless changed in the Federal Register notice: Biological Products Review Information.
 1. Label or labels and all other labeling (preferably mounted. Facsimile labeling is acceptable in lieu of actual container labeling), including labeling for export
 2. Representative advertising used during the past 5 years.
 3. The complete quantitative composition of the biological product.
 4. Animal safety data
 - A. Individual active components
 1. Controlled studies
 2. Partially controlled or uncontrolled studies
 - B. Combinations of the individual active components
 1. Controlled studies
 2. Partially controlled or uncontrolled studies
 - C. Finished biological product
 1. Controlled studies
 2. Partially controlled or uncontrolled studies
 5. Human safety data:
 - A. Individual active components:
 1. Controlled studies.
 2. Partially controlled or uncontrolled studies.
 3. Documented case reports.
 4. Pertinent marketing experiences that may influence a determination as to the safety of each individual active component.
 5. Pertinent medical and scientific literature.
 - B. Combinations of the individual active components:
 1. Controlled studies.
 2. Partially controlled or uncontrolled studies.
 3. Documented case reports.
 4. Pertinent marketing experiences that may influence a determination as to the safety of combinations of the individual active components.
 5. Pertinent medical and scientific literature.
 - C. Finished biological product:
 1. Controlled studies.
 2. Partially controlled or uncontrolled studies.
 3. Documented case reports.
 4. Pertinent marketing experiences that may influence a determination as to the safety of the finished biological product.
 5. Pertinent medical and scientific literature.
 6. Efficacy data:
 - A. Individual active components:

1. Controlled studies.
2. Partially controlled or uncontrolled studies.
3. Documented case reports.
4. Pertinent marketing experiences that may influence a determination on the efficacy of each individual active component.
5. Pertinent medical and scientific literature.
- B. Combinations of the individual active components:
 1. Controlled studies.
 2. Partially controlled or uncontrolled studies.
 3. Documented case reports.
 4. Pertinent marketing experiences that may influence a determination as to the effectiveness of combinations of the individual active components.
 5. Pertinent medical and scientific literature.
- C. Finished biological product:
 1. Controlled studies.
 2. Partially controlled or uncontrolled studies.
 3. Documented case reports.
 4. Pertinent marketing experiences that may influence a determination as to the effectiveness of the finished biological product.
 5. Pertinent medical and scientific literature.
7. A summary of the data and views setting forth the medical rationale and purpose:

A summary of the data and views setting forth the medical rationale and purpose (or lack thereof) for the biological product and its components and the scientific basis (or lack thereof) for the conclusion that the biological product, including its components, has been proven safe and effective and is properly labeled for the intended use or uses.

Advisory review panel report to the Commissioner

An advisory review panel shall submit to the Commissioner of Food and Drugs a report containing the panel's conclusions and recommendations with respect to the biological products falling within the category covered by the panel. Included within this report shall be:

1. A statement which designates those biological products determined by the panel to be safe and effective and not misbranded. This statement may include any condition relating to active components, labeling, tests required prior to release of lots, product standards, or other conditions necessary or appropriate for their safety and effectiveness.
2. A statement which designates those biological products determined by the panel to be unsafe or ineffective, or to be misbranded. The statement shall include the panel's reasons for each such determination.
3. A statement which designates those biological products determined by the panel not to fall within either paragraph (1) or (2) of this section on the basis of the panel's conclusion that the available data are insufficient to classify such biological products, and for which further testing is therefore required. The report shall recommend with as much specificity as possible the type of further testing required and the time period within which it might reasonably be concluded.

Proposed order

After reviewing the conclusions and recommendations of the advisory review panel, the Commissioner of Food and Drugs shall publish in the federal register a proposed order containing:

1. A statement designating the biological products in the category under review that are determined by the Commissioner of Food and Drugs to be safe and effective and not misbranded. This statement may include any condition relating to active components, labeling, tests required prior to release of lots, product standards, or other conditions necessary or appropriate for their safety and effectiveness.
2. A statement designating the biological products in the category under review that are determined by the Commissioner of Food and Drugs to be unsafe or ineffective, or to be misbranded, together with the reasons therefore. All licenses for such products shall be proposed to be revoked.
3. A statement designating the biological products not included in either of the above two statements on the basis of the Commissioner of Food and Drugs determination that the available data are

insufficient to classify such biological products Licenses for such products may be proposed to be revoked or to remain in effect on an interim basis.

Final order

After reviewing the comments, the Commissioner of Food and Drugs shall publish in the federal register a final order on the matters covered in the proposed order. The final order shall become effective as specified in the order.

Reserved

Court Appeal: The final order(s) published and any notice published constitutes final agency action from which appeal lies to the courts. The Food and Drug Administration will request consolidation of all appeals in a single court. Upon court appeal, the Commissioner of Food and Drugs may, at his discretion, stay the effective date for part or all of the final order or notice, pending appeal and final court adjudication.²⁰

Reclassification procedures

The biologics regulations establish procedures for the reclassification of all biological products that have been classified into Category IIIA.

All of these Category IIIA products will either be reclassified into Category I (safe, effective, and not misbranded) or Category II (unsafe, ineffective, or misbranded) in accordance with the procedures set forth below.

Advisory review panels

The Commissioner will appoint advisory review panels and use existing advisory review panels to

- (1) Evaluate the safety and effectiveness of all Category IIIA biological products.
- (2) Review the labeling of such products and
- (3) Advise the Commissioner on which Category IIIA biological products are safe, effective, and not misbranded.

Advisory review panel report to the Commissioner

An advisory review panel shall submit to the Commissioner a report containing the panel's conclusions and recommendations with respect to the biological products falling within the category of products reviewed by the panel. The panel report shall include:

- a. A statement designating the biological products in the category under review.
- b. A statement identifying those biological products designated that the panel recommends should be designated as safe and presumptively effective and should remain on the market pending completion of further testing because there is a compelling medical need and no suitable alternative therapeutic, prophylactic, or diagnostic agent that is available in sufficient quantities to meet current medical needs. For the products or categories of products so recommended, the report shall include: (i) A description and evaluation of the available evidence concerning effectiveness and an explanation why the evidence shows that the product has any benefit; and (ii) A description of the alternative therapeutic, prophylactic, or diagnostic agents considered and a statement of why such alternatives are not suitable.

Proposed order

After reviewing the conclusions and recommendations of the advisory review panels, the Commissioner shall publish in the federal register a proposed order containing:

- a. A statement designating the biological products in the category under review.
- b. A notice of availability of the full panel report or reports. The full panel report or reports shall be made publicly available at the time of publication of the proposed order.
- c. A proposal to accept or reject the findings of the advisory review panel.
- d. A statement identifying those biological products that the Commissioner proposes should be designated as safe and presumptively effective.

Final order

After reviewing the comments on the proposed order, the Commissioner shall publish in the federal register a final order on the matters covered in the proposed order. Where the Commissioner determines that there is a compelling medical need and no suitable alternative therapeutic, prophylactic, or diagnostic agent for any biological product that is available in sufficient quantities to meet current medical needs, the final order shall provide that the biologics license application for that biological product will not be revoked, but will remain in effect on an interim basis while the data necessary to support its continued marketing are being obtained for evaluation by the Food and Drug Administration. The final order shall describe the tests necessary to resolve whatever effectiveness questions exist.

Complete response letter to the applicant**Complete response letter**

The Food and Drug Administration will send the biologics license applicant or supplement applicant a complete response letter if the agency determines that it will not approve the biologics license application or supplement in its present form.

Description of specific deficiencies

A complete response letter will describe all of the deficiencies that the agency has identified in a biologics license application or supplement, except as stated in paragraph (a)(2) of this section.

Inadequate data

If FDA determines, after a biologics license application or supplement is filed, that the data submitted are inadequate to support approval, the agency might issue a complete response letter without first conducting required inspections, testing submitted product lots, and/or reviewing proposed product labeling.

Recommendation of actions for approval

When possible, a complete response letter will recommend actions that the applicant might take to place its biologics license application or supplement in condition for approval.

Applicant actions

After receiving a complete response letter, the biologics license applicant or supplement applicant must take either of the following actions:

Resubmission

Resubmit the application or supplement, addressing all deficiencies identified in the complete response letter.

Withdrawal

Withdraw the application or supplement. A decision to withdraw the application or supplement is without prejudice to a subsequent submission.

Failure to take action

- a. FDA may consider a biologics license applicant or supplement applicant's failure to either resubmit or withdraw the application or supplement within 1 year after issuance of a complete response letter to be a request by the applicant to withdraw the application or supplement, unless the applicant has requested an extension of time in which to resubmit the application or supplement. FDA will grant any reasonable request for such an extension. FDA may consider an applicant's failure to resubmit the application or supplement within the extended time period or request an additional extension to be a request by the applicant to withdraw the application.
- a. (2) If FDA considers an applicant's failure to take action to be a request to withdraw the application, the agency will notify the applicant in writing. The applicant will have 30 days from the date of the notification to explain why the application or supplement should not be withdrawn and to request an extension of time in which to resubmit the application or supplement. FDA will grant

any reasonable request for an extension. If the applicant does not respond to the notification within 30 days, the application or supplement will be deemed to be withdrawn.²¹

Approval process

According to 21 CFR 601.2 section,

(a) 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. The applicant, or the applicant's attorney, agent, or other authorized official shall sign the application.

An application for any of the following specified categories of biological products subject to licensure shall be handled:

- (1) Therapeutic DNA plasmid products;
- (2) Therapeutic synthetic peptide products of 40 or fewer amino acids;
- (3) Monoclonal antibody products for in vivo use; and
- (4) Therapeutic recombinant DNA-derived products.

(b) [Reserved]

(c) (1) To obtain marketing approval for a biological product subject to licensure which is a therapeutic DNA plasmid product, therapeutic synthetic peptide product of 40 or fewer amino acids, monoclonal antibody product for in vivo use, or therapeutic recombinant DNA-derived product, an applicant shall submit a biologics license application in accordance with paragraph (a).

(2) To the extent that the requirements in this paragraph (c) conflict with other requirements in this subchapter, this paragraph (c) shall supersede other requirements.

(d) Approval of a biologics license application or issuance of a biologics license shall constitute a determination that the establishment(s) and the product meet applicable requirements to ensure the continued safety, purity, and potency of such products. Applicable requirements for the maintenance of establishments for the manufacture of a product subject to this section shall include but not be limited to the good manufacturing practice requirements.

(e) Any establishment and product license for a biological product issued under section 351 of the Public Health Service Act (42 U.S.C. 201 et seq.) that has not been revoked or suspended as of December 20, 1999, shall constitute an approved biologics license application in effect under the same terms and conditions set forth in such product license and such portions of the establishment license relating to such product.²²

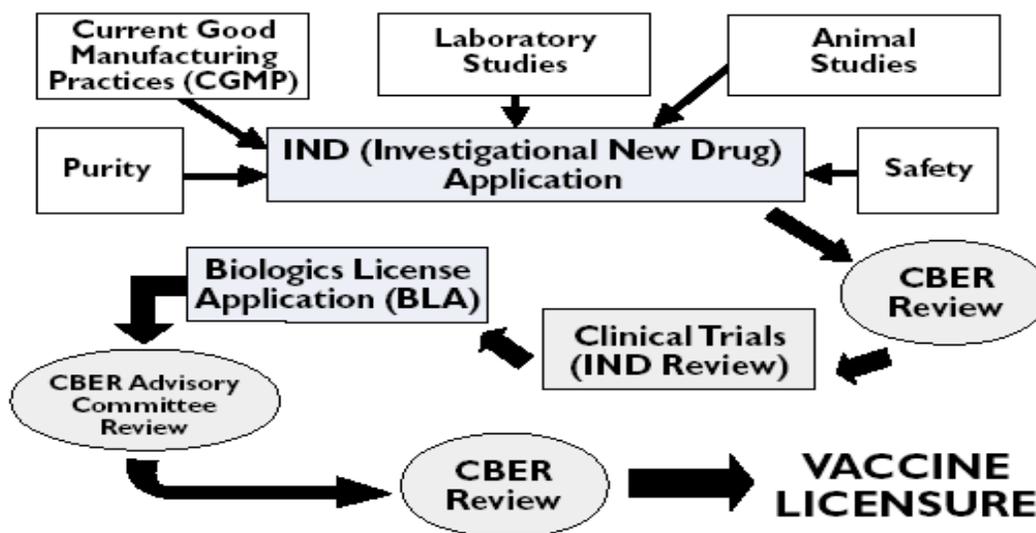


Fig. 4: The process of biological products licensure in the U.S

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 requiring supplement submission at least 30 days prior to distribution of the product made using the change.
3. Changes to be described in an annual report (minor changes).

1. Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes):

- Changes to a product, production process, quality controls, equipment, facilities, or responsible personnel that have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product require submission of a supplement and approval by FDA before a product made using the change is distributed.
- The applicant must obtain approval of the supplement by FDA prior to distribution of the product made using the change.
- In FDA's experience, the changes in a product, production process, quality controls, equipment, facilities, or responsible personnel have caused detrimental effects on the identity, strength, quality, purity, or potency of products as they related to the safety or effectiveness of the product even where applicants performed validation or other studies.
- FDA believes that these changes would generally have a substantial potential to have an adverse effect on a product's identity, strength, quality, purity, or potency as they may relate to its safety or effectiveness and that the agency's continued premarket review and approval of such changes is currently necessary to protect the public from products whose identity, strength, quality, purity, potency, safety, or effectiveness may be compromised.

Biological Products Including Whole Blood, Blood Components, Source Plasma, and Source Leukocytes:

1. Process changes including, but not limited to,
 - Extension of culture growth time leading to significant increase in number of cell doublings beyond validated parameters;
 - New or revised recovery procedures
 - New or revised purification process, including a change in a column
 - A change in the chemistry or formulation of solutions used in processing
 - A change in the sequence of processing steps or addition, deletion, or substitution of a process step or
 - Reprocessing of a product without a previously approved reprocessing protocol.
2. Any change in manufacturing processes or analytical methods that
 - Results in change(s) of specification limits or modification(s) in potency, sensitivity.
 - Specificity or purity.
 - Establishes a new analytical method.
 - Deletes a specification or an analytical method.
 - Eliminates tests from the stability protocol or
 - Alters the acceptance criteria of the stability protocol.
3. Scale-up requiring a larger fermentor, bioreactor, and/or purification equipment (applies to production up to the final purified bulk).
4. Change in the composition or dosage form of the biological product or ancillary components (e.g., new or different excipients, carriers, or buffers).
5. New lot of, new source for, or different, in-house reference standard or reference panel (Panel member) resulting in modification of reference specifications or an alternative test method.
6. Extension of the expiration dating period and/or a change in storage temperature, container/closure composition, or other conditions, other than changes based on real time data in accordance with a stability protocol in the approved license application.
7. Installation of new Water for Injection (WFI) system or modifications to an existing WFI system that would have a significant potential to stress or challenge the system, such as lengthy or complicated distribution system extensions to service new or remote production areas;

- Use of components of lesser quality or function
 - Expansions of ambient temperature water distribution loops or
 - Conversion from hot loop to ambient loop
8. Change of the site(s) at which manufacturing, other than testing, is performed, addition of a new location (including donor centers manufacturing platelets and/or performing automated pheresis procedures), or contracting of a manufacturing step in the approved license, to be performed at a separate facility.
9. Conversion of production and related area(s) from single to multiple product manufacturing area(s). (Addition of products to a multiple product manufacturing area could be submitted as a "Supplement - Changes Being Effected in 30 Days", if there are no changes to the approved and validated cleaning and changeover procedures and no additional containment requirements).
10. Changes in the location (room, building, etc.) of steps in the production process which could affect contamination or cross contamination precautions.
11. Major construction, or changes in location, involving or affecting environmentally controlled manufacturing or related support areas, such as
- New buildings
 - New production areas or rooms in existing buildings
 - Aseptic processing areas
 - Modifications to support systems with significant potential to affect air, water, or steam Quality
 - Installation of a new HVAC system involving or affecting environmentally controlled manufacturing or related support areas or
 - Modifications to an existing HVAC system that supplies aseptic processing areas.
12. Change in SOPs in the following categories:
- Donor suitability, including donor deferral;
 - Blood collection, including arm preparation;
 - High risk behavior questions/AIDS information;
 - Donor history forms, including informed consent;
 - Product manufacturing; or
 - Quarantine and disposition of unsuitable product.
13. Process changes:
E.g., Leuko reduction, irradiation, freezing/deglycerolizing/rejuvenating, manual to automated collection of Source Plasma, Fresh Frozen Plasma, or platelets, immunization programs; disease-state (as opposed to disease-associated) or high risk donor collections.

2. Changes requiring supplement submission at least 30 days prior to distribution of the product made using the change

Changes to a product, production process, quality controls, equipment, facilities, or responsible personnel that have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product require submission of a supplement to FDA at least 30 days prior to distribution of a product made using the change.

The requirements for the content of these supplements are the same as for those requiring approval prior to distribution.

Some examples of changes to the product, production process, quality controls, equipment, facilities, and responsible personnel that FDA currently considers to have moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product are set forth in the following list, which FDA has developed based on experience gained in reviewing submissions received in the past.

Biological Products Including Whole Blood, Blood Components, Source Plasma, and Source Leukocytes

1. Automation of one or more process steps without a change in process methodology.
2. Addition of duplicated process chain or unit process, such as a fermentation process or duplicated purification columns, with no change in process parameters.
3. Addition or reduction in number of pieces of equipment (e.g., centrifuges, filtration devices, blending vessels, columns, etc.) to achieve a change in purification scale not associated with a process change.

4. Change in the fill volume (per vial) from an approved production batch size and/or scale (excludes going from single dose to multidose vial or change in product concentration, both of which should be submitted as a supplement requiring prior approval).
5. Changes in responsible individuals specified in the approved application, including manufacturers' representatives, responsible experts, and other individuals designated to communicate with CBER.
6. Modification of an approved manufacturing facility or room(s) that is not likely to have an adverse effect on safety, sterility assurance, purity, or potency of product; e.g., adding new interior partitions or walls to increase control over the environment.
7. Manufacture of an additional product in a previously approved multiple product manufacturing area using the same equipment and/or personnel, if there have been no changes to the approved and validated cleaning and changeover procedures and there are no additional containment requirements.
8. Change in the site of testing from one facility to another (e.g., from a contract lab to the license holder; from an existing contract lab to a new contract lab; from the license holder to a new contract lab).
9. Change in the structure of a legal entity that would require issuance of new license(s), or change in name of the legal entity or location that would require reissuance of license(s).
10. Computer process control for steps to replace manual process control.
11. Downgrade of room or area environmental quality classification except for aseptic processing areas.
12. Installation of a new or modification to an existing, Purified Water system, not including pretreatment systems for WFI.
13. Change in automated collection equipment used in plasmapheresis.
14. Change in mailing address, move of a donor center at which blood components are prepared, move of an establishment or temporary or permanent closure of a facility.
15. Off-site storage, in a location listed in the establishment license application, of product for which a supplement is pending.
16. Alternate procedure request (under §640.120) where there are published FDA recommendations/criteria.
17. Infrequent donor collection variance at blood establishment.

In certain circumstances FDA may determine that, based on experience with a particular type of change, the supplement for such change is usually complete and provides the proper information. Likewise, there may be particular assurances that the proposed change has been appropriately submitted, such as when the change has been validated in accordance with a previously approved protocol. In these circumstances, FDA may determine that the product made using the change may be distributed at the time of receipt of the supplement by FDA. The following are changes that in FDA's experience have been submitted properly with the appropriate information, and could be implemented at the time of receipt of the supplement by FDA without a previously approved comparability protocol.

1. Addition of release tests and/or specifications or tightening of specifications for intermediates.
2. Minor changes in fermentation batch size using the same equipment and resulting in no change in specifications of the bulk or final product.
3. Modifications to an existing HVAC system involving or affecting environmentally controlled manufacturing or related support areas, but not aseptic processing areas, with no change in air quality.

In addition, applicants that use the protocol to validate a proposed change may request that a change usually subject to supplement submission and approval prior to distribution be reported as a change subject to supplement submission at least 30 days prior to distribution of the product made using the change, or as a "Changes Being Effectuated" supplement submission, in which event the product made using the change may be distributed immediately upon receipt of the supplement by FDA.

3. Changes to be described in an annual report (minor changes)

Changes to the product, production process, quality controls, equipment, facilities, or responsible personnel that have minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product are required to be documented in an annual report submitted each year within 60 days of the anniversary date of approval of the application. For changes under this category, the applicant is required to submit in the annual report a list of all products involved and a full description of the manufacturing and controls changes including: the manufacturing site(s) or area(s) involved, the date each change was made, a cross-reference to relevant validation protocol(s) and/or SOPs, and relevant data from studies and tests

performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product.

Some examples of changes that FDA currently considers to have minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product are listed below. The list is not all-inclusive but contains items that, in FDA's experience reviewing supplements have caused few instances in which an adverse effect on the product's identity, strength, quality, purity, or potency as they may relate to its safety or effectiveness has been observed.

Biological Products Including Whole Blood, Blood Components, Source Plasma, and Source Leukocytes

1. Addition of equipment for manufacturing processes which is identical to the primary system and serves as an alternate resource within an approved production room or area.
2. Upgrade or minor corrective change to production air handling, water, or steam supply systems using equipment of same or similar materials of construction, design and operating parameters, and not affecting established specifications; e.g., removal of dead legs in water for injection (WFI) system.
3. Relocation of analytical testing laboratories between areas specified in the license.
4. Room upgrades, such as installation of improved finishes on floors/walls.
5. Installation of non-process-related equipment or rooms to improve the facility, such as warehousing refrigerators or freezers.
6. Modifications in analytical procedures with no change in the basic test methodology or existing release specifications provided the change is supported by validation data.
7. Change in harvesting and/or pooling procedures which does not affect the method of manufacture, recovery, storage conditions, sensitivity of detection of adventitious agents or production scale.
8. Replacement of an in-house reference standard or reference panel (or panel member) according to SOPs and specifications in an approved license application.
9. Tightening of specifications for existing reference standards to provide greater assurance of product purity, identity, and potency.
10. Establishment of an alternate test method for reference standards, release panels, or product intermediates, except for release testing of intermediates licensed for further manufacture.
11. Establishment of a new Working Cell Bank derived from a previously approved Master Cell Bank according to an SOP on file in the approved license application.
12. Change in the storage conditions of in-process intermediates based on data from a stability protocol in an approved license application, which does not affect labeling, except for changes in storage conditions which are specified by regulation.
13. Change in shipping conditions (e.g., temperature, packaging, or custody) based on data derived from studies following a protocol in the approved license application (except for changes in shipping conditions that are required by regulation to be submitted as a Supplement).
14. A change in the stability test protocol to include more stringent parameters (e.g., additional assays or tightened specifications).
15. Addition of time points to the stability protocol.
16. Replacement of equipment with that of identical design and operating principle involving no change in process parameters.
17. Upgrade in air quality, material, or personnel flow where product specifications remain unchanged. Involves no change in equipment or physical structure of production rooms.
18. Relocation of equipment within an approved operating room, rearrangement of the operating area or rooms where production is performed or relocation of equipment to another approved area to improve product/personnel/raw material flow and improve segregation of materials with no change in room air classification.
19. Modifications to the pretreatment stages of a WFI system, including Purified Water systems used solely for pretreatment in WFI production.
20. Change in the simple floor plan that does not affect production process or contamination precautions.
21. Trend analyses of release specification testing results for bulk drug substances and drug products obtained since the last annual report.

Labeling changes

Changes to labeling are required to be submitted to CBER in one of the following ways: (1) As a supplement requiring FDA approval prior to distribution of a product with the labeling change

(2) As a supplement requiring FDA approval but permitting distribution of a product bearing such change prior to FDA approval or

(3) In an annual report. Some examples of changes to labeling that CBER currently considers to be appropriate for submission in each of these three categories are listed below. These lists are not intended to be comprehensive. Promotional labeling and advertising must be submitted to CBER at the time of initial dissemination or publication.

Labeling changes requiring supplement

Submission - FDA approval must be obtained before distribution of the product with the labeling change.

Any proposed change in the package insert, package label, or container label, except those described is required to be submitted as a supplement and receive FDA approval prior to distributing a product with the label change. In such a supplement, the applicant is required to present clearly the proposed change in the label and the information necessary to support the proposed change.

The following list contains some examples of changes that are currently considered by FDA to fall into this reporting category.

1. Changes based on post marketing study results, including, but not limited to, labeling changes associated with new indications and usage.
2. Change in, or addition of, pharmacoeconomic claims based on clinical studies.
3. Changes to the clinical pharmacology or the clinical study section reflecting new or modified data.
4. Changes based on data from preclinical studies.
5. Revision (expansion or contraction) of population based on data.
6. Claims of superiority to another product.
7. Change in container labels for licensed blood.

Labeling changes requiring submission in an annual report

A package insert, package label, or container label with editorial or similar minor changes or with a change in the information on how the drug is supplied that does not involve a change in the dosage strength or dosage form is required to be described in an annual report. Some examples that are currently considered by FDA to fall into this reporting category include:

1. Changes in the layout of the package or container label without a change in content of the labeling.
2. Editorial changes such as adding a distributor's name.
3. Foreign language versions of the labeling, if no change is made to the content of the approved labeling and a certified translation is included.²³

1. The Common Technical Document

The BLA shall be submitted in Common Technical Document (CTD) format. 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).

Module 5: Clinical Summary (clinical studies).

The CTD Triangle

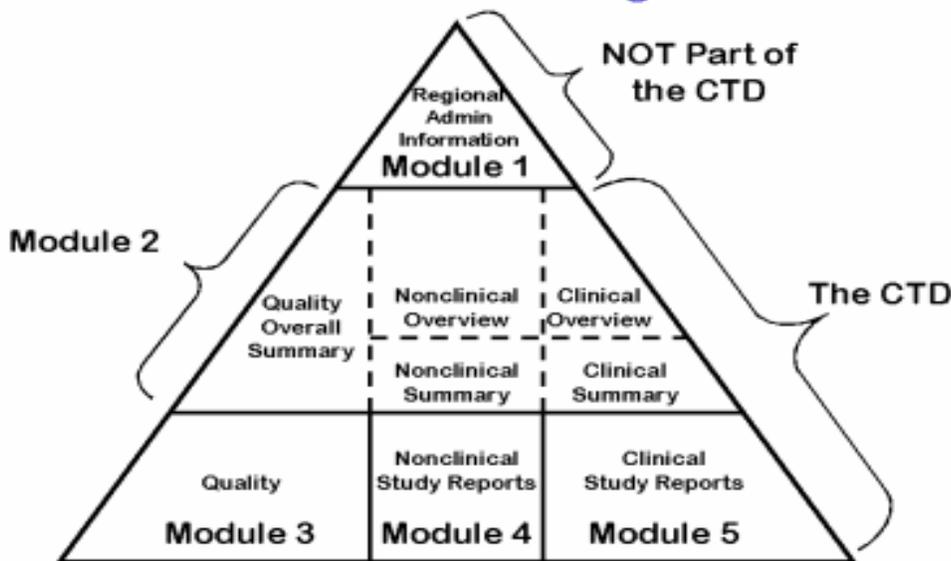


Fig. 4

Out of five modules, only Modules 2 to 5 are considered part of the CTD. Module 1 is administrative in nature and consists of region-specific documents as well as a complete table of contents encompassing the entire CTD.

Modules 2 to 5 contain the technical information of the product and documentation requirements. Since the safety, effectiveness and quality of a biologic are primarily dependent on its manufacturing environment and method of manufacture, additional application requirements for biologic's licensure are primarily contained in the modules related to quality.

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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