



Regulatory Prototype for Biological Products in the United States

G. M. Pavithra¹ and N. Venugopal^{2*}

¹Department of Pharmaceutical Regulatory Affairs, Sri Ramachandra Faculty of Pharmacy, Sri Ramachandra Institute of Higher Education and Research (DU), Porur, Chennai-600116, India.

²Department of Pharmaceutics, Sri Adichunchanagiri College of Pharmacy, Adichunchanagiri University, B G Nagar-571448, Nagamangala Taluk, Mandya District, Karnataka, India.

Authors' contributions

This work was carried out in collaboration between both authors. Author NV wrote the protocol, managed the literature searches and performed timely evaluation of the manuscript draft written by author GMP with intense data collection and interpretation of the manuscript data. Both authors read and approved the final manuscript.

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ABSTRACT

Biological products are used for the treatment of many disease, so the biological application submitted for the approval of products are also increasing. The progress of a biosimilar product is more difficult and expensive than a small molecule generic product. Biosimilars are not true generic drugs, but demonstrate a high degree of similarity to the reference biological product. In order to improve access to costly biological treatments, a biosimilar pathway in the US was established under the Biologics Price Competition and Innovation Act of 2009. The study highlighted the "Regulatory prospective for the registration of Biological products in US" and a brief description about the development, Manufacturing and approval process of biosimilar products. This article is also focused on the regulatory framework, Biological License Application, Purple book, and Pharmacovigilance of biological products.

*Corresponding author: E-mail: venukush27@gmail.com;

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1. INTRODUCTION

1.1 History of Biologics

- In 1902, Congress passed the Biologics Control Act, otherwise called as the Virus-Toxin Law. This act mainly focused on the procedures utilized in the manufacturing of biologics.
- In 1930, the Hygienic Laboratory has entitled to the National Institute of Health (NIH).
- In 1937, the Division of Biologics Control was established under the National Institute of Health (NIH).
- In 1944, the Public Health Service Act further added licensure of the biologic products itself as well as the facilities employed in their manufacture.
- In 1972, the Division of Biologics was reassigned from the 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 combined 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.
- In 1988, the Bureau of Biologics was transferred to the CBER within the U.S. Food and Drug Administration.
- In 1999, the FDA provides a final rule to execute a single biologics license. The CBER implements the regulations of the two laws governing biologic products: the FD&C Act and the PHS Act.
- In 2002, the FDA shifted a range of biologically manufactured medicines to CDER. CBER regulates a number of biologics-related products, including blood tests, computer software, and devices regarding transfusion [1,2].

1.1.1 Biologicals

As per section 351 of the Public Health Service Act describes a biological product, either as a therapeutic serum, virus, vaccine, toxin, antitoxin, blood products, or derivative, analogous product or allergenic product pertinent to the therapy, prevention or healing of a disease. Biologics are mainly produced by biotechnology techniques like recombinant DNA

technology, controlled gene expression, or antibody technologies. Biologics are used in the treatment of life-threatening and rare illnesses such as cancer, diabetes, anemia, rheumatoid arthritis, and multiple sclerosis. Biologics are generally large, complex molecules [3].

1.1.2 Reference product

The Reference product is the sole biological product, formerly approved by the Food and Drug Administration, towards which a suggested biosimilar product is as compared. A reference product is approved primarily based on the safety and effectiveness data. A present biosimilar product is as compared to and measured towards a reference product to guarantee that the product is extraordinarily similar and has no clinically meaningful differences [4].

1.2 How do Biologics Differ from Conventional Drugs?

Utmost all drugs comprised of chemical substances and their structures are familiar. However, biologicals are complex mixtures that aren't efficiently recognized or characterized. Biological products distinct from conventional drugs in that they have a tendency to be heat-sensitive and vulnerable to microbial contamination. This needs sterile processes to be employed from beginning manufacturing steps [5].

2. REGULATORY FRAMEWORK IN THE USA

The BPCI Act was established in 2009 in the context of The Patient Protection and Affordable Care Act (PPACA) has laid down regulations for approval of Biosimilar products [6]. The BPCI Act set up an abbreviated licensure pathway for biological products. Abbreviated licensure pathway, under section 351(k) of the general PHS Act, permits dependence on certain predominant knowledge around the safety & effectiveness of the reference product, and allows a biosimilar product to be licensed supported by preclinical and clinical data, specific thereto biosimilar product [7]. The BPCIA extend 12 years exclusive rights to biologics, this implies that the FDA cannot permit a biosimilar up to

12 years after it approves the reference product [8]. FDA generally regulates biologics under the general Public Health Service Act (PHSA), but regulates some biologics as drugs under authorities within the Federal Food, Drug and Cosmetic Act (FFDCA). The CBER and CDER evaluate biologics [9].

2.1 FDA's Role Regarding Biological Products

The approval process for biologics resides within the PHS Act. Although, biologics are subject to regulation under the Federal Food, Drug, and Cosmetic Act therefore numerous biological products also fulfill the definition of "drugs" mentioned in this Act. Likewise, few medical devices are utilized to generate biological products are regulated by CBER within the FD&C Act's Medical Device Amendments of 1976.

2.1.1 FDA role

1. FDA reviews, latest biologics, new indications, and usage of previously approved products for the approval of products.
2. Protect against risks of emerging infectious diseases
3. Provide information to the public for the safe and proper use of biological products.
4. Conduct inspections of manufacturing facilities before biological product approval is granted.
5. After marketing monitors the safety of the products.

2.2 The PHS Act

- Permits FDA to approve biological products and instantly suspend licenses where there exists a risk to public health.
- Permits the agency to prepare the products in the critical health needs and in case of shortages.
- Implement regulations to prevent the spread of communicable diseases within the country [10].

2.3 CDER-CBER Inter-center Agreement

CDER and CBER appoint approval authority for a drug or biological product on the basis of the product class. One center is responsible for the manufacturing of the product and its quality, but the other center would not be prevented from

engaging in the oversight. CDER regulates products from solid human tissue sources, nonhuman animals, antibiotics, chemically synthesized molecules, and hormone products. CBER regulates products subject to BLA's, drugs associated with blood banking and synthetically produced allergenic products.

One distinctive feature of this Agreement was the designation of responsibility for medical reviews and pharmacology or toxicology reviews. Products approved by CDER and CBER implicate concerned for human health, safety, and exposure.

Approval of the product by anyone Center might be conditioned over the incorporation of an analysis of the product effect in the fields of clinical immunology, allergy, rheumatology, oncology, and haematology.

If CDER gained approval jurisdiction for a product comprehends the human source material, then CBER could be awaited to discuss appropriate tests for unpredicted agents within the product [11].

2.3.1 CDER regulated biological products

- Proteins intended for therapeutic use
- Growth factors regulate the cell division and cell survival
- Monoclonal antibodies for in vivo use like ulcerative colitis, rheumatoid arthritis, and psoriasis.
- Immuno-modulators

2.3.2 CBER regulated biological products

- Cellular products
- Gene therapy products
- Antitoxins, antivenins, and venoms
- Allergenic extracts
- Blood, blood components, and
- Plasma-derived products [12].

3. DEVELOPMENT OF BIOLOGICS

Biologics are developed using living cells or organisms, like yeasts, viruses, bacteria, or other animal cells [13].

For the development of a biological product, a company must first demonstrate that it has a viable product to develop. This includes a demonstration of the ability to manufacture the product constantly [14]. The development process for biologics are shown in Fig. 1.

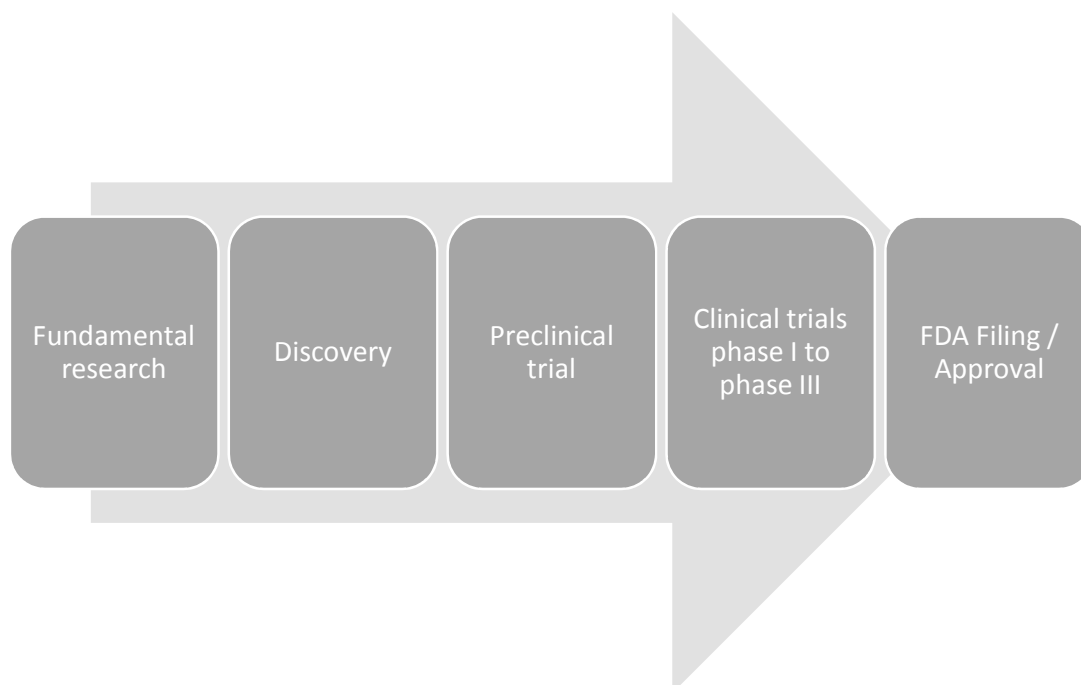


Fig. 1. Development of biologicals

3.1 Preclinical Trial

In vitro and animal studies are carried out in conformance with GLP. The results of these studies are submitted to the FDA by the manufacturer as part of an IND application. The results are reviewed by the FDA before clinical trials can begin. An IND comprises of investigational plan, chemistry, manufacturing, and control information and preclinical data. Within 30 days the FDA reviews the application.

3.2 Clinical Trial

Phase I: Safety and human pharmacology testing in approximately 20 to 80 healthy volunteers.

Phase II: Basic efficacy and dose range testing in around 100 to 200 patients.

Phase III: Large scale, multicenter trial performed in patients with the target disease. In this phase, the safety and effectiveness are determined in a larger number of patients. After completion of phase III the sponsor submits BLA to the FDA.

4. BIOLOGICAL LICENSE APPLICATION

Biological License Application is a request for a license to introduce the biological product in the market submitted by a sponsor or entity. Form 356h is used to submit the Biological License Application [15]. Companies have gained approval via BLA pathways for biologicals in the year of 2017 to 2020 are shown in Table 1.

Table 1. Biological license application approvals in 2017 to 2020

Product name	Company Name	Indication for use	Approval Year
Tecartus	Kite Pharma	Refractory mantle cell lymphoma	2020
Blood Grouping Reagent	Millipore (UK) Ltd.	Diagnostic reagent for in vitro use	2020
<i>MenQuadfi</i>	Sanofi Pasteur, Inc.	Meningococcal disease	2020
<i>SEVENFACT</i>	Biotechnologies SA	Hemophilia A or B	2020
<i>AUDENZ</i>	Seqirus Inc.	Influenza	2020
<i>PALFORZIA</i>	Immune Therapeutics, Inc.	Mitigation of allergic reactions, including anaphylaxis	2020

Product name	Company Name	Indication for use	Approval Year
ERVEBO	Merck Sharp & Dohme Corp.	Prevention of disease caused by Zaire ebolavirus	2019
JYNNEOS	Bavarian Nordic A/S	Prevention of smallpox and monkeypox disease	2019
Alinity s Chagas	Abbott GmbH & Co. KG	Detection of antibodies to <i>Trypanosomacruzi</i>	2019
cobasBabesia	Roche Molecular Systems, Inc.	Detection of <i>Babesia</i> DNA and RNA in whole blood.	2019
XEMBIFY	Grifols Therapeutics LLC	Treatment of Primary Humoral Immunodeficiency	2019
ZOLGENSMA	AveXis, Inc.	Pediatric patients less than two years of age with spinal muscular atrophy	2019
DENGVAXIA	Sanofi Pasteur Inc.	Prevention of dengue disease	2019
ASCENIV	ADMA Biologics, Inc.	Humoral immunodeficiency in adults	2019
ESPEROCT	Novo Nordisk, Inc.	Hemophilia A	2019
ProcleixBabesia Assay	Grifols Diagnostic Solutions Inc.	Detection of RNA from Babesia species	2019
VAXELIS	MCM Vaccine Company	Prevent diphtheria, tetanus, pertussis, poliomyelitis, hepatitis	2018
CUTAQUIG	OctapharmaPharmazeutika	Primary humoral immunodeficiency (PI) in adults	2018
JIVI	Bayer HealthCare LLC	Control of bleeding episodes	2018
PANZYGA	OctapharmaPharmazeutika	Chronic immune thrombocytopenic purpura	2018
ALBUMINEX	Bio Products Laboratory	Indicated for hypovolemia, ascites, hypoalbuminemia	2018
ANDEXXA	Portola Pharmaceuticals	Indicated for patients treated with rivaroxaban and apixaban	2018
Blood Grouping Reagent, Anti-s	Diagast ParcEurasante	Determine the presence of blood group antigens on the surface of human red blood cells	2018
LUXTURNA	Spark Therapeutics	Biallelic RPE65 mutation-associated retinal dystrophy	2017
HEPLISAV-B	Dynavax Technologies	Hepatitis B	2017
SHINGRIX	GlaxoSmithKline Biologicals	Prevention of herpes zoster	2017
YESCARTA	Kite Pharma Inc.	Refractory large B-cell lymphoma	2017
Anti-Human Globulin	Alba Bioscience	Bundled submission	2017
KYMRIAH	Novartis Pharmaceuticals	B-cell precursor acute lymphoblastic leukemia	2017
KEDRAB	Kamada Ltd.	transient post-exposure prophylaxis	2017
HAEGARDA	CSL Behring GmbH	Prevent Hereditary Angioedema	2017
FIBRYNA	OctapharmaPharmazeutika	Acute bleeding episodes in adults	2017
Rubber Panel	SmartPractice Denmark ApS	Diagnosis of allergic contact dermatitis	2017
T.R.U.E. TEST			
Odactra	Merck Sharp &Dohme Corp.	Immunotherapy for house dust mite	2017

4.1 Contents of BLA

1. Safety, Purity, Potency
2. CBER or CDER
3. Archival and Review Copies of BLA
4. The Application Form- 356h
5. Index
6. Summary
7. Chemistry, Manufacturing and Controls Section (CMC)

8. Establishment Description
9. Nonclinical Pharmacology and Toxicology Section
10. Human Pharmacokinetics and Bioavailability Section
11. Microbiology Section (Only for Submissions to CDER and If Anti-Infective Agent)
12. Clinical Data Section
13. Statistical Section
14. Case Report Forms and Tabulations
15. Labeling
16. Patent Information [16].

unique cell line and develops its unique manufacturing process Fig. 2.

1. From the selected protein genetic code is detected and functional DNA sequence created.
2. The genetic code is inserted into various host cell lines like bacteria or yeast, thus the host cells generate this protein.
3. The host cell line produces the protein most efficiently.
4. The cell line is grown in machines called bioreactors, this process is called fermentation.
5. Through filtration, the protein is separated from the bioreactor.
6. Then the particular protein is purified, stabilized and processed into medicine [17,18].

4.2 FDA Review of BLA

The FDA attentively investigates data from all phases of development to verify that the manufacturer has complied with regulations. The FDA might refuse to accept the BLA for filing and substantive review if particular criteria are not fulfilled. After accepting for review also, the FDA may require additional information before approval of the BLA. If regulatory requirements are not satisfied the FDA refuses approval of BLA.

5. MANUFACTURING PROCESS

Biologicals are produced from genetically modified cells. Genetically modified cells whose genes are changed, using recombinant DNA techniques, they produce a particular substance. Biologicals manufacturer, producing a

6. THE PURPLE BOOK

The purple book consists of biologicals, biosimilars, and interchangeable biologic drugs approved by the FDA under the PHS Act. Information on interchangeability for each biologic are also listed in the purple book. Distinguishes whether a patient was receiving a biologic drug or a biosimilar drug. However, with continuous use and a rise in the number of approved biosimilars, the utilization of this naming convention should become well-known to providers and pharmacists [19].

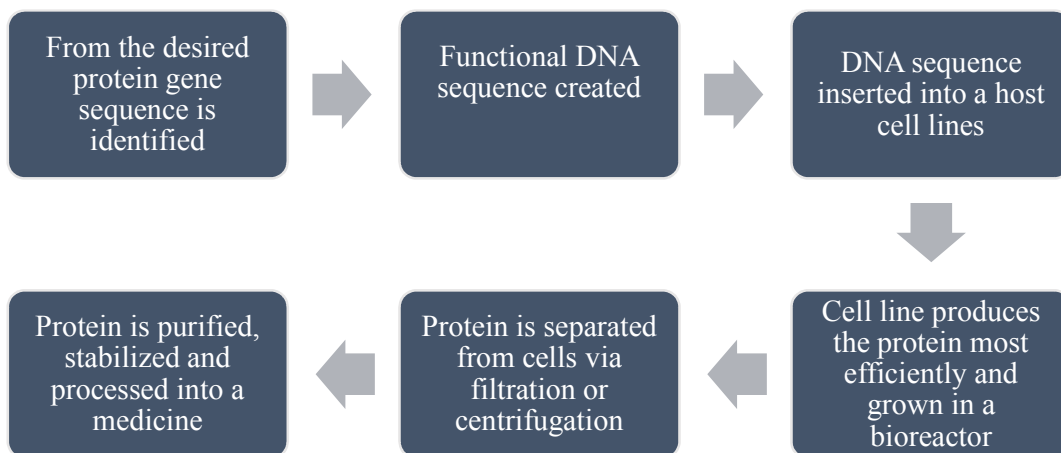


Fig. 2. Manufacturing of biologicals

Table 2. Difference Between biologics and biosimilars [20]

Characteristics	Biologics	Biosimilars
Special features	Produced inside living organisms	Similar in nature to biologics, but not identical
Manufacturing process	Produced by the biological process in host cell lines	Produced by the biological process in host cell lines
Clinical development	Extensive clinical studies, including Phase I-III	Extensive clinical studies, including Phase I-III
Development period	15 years to develop	8-10 years to develop
Development cost	\$1.2 billion	\$100-200 million
Patent	Patentable	Non patentable
Analysis phase	Less extensive	Highly extensive
Use of recombinant technologies	Yes	No
Approval pathway	Biologics license application 351(a)	Biologics license application 351(k)
Approval requirements	Full report of safety and efficacy investigation	Highly similar to a 351(a) product

7. INTERCHANGEABLE PRODUCT

Interchangeable product is described as a biological product, which can be alternative to the reference product excluding the interpolation of the health professional who prescribed the reference product. An interchangeable product is a biosimilar product that comes across further requirements enclosed by the BPCIA [21].

For determinations of interchangeability, the FDA has not created a pathway. Biosimilars demonstrating that switching between the reference product and the biosimilar within the same patient creates no immunogenic and other safety concerns could also be designated interchangeable with the reference product. The implications of being an interchangeable biosimilar are discussed later.

Interchangeable biologics are approved under the biosimilar pathway, however must meet higher standards [22].

8. DEVELOPMENT OF BIOSIMILARS

Biosimilars are developed in a systematic, step-by-step approach. The goal of this approach is to guarantee that the proposed biosimilar product is highly comparable to the reference product with regard to quality, safety, and efficacy.

Characterize reference product – Thereference product is described using advanced analytics tools and existent clinical information. Extended structural and functional depiction of both the biosimilar product and the reference product is the foundationfor the biosimilar development program. [23].

Develop manufacturing process for biosimilar–For the biosimilar product, the development and manufacturing process is matched to the reference product.

Develop biosimilar –At this stage, scale up on the manufacturing process might be performed to enhance the product yield. The development process must be conducted under good manufacturing practices and the reproducibility of the manufacturing process needs to demonstrate [24].

Comparability studies – Once the biosimilar medicine is produced then it is compared to the reference biologic in a comparability exercise. Mainly there are three steps in the comparability studies.

- 1. Quality comparability** is important and includes extensive characterization and correlation of physicochemical and biological properties; the similarity is demonstrated at this level might determine the amount of additional proof that requires to be generated at later stages.
- 2. Preclinical comparability** provides assurance on similar effects. Preclinical comparability involves functional in-vitro assays to define and compare the mode of action:

In vitro studies cover the functional aspects as always required. The level of concern is determined by quantitative and qualitative differences in critical quality attributes.

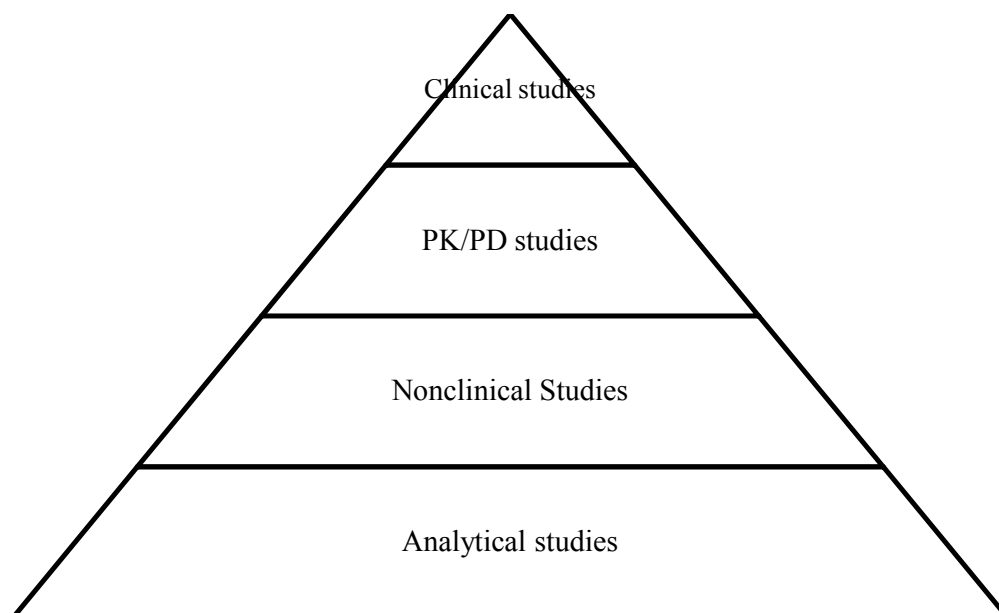


Fig. 3. Totality of evidence (TOE)-based pathway to demonstrate biosimilarity to reference product

***In vivo*, PK / PD and safety studies** may be essential in the case of e.g., a new expression system.

- Clinical comparability** studies are conducted in a profound population and dose at a sensitive time point using a suitable statistical model and testing method [25].

8.1 Totality of Evidence

The totality of evidence contains the fundamental comparative physicochemical and Characterization studies, and the supporting pre-clinical and clinical studies [26].

Despite their complexity, prior art analytical technology permits a comprehensive physicochemical characterization of biologics today. Together with a complete, functional characterization and increased understanding of the structural relationships, these studies previously enable a significant prediction of the clinical performance. Subsequently, pre-clinical and clinical studies are required to deal with any uncertainty regarding the biosimilarity, the extent of which is described via the confidence in the analytical similarity in Fig. 3 [27].

9. MANUFACTURING OF BIOSIMILARS

Manufacturing of biosimilars needs the design of complicated procedures using mammalian and

microbial cell cultures to produce therapeutic proteins [28].

Numerous parameters are observed in the manufacturing of biosimilars. The safety and efficacy of the biosimilar product are determined by clinical and post-marketing studies.

It is difficult to produce biologics similar to the reference biologics being the complexity of the reference drugs. The manufacturers of the biological drugs develop their own procedures for producing the biologics, which is substantially similar to the reference drug [29]. The complete Biosimilars manufacturing process are shown in Fig. 4.

9.1 Challenges Faced in the Manufacturing of Biosimilars

- The manufacture of biologics needs a greater number of batch records, greater critical process steps, additional product quality tests, and more process data entries.
- Biologic product manufacturers should practice flexibility in all manufacturing processes. Manufacturers carried out impurity and activity profiling thoroughly.
- Determining the bioequivalence between a biosimilar product and reference product is difficult compared to the generic drug.

- Biological products are very sensitive to changes in manufacturing conditions.
- Analytical procedures are usually less accurate and sensitive for biologic products than generics [30].

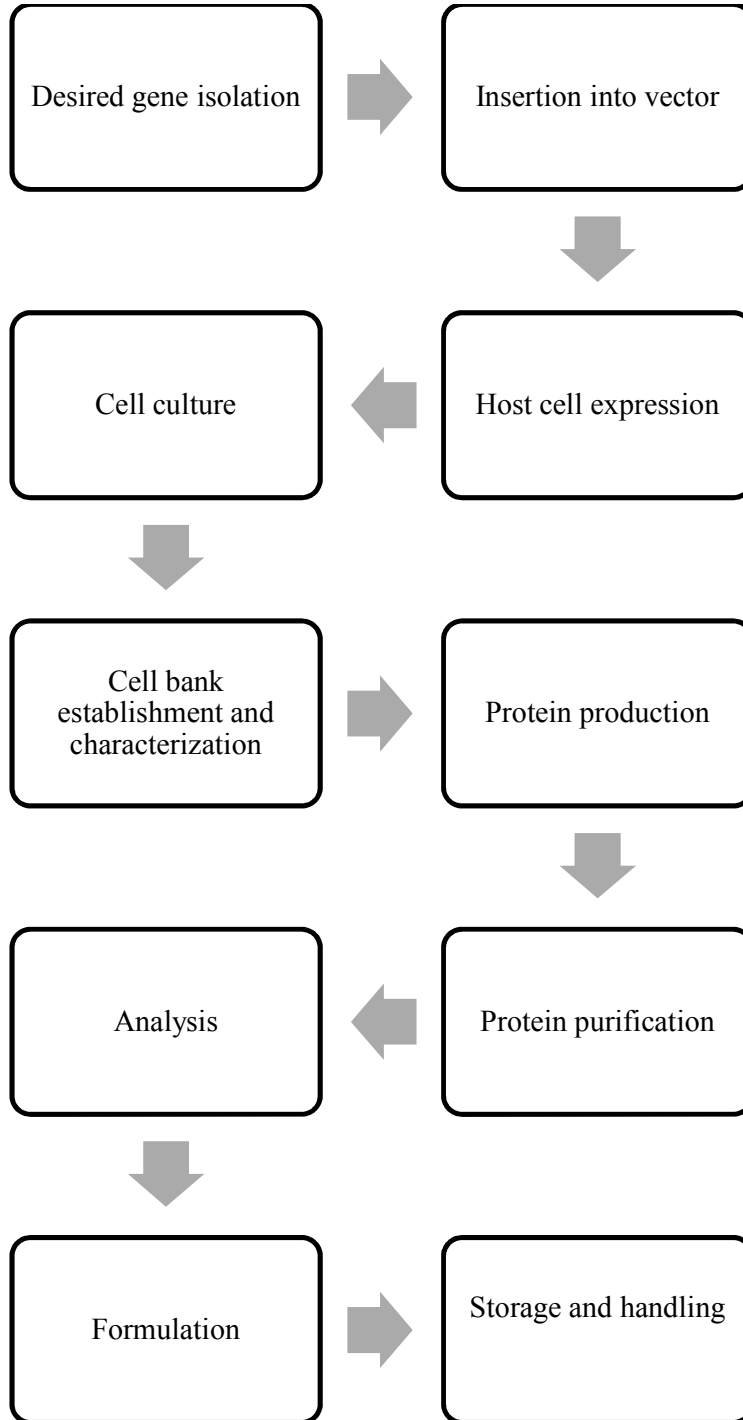


Fig. 4. Biosimilars manufacturing process

10. APPROVAL PATHWAYS FOR BIOSIMILARS

The approval of a biosimilar product is based on the comparability exercise. The reference biologic manufacturer demonstrated safety and effectiveness in the initial 351(a) application to FDA (Fig. 5).

Sponsors need to demonstrate that the biosimilar doesn't have any "clinically meaningful differences". A comparison of the biosimilar to the reference biologic in the domains of structure, in vitro toxicity studies, in vivo PK/PD studies, immunogenicity studies, and other clinical studies to compare the efficacy and safety [31].

Authorization of a biosimilar is established on the standard - "totality of the evidence", which can be defined as the summary of data obtained from analytical, animal, and human studies [32]. List of Biosimilar products approved in the US are described in Table 2.

10.1 Data Required for Approval

The data confirming biosimilarity to reference product is must require for a biosimilar product. This generally includes data from:

- Analytical data demonstrating high similarity between reference product and the biosimilar product.
- Animal Toxicity assessment data.
- A clinical trial, adequate to prove the safety, purity, and potency of the biosimilar product.
- Data in assessing immunogenicity, pharmacokinetics, pharmacodynamics.

For interchangeable products, additional data signifying that:

- The interchangeable product must yield the equivalent clinical effect as the reference biologic in patients.
- Substituting between the reference product and the proposed interchangeable product doesn't increase safety hazard or decrease effectiveness [33].

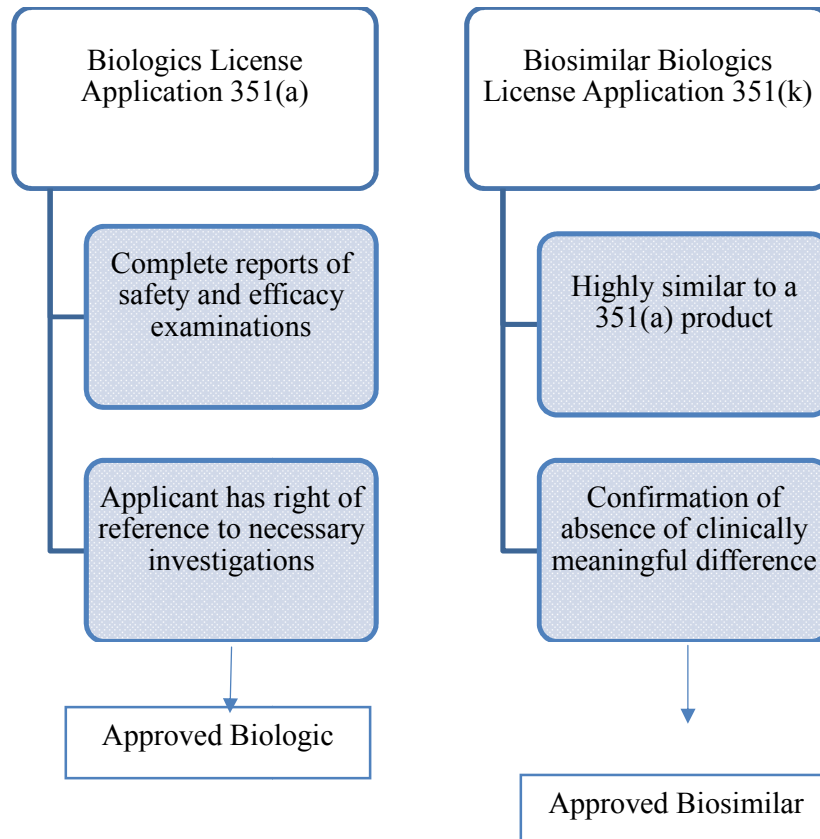


Fig. 5. Approval process

Table 3. List of biosimilar products in US [34]

Product (proper) name	Proprietary name	Date of licensure (mo/day/yr)
Filgrastim-sndz	Zarxio	03/06/15
Infliximab-dyyb	Inflectra	04/05/16
Etanercept-szsz	Erelzi	08/30/16
Adalimumab-atto	Amjevita	09/23/16
Bezlotoxumab	Zinplava	10/21/16
Infliximab-dyyb	Inflectra	04/05/17
Infliximab-abda	Renflexis	04/21/17
Adalimumab-adbm	Cyltezo	08/25/17
Trastuzumab-dkst	Ogivri	12/01/17
Infliximab-qbtx	Ixifi	12/13/17
Epoetinalfa-epbx	Retacrit	05/15/18
Pegfilgrastim-jmdb	Fulphila	06/04/18
Fremanezumab-vfrm	Ajovy	09/14/18
Adalimumab-adaz	Hyrimoz	10/30/18
Pegfilgrastim-cbqv	Udenyca	11/02/18
Rituximab-abbs	Truxima	11/28/18
Trastuzumab-pkrb	Herzuma	12/14/18
Trastuzumab-dttb	Ontruzant	01/18/19
Trastuzumab-qyyp	Trazimera	03/11/19

11. PHARMACOVIGILANCE OF BIOLOGICS AND BIOSIMILARS

Pharmacovigilance is a necessary aspect of the post-approval process for biologics and biosimilars. The purpose of this PV is to assess the safety & risk-benefit profile of a biologic to sustain regulatory decision-making. The main aim of Pharmacovigilance was to identify, describe a safety hazard, verify the safety profile of medicine, and measure the effectiveness of risk-management measures.

A strong PV strategy must cover safety specifications of the biologic or biosimilar, to identify potential risks, and recognizes the information that is to be provided with the medicine. PV approaches are moreover important for recognizing possible variation evidences in safety [35].

12. CONCLUSION

In spite of the limited number of biological products that have enrolled in the US market and their modest cost-savings to date, biological products offer the potential to perform a vital role in increasing the US prescription drug prices. The biosimilar approval pathway in the USA aims at striking a balance among the innovation and the lower expenditure for biological products without compromising the quality, safety, and efficacy. Biosimilar manufacturer requires to face

unusual difficulties in the development, clinical trials, manufacturing, registration and product marketing contrasted with customary generic products. The BPCIA should decline the time period for the approval of biological products, and the potential for interchangeability of a biosimilar product with its reference product will promote facilitate cost savings. Pharmacovigilance will be crucial to find any safety and efficacy problems that may arise from the use of the biological products.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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