Regulatory requirements for Biologics

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WHAT ARE BIOLOGICS?

- Biologics are the products manufactured, extracted from or semi synthesized from a biological source which are regulated by FDA and are used to prevent cure and treat diseases and medical conditions.
- These are generally large, complex molecules produced through biotechnology in a living system such as a microorganism, plant cell or animal cell.
- These could be made of sugars, proteins, nucleic acids or complex combinations of these substances or may be living entities.

- These are complex mixtures that are not easily identifiable and charcterized these tend to be heat sensitive and susceptible to microbial contamination hence, it is necessary to use aspetic principles from intial manufacturing process.
- EXAMPLES: Botox, Herceptin, Vaccines, Enbrel

Biologic licence application (BLA)

- Under the public health service act, the federal food and drug administration (FDA) has been given the authority, concurrent with its authority under the food drug and cosmetic act to regulate biologics.
- The FDA regulates a wide range of biologics, including vaccines, blood and cellular products.
- With in the FDA , the center for biologic as well as the center for drug evaluation and research, can be responsible for the regulation of biologics .
- Biologics are evaluated for market by the FDA through the filling of a biologics licence application (BLA).
- A BLA, although similar to a new drug application (NDA), as its own set of complex requirements.

Sources and types of Biologics

SOURCES

- Mammalian cell culture
- Bacteria
- Insect cell culture
- Plant cell culture
- Yeast
- Transgenics
- Avian cell culture
- Humans

Types

- Blood derivatives
- Vaccines
- Allergenic extracts
- Whole blood
- Blood components
- Proteins
- Human tissues
- Cellular and gene therapies
- Xenotransplantation products

Difference b/w biologics & chemical drug

Properties	Biologics	Chemical drug
Size	Large	Small
Structure	Complex	Simple
Stability	Unstable	Stable
Modification	Impossible to ensure identical copy	Identical copy can be made
Manufacturing	Many options	Well defined
Characterization	Impossible	Easy

Biologic and it’s regulatory guidelines

Biologics and biological products

- **Biological product is 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 vs drugs

- **Biologic product generally more complex**
- **Many innovative products**
- **Virtually every of product comparability is more difficult**
- **Changes in manufacturing and scale up can obstruct overall approval process.**

- Biologics control act- 1902
- Authorized hygienic laboratory

- In 1934 hygienic laboratory renamed to NIH

- In 1948 divisions of biologics control within NMI
- In 1944 BCA incorporated into Section 351 of PHSA (CFR tittle 21 parts 600-680)

- In 1955 salk polio vaccine - DBS
- In 1972 DBS transferred to FDA as Bureau of Biologics

- In 1982 BB merged with NCDB (National centre for drugs and biologics)

- In 1988 NCDB Splitted into 2 centres
- 1.CBER and 2. CDER

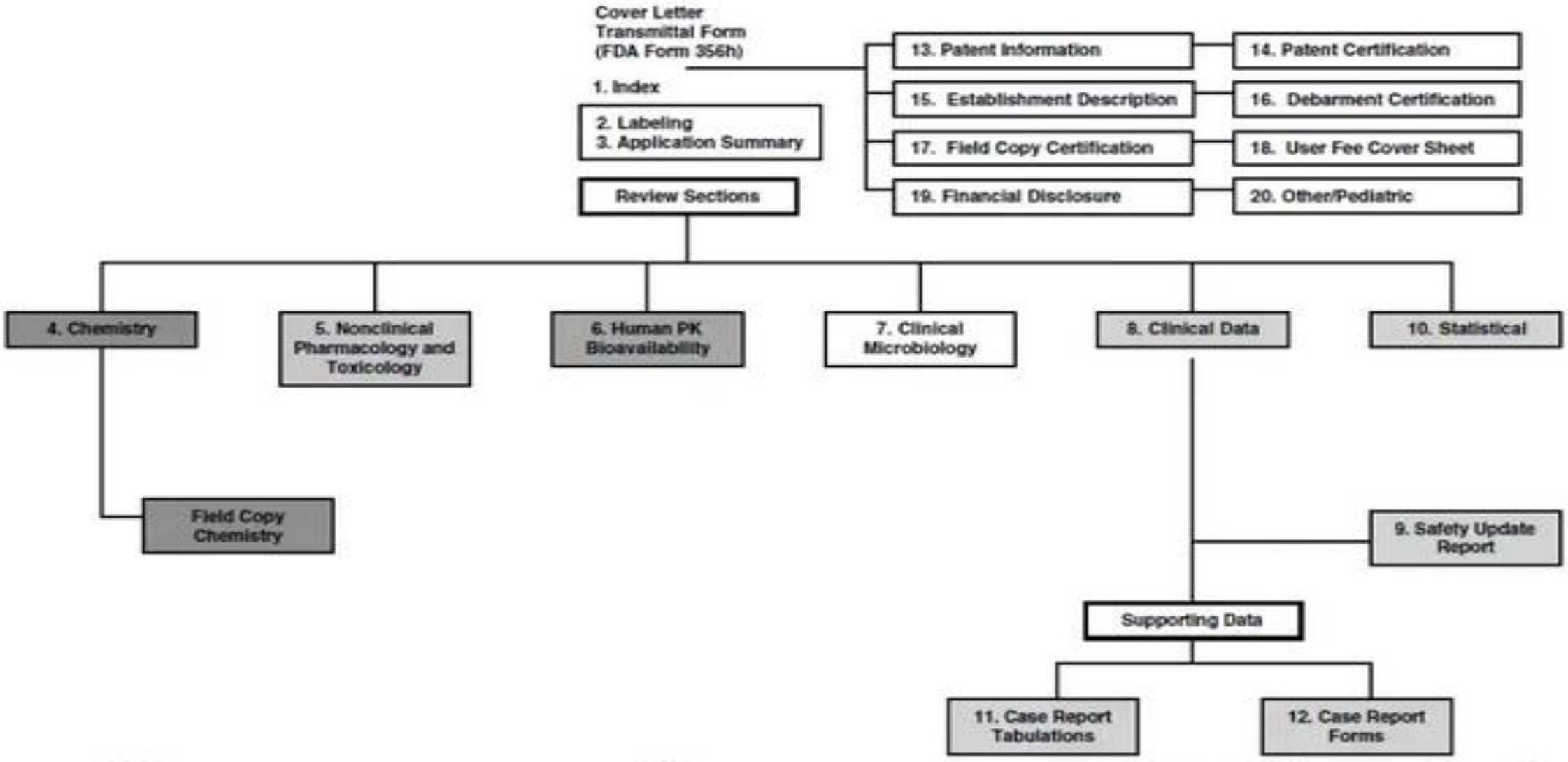
DEVELOPMENT AND APPROVAL PROCESS

- Advertising and Labeling
- Investigational New Drug Application (IND) or Device exemption process (IDE)
- Expanded Access
- Premarket Approval (PMA)
- Biologics License Application (BLA) New Drug Application Process (NDA).
- Biologics Approvals By Year.

BIOLOGICS LICENSE APPLICATION (BLA)

- The Biologics License Application (BLA) is a request for permission introduce or deliver for introduction a Biologic product into the market.
- It is mainly regulated by 21 CFR 600-800. It is submitted by any legal person or entity, who engaged in manufacture or an applicant for a license who takes responsibilty for compliance with product and establishment of standards.
- A Biologic License application generally applies to vaccines and other Allergenic drug products and cellular and genetic therapies.

NEW DRUG OR BIOLOGIC APPLICATION



- A cover letter should always accompany any FDA submission. Addressed below are the Form FDA 356(h), the cover letter, and all 20 sections of the BLA application.
- Before each section is addressed individually, it is worth emphasizing the importance of the application form [Form FDA 356(h)], the cover letter, and the first three sections.
- **Cover Letter**: It consists of basic administrative information requested about the BLA application (e.g., sponsor name and address, etc.). The cover letter should provide at least seven types of information:

  1. Name and address of sponsor and others
  2. Product name
  3. Reason for submission(e.g original submission, supplement, amendment, etc.).
  4. Information contained in the submission..
  5. Agreements with the FDA.
  6. Other documents relating to submission.
  7. special circumstances.
  8. Fast track review.

- **Application Form FDA 356(h):**First, it is an administrative document providing CBER with information on the **applicant, product, and application.**
- Second, it is a legal contract binding the applicant, contractors, suppliers, and physicians to FDA laws and regulations.
- **Section 1:Index** It influences speed and efficiency of the reviewer. Applicants can use this format for indexing the BLA:

Item	Description	Volume/Page
2	Labelling	1.010

- **Section 2:Labeling Section:** This section encompasses the initial draft labeling submitted with the BLA and the final printed labeling that is submitted just prior to licensure. Labeling includes the immediate container label, carton label, insert, and user instructions.
- **Section 3: Summary Section:** It serves as a guide to the full application.
- It explains the application's intent-to-establish the biologic's safety and effectiveness for a particular indication.
- It can build CBER's confidence in the applicant, the validity of the BLA's information, and the product itself.
- It acts as pivotal in establishing a foundation for product approval.

Summary Format includes

1. Description of drug and formulation
2. Annotated draft insert
3. Product pharmacological class
4. Scientific rationale for use of product
5. Clinical benefits
6. Foreign marketing history
7. CMC summary

a. Drug substance

b. Drug product

c. Stability

d. Investigational summary (listing of batches used in the clinical studies)

8. Nonclinical summary

a. Pharmacology

b. Toxicology

9. Human pharmacokinetics and bioavailability

10.Microbiological summary

11. Clinical summary

12.Benefit/risk relationship

Section 4: Chemistry Section

The BLA's chemistry section is composed of three parts:

1. Chemistry, manufacturing, and controls information;

2. Samples;

3. Methods validation package.

Section 5: Nonclinical Pharmacology and Toxicology Section

- The CBER reviews these studies to evaluate their adequacy and comprehensiveness and to ensure that there are no inconsistencies or toxic effects.

Section 6- Human pharmacokinetics and bioavailability

Section 7- Clinical microbiology

Section 8- Clinical data section

Section 9- Safety update report

Section 10-Statistical section

- Section 11- Case report tabulations
- Section 12- Case report forms
- Section 13- Patent information
- Section 14- Patent certification
- Section 15- Establishment description
- Section 16- Debarment certification
- Section 17- Field copy certification
- Section 18- User fee cover sheet
- Section 19- Financial information
- Section 20- Other

BLA Review Process

- Then current CBER BLA review process is developed to meet requirements of Prescription Drug User Fee Act(PDUFA) of 1996.
- According to this act FDA agreed to institute standards and timelines in exchange for user fees paid by BLA sponsors.
- The goal is to standardize both review process and review content.
- CBER issued no. of guidance documents which provide type of information to be included in BLA for each biologic product class:

- Few of them Guidance for Industry for the Submission of Chemistry, Manufacturing , and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for *in vivo* Use **- August 1996**
- Guidance For the Submission of chemistry, Manufacturing and Controls Information and Establishment description for Autologous Somatic Cell Therapy Products - **January 10, 1997**
- Guidance for Industry- Changes to an Approved application for Specified Biotechnology and Specified Synthetic Biological Products **- July 24, 1997.**
- The review committee will intially review BLA to make a refusal to file(RTF) decision within 60days.
- If the review committee determines that BLA is complete for filing purpose it will be filed and a complete review is performed as outlined in SOPP 8405.
- Following complete review CBER will issue either a complete response letter , indicating that there are deficiencies or an Approval letter , indicating a marketing license be granted.

AMENDING THE LICENSE APPLICATION: During the review of the BLA , FDA's request to address unresolved issues regarding the original submission and a response to such a request is generally referred to as an amendment.

Or

A change to any unapproved application is called an Amendment (IND, BLA, and NDA).

SUPPLEMENT TO THE ORIGINAL BLA: Amendments are submitted to update or modify an unapproved BLA, supplements are submitted to modify approved license applications.

- ✓ The holder of an approved BLA may seek to change its manufacturing methods, expand the product's indication, or make other changes that reflect new technology or make its product or processes more competitive.