Navigating the Regulatory and Approval Process for Biosimilar Medicines: A Comprehensive Review

[1]R. Nithishkumar, [2]K. Kathiresan

[1]PG Student, Department of Pharmacy, Annamalai University, Chidambaram.
[2]Associate Professor, Department of Pharmacy,
Annamalai University, Chidambaram.

Email: rsnnithishkumar@gmail.com

Email: dr.kathiresan123@rediffmail.com

Abstract

The person applying is urged to include a thorough explanation of the Biosimilars are more and more alluring to remunerator all over the world by cause of proliferating monetary constraint from excessive price on pricey biologics. Biotherapeutics, patent termination wide the gateway to super opposition between pharmaceutical corporations worldwide. At economical level the demand of biosimilars are continuously raising across the world market. Predicted the rise about 25% by 2026 as compared to the fee in 2020. Biotherapeutics can probably have safeness, effectiveness and first-rate(quality) concerns. So, numerous autocracies are strive to improve the employment of biotherapeutics by utilizing administrative medium in aspiration of inflating market. This overview shows the challenges of biotherapeutics in regulators aspects, strides essential to conquer the hurdles and to use the biologically similar product successfully. Clinical investigations are needed for biological substances that are comparable to one another, or biosimilars, in addition to the studies of bioequivalence needed to support the registration of a generic small molecule therapeutic agent. methodology employed to show that the quality, safety, and effectiveness characteristics of the product being used as a reference and the biosimilar are comparable.

Keywords*:* Biosimilars, Biotherapeutics, Pharmacovigilance, Regulatory aspects, Clinical data, Non-clinical data, Extrapolation[1].

[1]Nithishkumar R

1. Introduction

The World Health Organization (WHO) suggestions for biotherapeutics, which had been concluded in 2009, have been uses as a parent for most of these international location. Those suggestion confirm key principles of biosimilarity, which include production process, development of predict and demonstrated comparability.[1] The approval of those established similar biologics on the identical confirmation collate to the innovator's drug product. This curtail sanction removes the expensive clinical studies of drug development and let in drug producers to provide little fragmented nonproprietary at a decreased cost.[2] This type of biopharmaceuticals need special regulatory pathway. Example: Traditional generic medication do not require the findings of pharmacological and toxicological test data are presented for the purpose of performing clinical trials on comparable biologics.[3] In contrast to biosimilars, which cost between $1 and $4 million and take two years to produce, biological product, or innovator's products, require investment of one hundred million dollars to two hundred and fifty million dollars and take seven to eight years to develop.

2. Biosimilar development and approval process

1. Physico-chemical resemblance
2. Biological resemblance
3. Preclinical resemblance
4. Clinical resemblance

The comparison criteria to illustrate each merchandise have comparable characteristics in regard to first-rate, safeness and effectiveness are one in every of the altercation points inside the biotherapeutics firestorm. Presently, because of the nation of the art in technological know how it's far somewhere impractical to how that two biologic medicine have the identical qualitative and quantitative composition.[4]

2.1. Physicochemical comparability: For comparative assessment of both biologics and reference product a biochemical characterization is required. Peptide mapping, glycosylation, protein concentration, molecular mass are some techniques for protein characterization. In order to acquire a precise protein structure atleast two analytical method results are considered. Primary structure characterization done by using mass spectroscopy. Second and tertiary structure are determined by Infrared Spectroscopy (IR), Differential Scanning Colorimetry (DSC), Nuclear Magnetic Reonance (^{1}NMR), Dynamic Light Scattering (DLS).[2]

2.2. Biological comparability: For biological comparative assessment of both biologic and reference product a biochemical characterization is required. In vitro studies and in-vivo studies are performed. In vitro studies are carried out to determine receptor binding activity and cell proliferation activity. Enzyme Linked Immuno Sorbent Assay (ELISA), Affinity Capillary Electrophoresis (ACE), Affinity chromatography are some techniques used to determine specific binding properties.[2]

2.3. Pre-clinical comparability: Pre clinical studies carried out to determine the safety, efficacy of biologics. This can be performed by pharmacodynamic studies.[4]

2.4. Clinical comparability: Clinical studies are carried out in healthy volunteers to determine pharmacokinetic and pharmacodynamic properties of biologic. [4]

2.5. Immunogenicity testing: Immunogenicity examine is one of the safeness exams regarding resistant response in biological structures. Modified effectiveness method to motive the lack of effectiveness, move-response and changed pharmaceutical kinetics and cause anaphylaxis and allergy.[2]

2.6. Pharmacovilance: A pharmacovigilance examine is wanted for the submit protection approval monitoring of biotherapeutics Spontaneous Reporting Structures (SRS) and Active Surveillance (AS) structures are implanted to reveal product fie adjustments and product production, appropriately.[2]

2.7. Extrapolation: Extrapolation is a scientific rationable that connect all of the evidence-that is**,** all of the data gathered-from a single biosimilar product indication to every indication that the original product was first approved for. It is reasonable to believe that a biosimilar that has proven to be equally safe and effective in the "most sensitive" indication will also be safe and effective in another indication of the reference product.[4]

3. Common technical document

The Common technical document is organized into 5 divisions which is necessary for accommodate biotherpeutics.

3.1. Division 1: Active substance, raw material and manufacturing process for biosimilars are given as summaraize form.

3.2. Division 2: It includes the normal requirements.

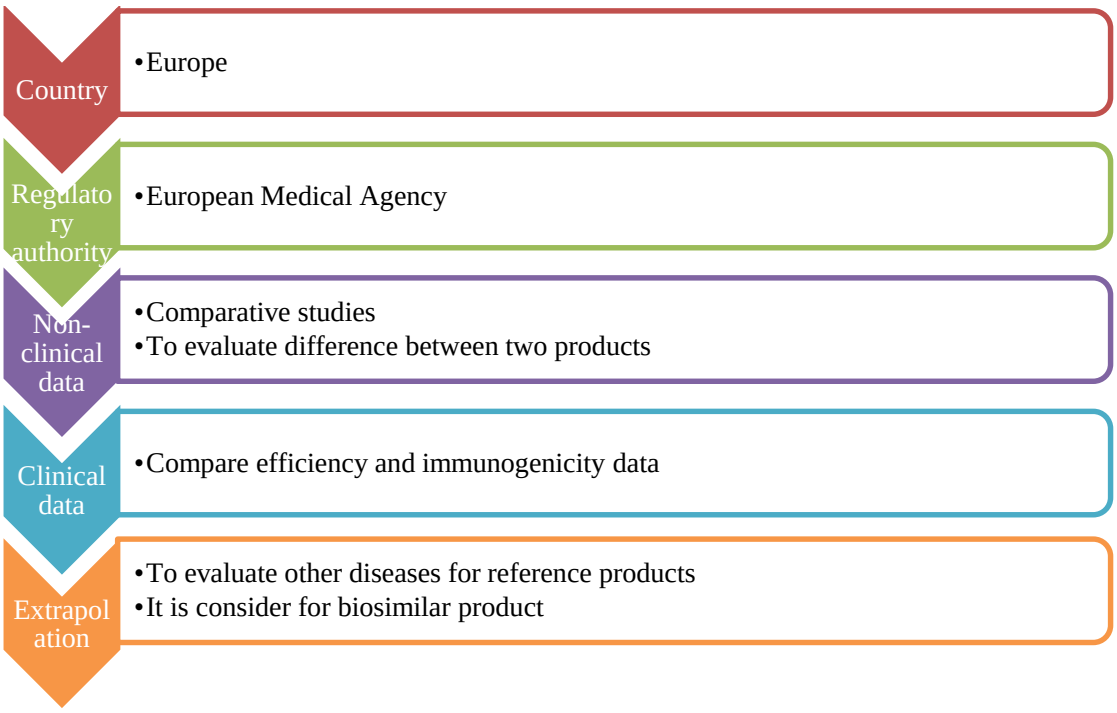
- First-rate summing up.
- Non-clinical overview.
- Clinical overview

3.3. Division 3: It contain first-rate related details (chemical, pharmaceutical and biologic information)

3.4. Division 4: It is advisable to do non-clinical investigations prior to beginning clinical development. In Division 4, the method chosen to highlight the parallels and discrepancies between the reference product and the biosimilar must be fully justified.

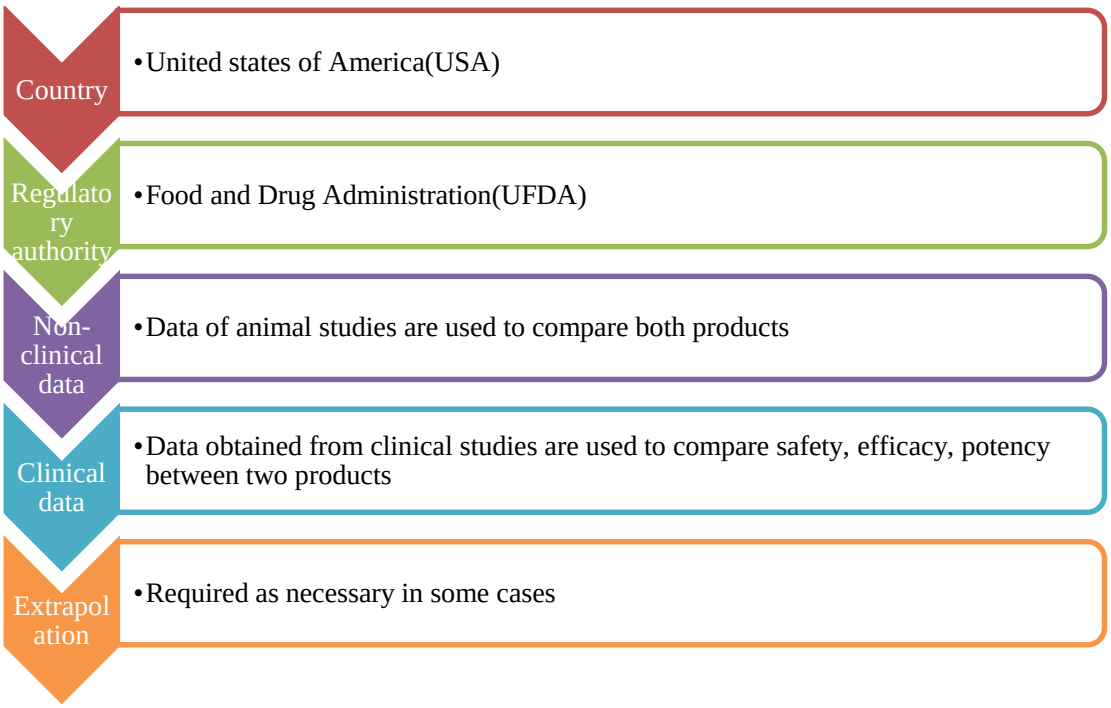
3.5. Division 5: It is well acknowledged that non-clinical research is insufficient to prove the safeness and effectiveness of a biotherapeutics; instead, clinical trials must verify these claims.

4. Data required for approval of biosimilar by various regulatory authorities of different countries



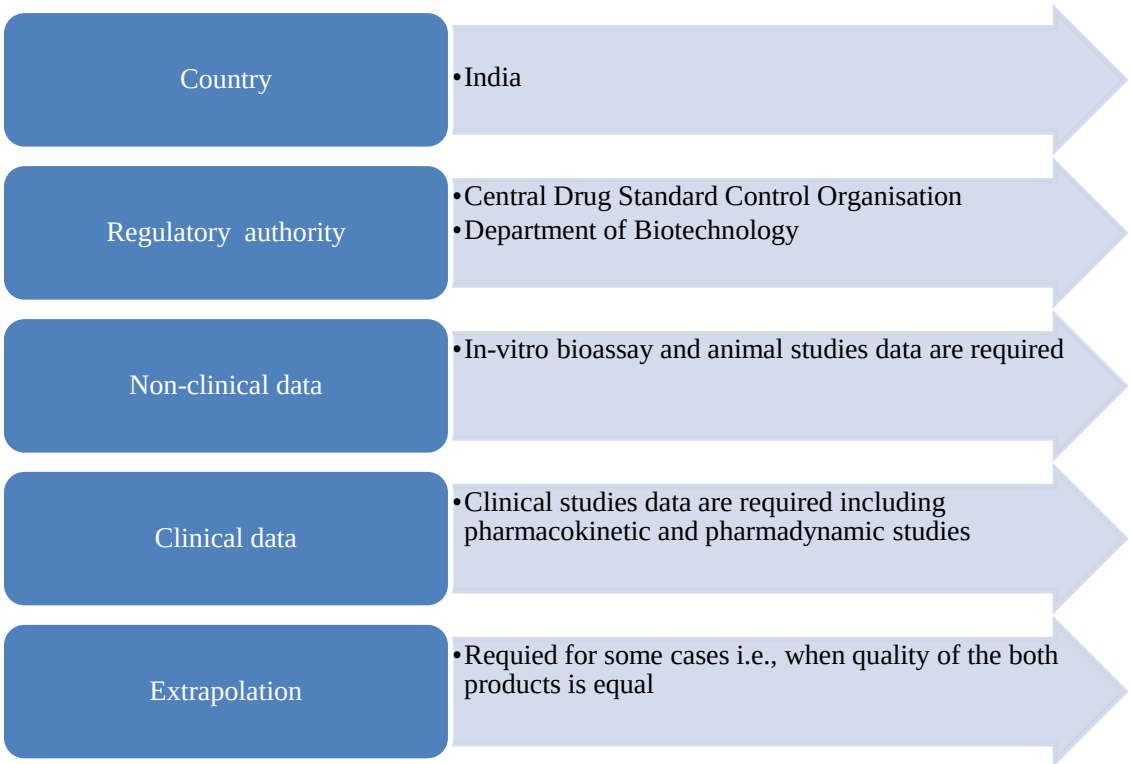
[5]

Figure 1. Regulatory authority of Europe



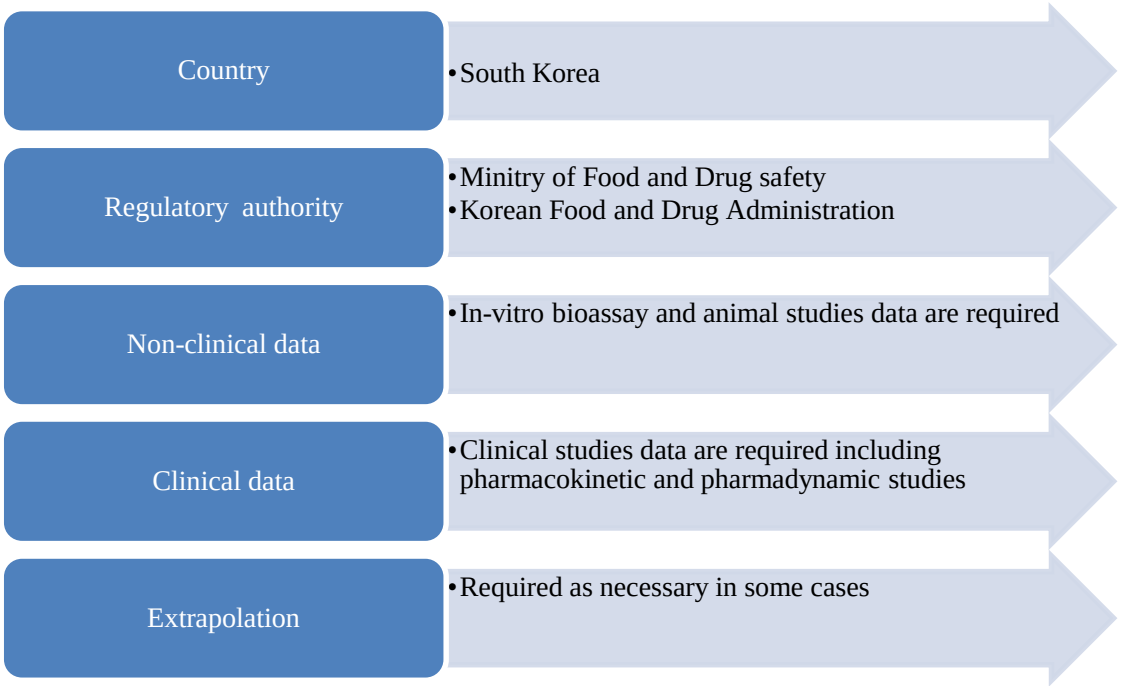
[5]

Figure 2. Regulatory authority of United States of America



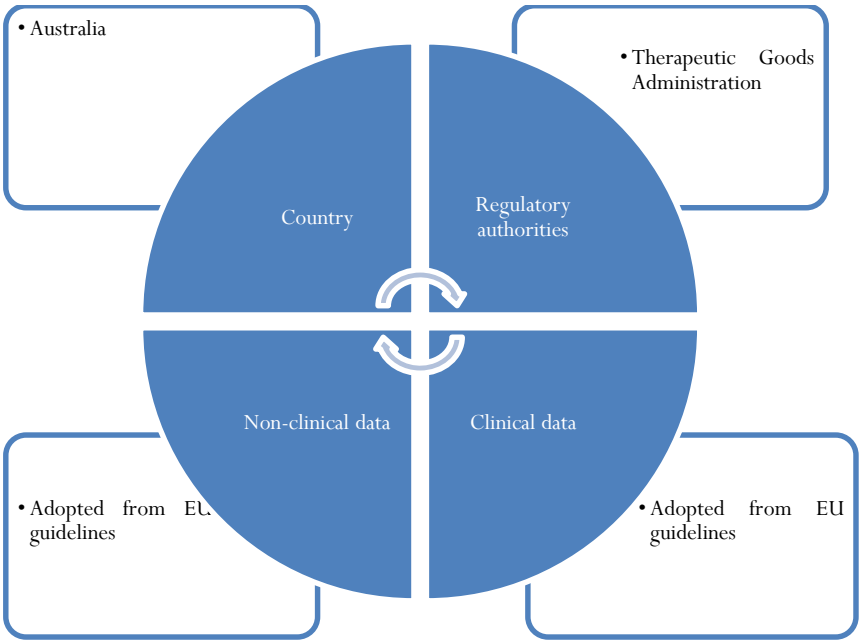
[5]

Figure 3. Regulatory authority of India



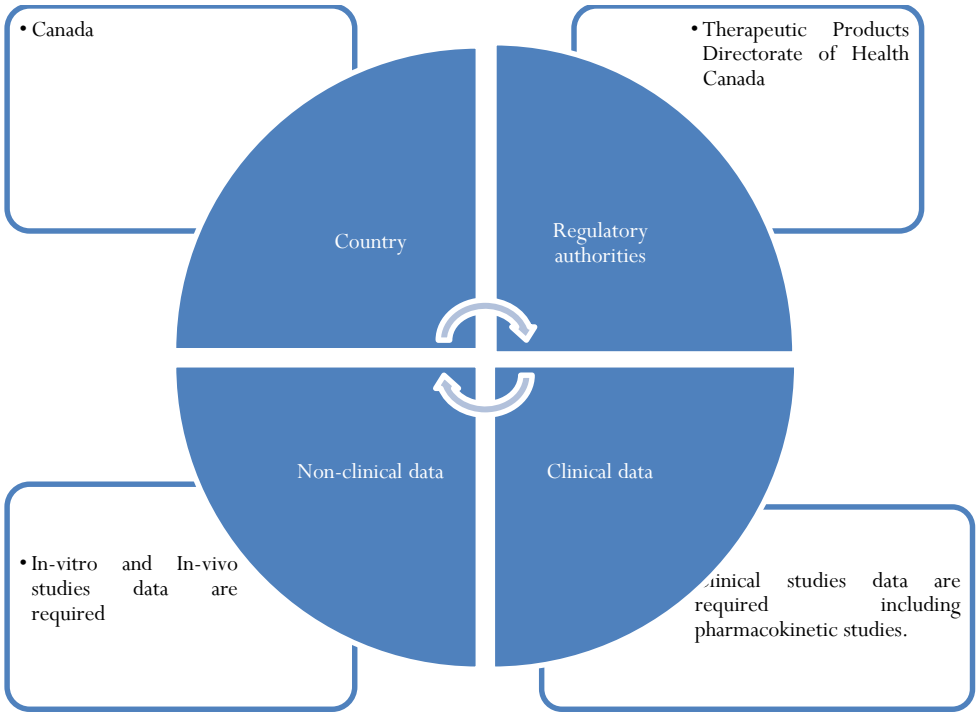
[5]

Figure 4. Regulatory authority of South Korea



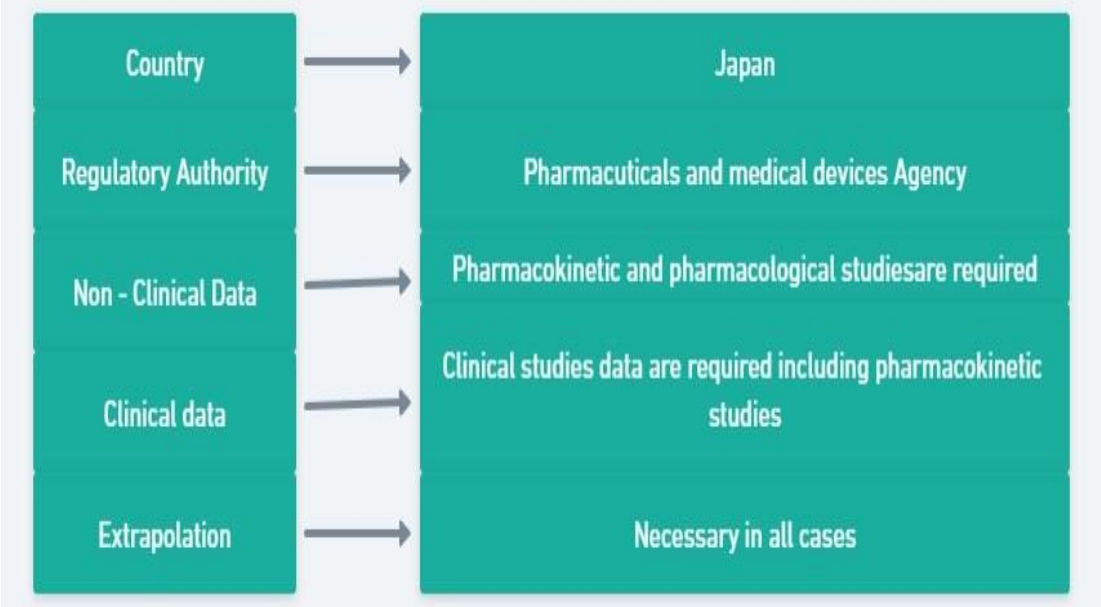
[5]

Figure 5. Regulatory authority of Australia



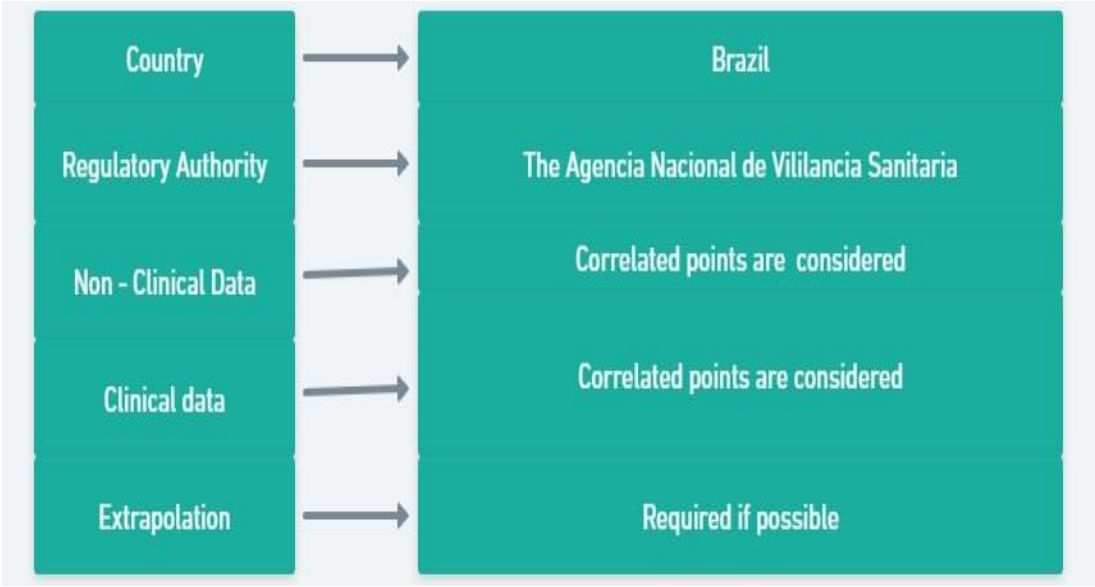
[5]

Figure 6. Regulatory authority of Canada



[5]

Image 1. Regulatory authority of Japan



[5]

Image 2. Regulatory authority of Brazil

[5]

Table 1. Regulatory authority of Argentina

Country	**Chile**
Regulatory authority	Intitio de Salud Publica

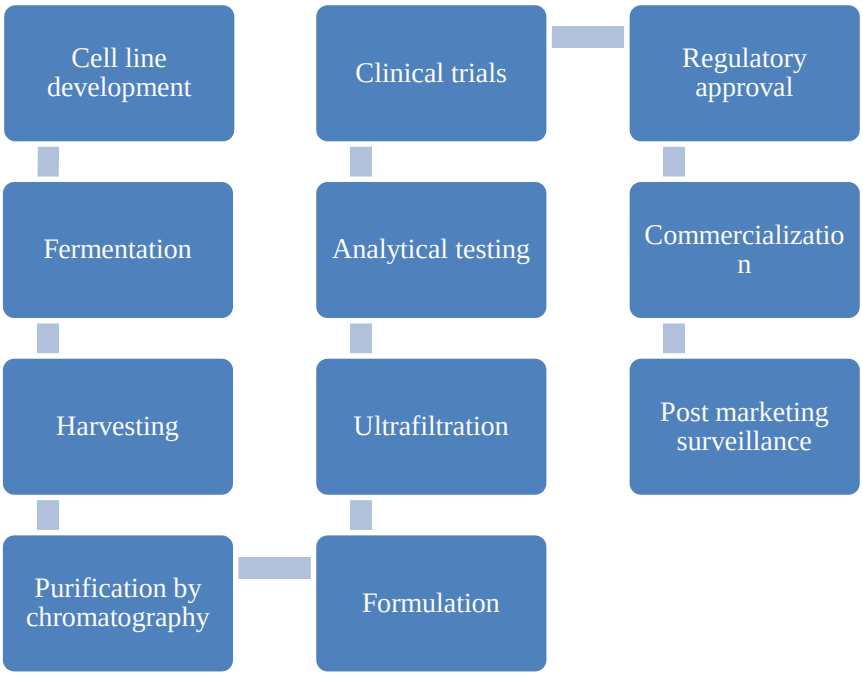
Country	Argentina
Regulatory authority	The Administration Nacional de Medicamentos. Alimetos Y Tecnologia Medica
Non-clinical data	Correlated points are considered
Clinical data	Correlated points are considered
Extrapolation	Not necessary
Non-clinical data	Correlated points are considered
Clinical data	Correlated points are considered
Extrapolation	Possible once biosimilarity established

[5]

Table 2. Regulatory authority of Chile

5. Manufacturing considerations

The huge size of molecules, insufficient permeability, and gastrointestinal stability of these biological products create several development-related difficulties. These factors explain why the majority of biological product are provided solely in injectable formulations. Further more, the amino acid genome that are wrapped into particular arrangements make up protein-based biological products. Weak interactions between molecules and weak link between peptide maintain the skeletal system of amino acids. As a result, even a slight alteration in the structure of the antibody could affect could affect how selective it is to the receptor, changing the course of medical responses as well as allergic reactions. Inverse engineering and biotechnological synthesis during the development stage are two highly process-dependent methods used in the production of biosimilars.[4]



[4]

Figure 7. Manufacturing process and commercialization of biosimilars

6. Conclusion

Consumers may benefit personally from biosimilars' pricing rivalry along with price reductions by decreased rates for insurance and personal expenditures, which encourage many more people to use the medication that was prescribed. Manufacturers are ready to give discounts for the drug products when they enter into the bulk production. Regrettably, payers, patients, and doctors have not always accepted biotherapeutics to the best of abilities, especially in the US. So, all the health care system of their country should run programmeslike 340B which is adopted by EU. The EU has shown that its tactics are effective. We must modify such tactics for our medical system in order to lessen the burden of money on it and provide consumers with more opportunities for drugs that they may not have been capable to buy. After adopted this guidelines biosimilars usage is increases due to less cost comparable to originator's of reference product. So strong regulatory framework is required. Unless a strong regulatory framework it cause health concern of people in larger proportion (i.e. middle class people). It also cause indirect burden to Government by using of less standard biosimilars.

References

[1]. Azevedo VF, Sandorff E, Siemak B, Halbert RJ. "Potential regulatory and commercial environment for biosimilars in Latin America". Value in health regional issues. 1;1(2):228-34(Dec 2012). https://doi.org/10.1016/j.vhri.2012.09.015.

[2]. Zuñiga L, Calvo B. "Biosimilars approval process. Regulatory Toxicology and Pharmacology". 1;56(3):374-7(Apr 2010). https://doi.org/10.1016/j.yrtph.2009.11.

[3]. Kvien TK, Patel K, Strand V. “The cost savings of biosimilars can help increase patient access and lift the financial burden of health care systems”. InSeminars in Arthritis and Rheumatism (Vol. 52, p. 151939) (Feb 2022). https://doi.org/10.1016/j.semarthrit.2021.11.009.

[4]. Ratih R, Asmari M, Abdel-Megied AM, Elbarbry F, El Deeb S. “Biosimilars: Review of regulatory, manufacturing, analytical aspects and beyond”. Microchemical Journal. 1;165:106143 (Jun 2021). https://doi.org/10.1016/j.microc.2021.106143.

[5].Bennett CL et.al, Chen B, Hermanson T et.al, Wyatt MD et.al, Schulz RM et.al, Georgantopoulos P et.al, Kessler S et.al, Raisch DW et.al, Qureshi ZP et.al, Lu ZK et.al, Love BL et.al. “Regulatory and clinical considerations for biosimilar oncology drugs. The Lancet Oncology”. 1;15(13):e594-605(Dec 2014). https://doi.org/10.1016/S1470-2045(14)70365-1.