AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Regulatory Requirements For Biosimilars As Per CDSCO and UAE

Ashok Kumar P*, Bhavana. S, Jayashree. A, Kavya. N, Mahalakshmi. K.S, Manasa. T.G

Sree Siddaganga College of Pharmacy, 1st Left cross, 3rd block, Mahalakshmi nagara, Near railway gate, 80 feet road, Batawadi, Tumkur- 572103, Karnataka, India.

ABSTRACT

The term biosimilar is used for a subsequently launched version of a biologic product which is similar in terms of quality, safety, and efficacy to an already licensed "Reference Biologic" product. The primary purpose of biosimilars is to reduce the healthcare costs associated with the use of biologics and thereby increase access to healthcare. Unlike small molecule generics, the bioequivalence approach is not considered appropriate for the approval of biosimilars. The approval of biosimilars is based on a stepwise comparability exercise with the "Reference Biologic", starting with a comprehensive physicochemical and biological characterization. The extent and nature of the required nonclinical in vivo studies and clinical studies depend on the level of evidence obtained from the previous steps. Regulations require that the "Reference Biologic" should have been licensed/approved in the same country/region or in other ICH countries based on a full registration dossier. Apart from the comparability exercise, regulations also deal with indication extrapolation, pharmacovigilance, and substitution and interchangeability. This chapter also briefly describes the considerations for exclusivity, market access, and commercialization of biosimilars.

Keywords: Biologics; biosimilars; comparability; efficacy; immunogenicity; safety; tolerability

*Corresponding Author Email: ashokkumarscp@gmail.com

Received 09 September 2023, Accepted 15 October 2023

Please cite this article as: Kumar P *et al.*, Regulatory Requirements For Biosimilars As Per CDSCO and UAE. American Journal of PharmTech Research 2023.

INTRODUCTION

The surging costs of biological medicines worldwide have necessitated the development of biosimilars. These highly similar versions of off-patent biological products entered the EU in 2006 and the U.S. in 2015. Unlike small molecule generic drugs, which are chemically identical to their originator products, biosimilar products cannot be identical because of the nature of biological molecules. However, as more than a decade of experience in Europe has demonstrated, the slight differences between a biosimilar and its originator do not result in clinically-meaningful differences in the drug's efficacy and safety. The complexity of biosimilars has led the major regulatory agencies to establish unique biosimilar regulatory protocols. In order to earn approval for these products, biosimilar developers must present thorough analytical characterization packages, pharmacokinetic and pharmacodynamic profiles, and comparative clinical trial data to eliminate any residual uncertainty. Beyond development and regulatory complexities, much of the fascination with biosimilars stems from ongoing efforts to establish unique commercialization blueprints, educate stakeholders, and collect and present real-world evidence from ongoing treatment and post-marketing "switching trials" to demonstrate biosimilars' safety and efficacy in everyday use. Varying healthcare and reimbursement frameworks worldwide have given rise to dynamic case studies highlighting the diversity of the burgeoning biosimilar market.

Background:

Biosimilars provide opportunities for improving healthcare access and outcomes and reducing overall healthcare costs for patients with cancer.

Precursors of biologics began in Europe with the work of pioneering scientists in the 1800s. In Germany, Robert Koch investigated and isolated organisms responsible for cholera (Koch, 1884) and tuberculosis (Koch, 1891), and Louis Pasteur developed the first vaccine for fowl against chicken cholera in the latter part of the 19th century (Pasteur, 1881). The United States soon followed the growing science of immunology and biologic therapies, with Theobald Smith and Daniel E. Salmon pioneering heat-killed vaccines against hog cholera (Salmon, 1886). During the 20th century, new vaccines and antitoxins were developed that offered preventive and curative options for some of the most dreaded diseases afflicting mankind, including diphtheria and tetanus (Poland & Barrett, 2009; U.S. Food and Drug Administration [FDA], 2002).

Under the Biologics Control Act of 1902, the United States accelerated what Europe has pioneered, with state and national laboratories initially providing the essential components of the regulations for the commercial manufacturing and licensing of biologics. The regulation of biologics was under the responsibility of the Surgeon General of the U.S. Marine Hospital Service

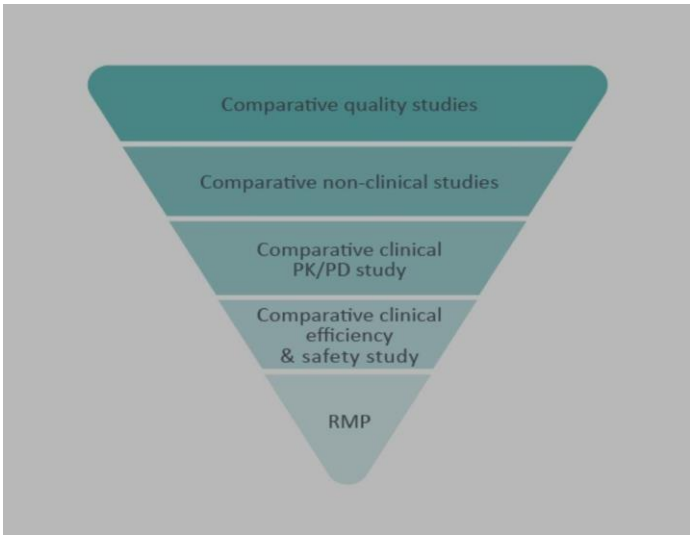
and the Joint Army and Navy Board. The board was tasked with the enforcement of regulations for licensing establishments engaged in the preparation of viruses, serums, toxins, and antitoxins, as well as analogous products and their sales in international commerce (FDA, 2002). In 1948, the National Institutes of Health (NIH) gained authority to regulate the manufacturing and licensing of biologics under the Public Health Service Act in 1944. In 1972, the responsibility for regulating the biologics industry was transferred from NIH to the FDA (Culliton, 1972). Biosimilars also became the responsibility of the FDA in 2010 (Public Health Service Act, 2018).

Although Europe has pioneered the development and therapeutic applications of early biologic products like vaccines and antitoxins, the United States has been leading the innovations in biotechnology and biologic therapies in the 21st century (Carver, Elikan, & Lietzan, 2010; Leach et al., 2010), particularly in the development and licensing of Mabs for cancer .

Principle:

Proof of biosimilarity at all levels is key At Valerius, we are committed to develop biosimilars of highest quality by complying with the rigorous directives imposed by leading health authorities for highly regulated markets. Our ultimate goal is to deliver biosimilars that are interchangeable with their reference product. This implies that, despite of potential micro heterogeneities, our biosimilars are developed to be as safe and as effective as the corresponding branded drugs.

To accomplish this, a holistic comparability approach is required and integrated in our development programs:



Approval process:

The approval process for biosimilar drugs is divided into pre-clinical trial, clinical trial and post clinical trial stages with each stage having different data package requirements. Data packages may also differ based on the risk classification assigned to the GMOs) under the Genetically

Engineered Microorganisms Rules, as prior authorization from the IBSC and subsequent approval of the RCGM is required for conducting experiments involving LMOs classified in risk categories 3 or higher.

In addition to RCGM permission, the approval of the GEAC is also required for activities involving large scale use of hazardous microorganisms and recombinants in research and industrial production. The GEAC is also responsible for approval of proposals relating to release of GMOs and products into the environment including experimental field trials.

Pre-clinical Trial Stage:

Data packages must demonstrate the consistency of process and product, product characterization, and product specifications to comply with RCGM requirements. The application to the RCGM should be accompanied by approval of the IBSC and the approval of the Institutional Animal Ethics Committee ("IAEC") along with details of the personnel involved such as study director, principal investigator, pathologist, other investigators and quality assurance officer.

The information in the data package may include the following.

Basic Information about Reference Biological Information about drug, route of administration, absorption and elimination rate, therapeutic index, dose, vehicle, mode of administration, dose response etc. Bioequivalence range, if available, Tissue-specific localization, if available, Available toxicity data on reference biologic, and

Mode of action:

Basic Information about the Similar Biologic Known/proposed clinical use, Target population (age, sex, pregnancy, lactating, children etc.), Dosage units (frequency and intervals),

Route/alternate routes of administration:

Final formulation of adjuvants and additives including toxicity data of such adjuvants and additives, Diluents, and Presentation e.g. pre-filled syringe, cartridge, vial.

Post-Clinical Trial Stage:

Post-marketing surveillance is particularly important in the case of biosimilars, as a biosimilar is approved based on a reduced pre-clinical and clinical trial data package. Therefore, a formal Risk Management Plan must be established to monitor and detect both known inherent safety concerns and potential unknown safety signals that may arise from the biosimilar. A comprehensive pharmacovigilance plan must also be put into place which shall include the submission of periodic safety update reports ("PSUR").

Data are required for approval of a biosimilar product:

FDA evaluates each proposed biosimilar individually and advises manufacturers on the scope and

extent of testing needed to show biosimilarity. Analytical studies are the foundation of biosimilar development. Data also come from a variety of clinical and nonclinical studies. An application for a proposed biosimilar generally must include information showing that the proposed product is biosimilar to a reference product. Below is some information on the data typically included in an application. More information can be found here.

Analytical studies:

Comparative analytical data provide the foundation of biosimilar development. These studies provide data to support the structural and functional similarity of the proposed product to the reference product and to evaluate the impact of any differences identified.

Animal studies:

These may provide toxicology or pharmacology information. A clinical study or studies. Pharmacology studies may demonstrate that the proposed biosimilar moves through the body in the same way and provides the same effects as the reference product. An immunogenicity assessment evaluates a patient's immune response to the proposed biosimilar. Other comparative clinical studies are sometimes conducted after the completion of other studies to address any remaining uncertainty about whether the proposed biosimilar has any clinically meaningful differences from the reference product. Learn more about comparative clinical studies. FDA has discretion to determine that an element is unnecessary in a proposed biosimilar application. FDA evaluates all the evidence, based on comparisons between the biosimilar and the reference product, in the context of the Agency's previous finding that the reference product is safe and effective

Examples of Some Biosimilars Approved In India:

Product name	Active drug	Indications
Glaritus	Insulin glargine	Diabetes Mellitus
Grafeel	Filgrastim	Neutropenia
Epofer	Epotein alfa	Anemia
Krabeva	Adalimumab	RA, Crohn`s disease
Erbitux	Cetuximab	Colorectal carcinoma
Krabeva	Bevacizumab	Colorectal cancer

Guidelines:

After the abbreviated pathway was legally established and finally enacted, many questions were left open regarding which data, analyses, and studies had to comprise an application package to receive regulatory approval by the FDA. The law left a lot of design possibilities for implementation of the a BLA which had to be discuss, developed, and defined by the FDA involving the public, resulting in guidance documents for industry. Detailed guidance was missing until 2012 when the first and long awaited "draft guidelines" were published by the FDA.

Although the issuance of guidance by the FDA was not a prerequisite for the FDA to assess an application submitted under351 (k)of the PHS Act [81], no application was submitted before2014. Guidance documents are not legally binding for sponsors. However, if uncertainties about the required documentation occur and if the sponsor favours different approaches than proposed by the FDA's guidance documents, the sponsor should seek advice from the FDA and discuss their approach with the FDA early during the development process.

REGULATORY REQUIREMENTS FOR BIOSIMILARS IN INDIA:

Key points regarding the regulatory requirements for biosimilars in India as per CDSCO and WHO:

1. Data Requirements:

Biosimilar manufacturers in India are required to provide extensive data demonstrating the similarity between the biosimilar product and the reference biologic. This includes analytical, pharmacological, and clinical data.

2. Comparability Studies:

Comparative analytical and functional studies are essential to establish similarity between the biosimilar and the reference biologic.

3. Clinical Trials:

Clinical trials are typically required to demonstrate the safety and efficacy of the biosimilar in Indian patients. The extent of clinical data needed may vary based on the specific biosimilar and the reference product.

4. Quality and Manufacturing Standards:

Biosimilar manufacturers must adhere to strict quality and manufacturing standards, which are usually in accordance with Good Manufacturing Practices (GMP) guidelines.

5. Regulatory Pathway:

India follows a pathway similar to the WHO's guidelines for the evaluation of biosimilars. The biosimilar approval process may involve a stepwise approach, with an emphasis on analytical and preclinical data before proceeding to clinical trials.

6. Pharmacovigilance:

Post-marketing surveillance and pharmacovigilance activities are important to monitor the safety and effectiveness of biosimilars once they are on the market.

REGULATORY REQUIREMENTS OF BIOSIMILARS AS PER UAE:

The UAE (United Arab Emirates) and CDSCO (Central Drugs Standard Control Organization) are two distinct entities involved in the regulation and oversight of pharmaceuticals and healthcare

products, but they serve different regions and have different functions. Here's a comparison between the two:

1. Location and Jurisdiction:

UAE: The UAE is a country located in the Middle East, and its regulatory authority for pharmaceuticals and healthcare products is primarily governed by the Ministry of Health and Prevention (MOHAP).

2. Regulatory Focus:

UAE: MOHAP in the UAE oversees the regulation of pharmaceuticals, including the approval and monitoring of drugs, biologics, and medical devices. They also set standards and guidelines for healthcare products.

3. Regulatory Processes:

UAE: The UAE follows its own regulatory processes for the approval of pharmaceuticals and healthcare products, including registration, clinical trials, and quality control, as mentioned in my previous response.

4. Geographic Reach:

UAE: The regulatory authority in the UAE focuses primarily on ensuring the safety and quality of healthcare products within the UAE.

5. Cultural and Legal Differences:

UAE: The UAE has its own cultural norms, healthcare system, and legal requirements that influence the regulation of healthcare products.

6. International Collaboration:

Both the UAE and India may collaborate with international regulatory bodies and organizations to ensure compliance with global standards and best practices.

GLOBAL BIOSIMILAR MARKET SIZE:

The global biosimilar market is predicted to grow from $5.95 billion in 2020 to $34.96 billion in 2027, with a CAGR of 28.4%. This growth is attributed to the rising prevalence of chronic diseases, increasing demand for affordable treatment options, and patent expiration of blockbuster biologic drugs.

Market Opportunity:

The US and Europe are the largest markets for biosimilars, with a combined share of over 80%. The Asia Pacific region is expected to have the highest CAGR during the forecast period, due to the increasing demand for biologics and biosimilars in the region.

Key Players:

The biosimilar market is highly competitive, with key players including Pfizer, Amgen, Novartis, and Biocon. Many companies are focusing on innovative strategies such as partnerships and collaborations to expand their biosimilar product portfolios.

Challenges:

The biosimilar market still faces several challenges, including regulatory hurdles, expensive development costs, and the need for extensive clinical trials to demonstrate safety and efficacy. However, the potential benefits of biosimilars, including increased patient access to affordable treatment options, make the market an attractive opportunity for investors.

UAE Biosimilars Market Analysis:

$ 3999

The UAE biosimilars market size was valued at $96 Mn in 2022 and is estimated to expand at a compound annual growth rate (CAGR) of 23.2% from 2022 to 2030 and will reach $510 Mn in 2030. The market is segmented by product type and indication type. The UAE Biosimilars market will grow as biosimilars are less expensive than their reference products, and patients can afford to use biosimilars as a therapy alternative. The key market players are Neopharma, Julphar, Pfizer

UAE Biosimilars Market Executive Summary:

The UAE biosimilars market size was valued at $96 Mn in 2022 and is estimated to expand at a compound annual growth rate (CAGR) of 23.2% from 2022 to 2030 and will reach $510 Mn in 2030. The United Arab Emirates (UAE) offers a sophisticated healthcare system with first-rate facilities and cutting-edge medical technology. The government offers free or inexpensive healthcare services to its inhabitants and residents, and the private sector meets the requirements of those who can afford to pay for private medical treatments. The country's healthcare system is a hybrid of the public and private sectors. The UAE government has made considerable investments

in the healthcare industry over the years and is dedicated to offering top-notch services to its inhabitants and citizens. The government's spending on healthcare has been rising rapidly, and in 2021 it was projected to total around USD 16.7 billion. This accounts for a considerable amount of the nation's GDP, demonstrating how important it is to the government that its citizens have access to quality healthcare services. In recent years, the UAE healthcare industry has seen a growth in the use of biosimilars as regulators and healthcare providers seek to expand access to reasonably priced biologic medicines. The Ministry of Health and Prevention (MOHAP) is in charge of the UAE's thorough regulatory framework for biosimilars. This framework, which is based on the rules established by the World Health Organization (WHO) and the European Medicines Agency (EMA), demands that biosimilars show resemblance to the reference product in terms of quality, safety, and efficacy. The UAE market now offers a number of biosimilars, including versions of the drugs infliximab, etanercept, and rituximab. Rheumatoid arthritis, psoriasis, and cancer are just a few of the illnesses that are being treated with these products. Hence, the biosimilar market will grow across the nation during the forecast period.

APPLICATIONS:

1. Cancer Treatment:

Biosimilars are used in the treatment of various cancers, such as breast cancer, colorectal cancer, and leukemia, as supportive care or in combination with other therapies**.**

2. Autoimmune Diseases:

They are employed in the management of autoimmune disorders like rheumatoid arthritis, psoriasis, and inflammatory bowel diseases.

3. Blood Disorders:

Biosimilars can be used to treat conditions like anemia and neutropenia in patients with blood disorders.

4. Infectious Diseases:

Some biosimilars are used to treat infectious diseases, including hepatitis B and certain viral infections.

5. Growth Hormone Deficiencies:

Biosimilar growth hormones are used to treat growth hormone deficiencies in children and adults.

6. Diabetes: Biosimilar insulins are used in the management of diabetes.

7. Neurological Disorders:

They may be applied in the treatment of neurological conditions like multiple sclerosis.

8. Chronic Kidney Disease:

are used in the management of anemia associated with chronic kidney disease.

9. Oncology Supportive Care:

Biosimilars can be used to manage side effects of cancer treatment, such as neutropenia and anemia.

10. Fertility Treatment:

Biosimilars are used in fertility treatments to stimulate follicle development in women undergoing assisted reproductive techniques.

11. Transplant Medicine:

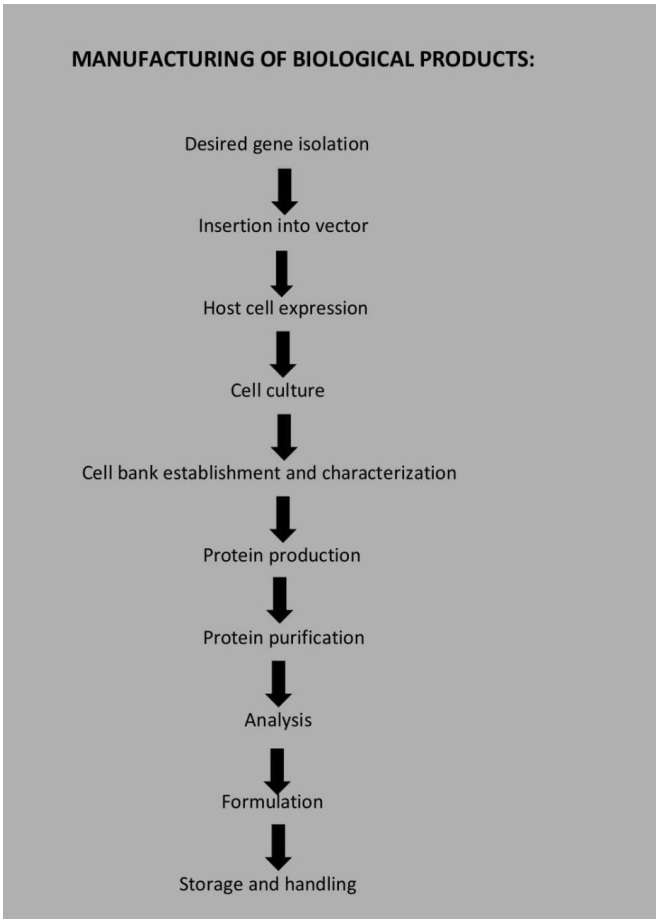
Biosimilars are used to prevent organ rejection in transplant patients.

12. Dermatology:

Biosimilars can be used in dermatological conditions such as psoriasis.

13. Ophthalmology:

Some biosimilars are used in the treatment of eye diseases, including macular degeneration. These applications highlight the versatility of biosimilars in providing cost-effective and accessible treatments for a wide range of medical conditions, making them an important part of modern healthcare.



Efficacy:

A number of properly designed clinical studies with a large number of patients have shown that biosimilar drugs are as effective as their reference biologic drug.

Biosimilar drugs work the same way as their reference biologic drug. If a patient switches from a biologic drug to a biosimilar drug or starts their treatment with a biosimilar drug, the outcome will be the same as if they were treated with the reference biologic drug.

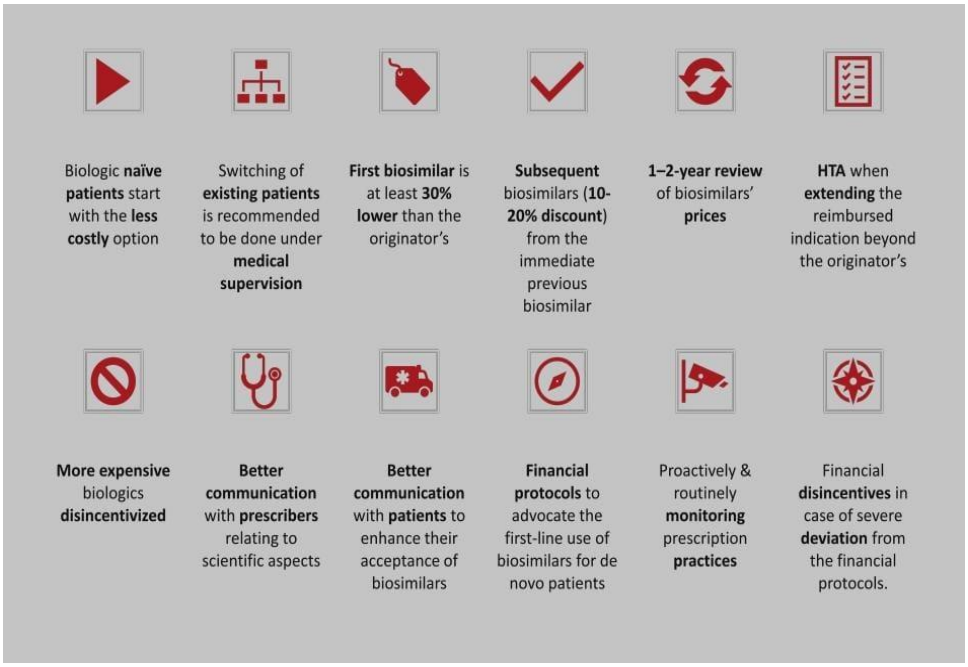
Advantages:

For equal efficacy and safety, biosimilar drugs require much less research and development than their reference biologics, since they are a very similar copy. This means they are much cheaper to produce. The money saved can be reinvested.

1. Similar drugs have same efficacy and safety comes to market
2. Great range of therapeutic choice • Continuity of supply
3. Increased accessibility
4. Development cost and time are relevantly less for biosimilars
5. The margin of profit can be slightly greater than the generic drugs

Disadvantages:

1. Sensitivity of biosimilars is high
2. The difference in the manufacturing cost and the necessary capital amount put in for equipment, plant and property between biosimilars and generics is huge
3. As pharmacopeia monographs do not exist for biosimilars, hence such medicines brought into market and thereby sold, need not abide by the appropriate monograph



CONCLUSION:

The survey results and the workshop have shown a positive attitude of the experts toward using biosimilars. The recommendations reflect the potential of biosimilars to improve spending efficiency within the healthcare system in the UAE. Moreover, the recommendations mostly align with the policies adopted worldwide in high-income countries, aiming to enhance patient access while sustaining healthcare financing and getting headroom for innovation.

REFERENCES:

1. Khalid A. Alnaqbi TW, Michele Pistollato, Kirsty Ross-Stewart, Rowan Saada, Pablo Barquin,Unlocking the Potential of Biosimilars: A Roadmap for Biosimilar Policy Sustainability Biosimilar Policy Landscape & Sustainability Assessment. In. Charles River Associates; 2022.
2. Ahmad Nader Fasseeh BE, Kareem Ahmed El-Fass, Mary GamaI, Ahmed Seyam, Noha Hayek, Nagwan Abdel Rahman, Sohir Abdelhamid, Nader Fasseeh, Amr Shafik, Ahmed Elagamy, Akram Mahmoud, Amal Samir Sedrak,, Khaled Elshazly, Mariam Eldebeiky, Monica Talaat, Noura Maher Mohamed, Rania Ahmed Abdelaziz, Remonda Refaat, Shaimaa Akeel, Sherif Abaza, Zoltán Kaló: Towards Maximizing Benefits of Biosimilars in Egypt: Optimizing the Policy Framework manuscript submitted for publication 2023.
3. Farghaly M, Sara Ahmad MA, Sharma Y, Sultana SS, Mohammed O: EE374 Budget Impact of Adalimumab Sandoz (BIOSIMILAR) in Comparison to Adalimumab- Reference Product in the Management of Autoimmune Diseases in Dubai. Value in Health 2022, 25 (7, Supplement): S408.
4. Hemmington A, Dalbeth N, Jarrett P, Fraser AG, Broom R, Browett P, Petrie KJ: Medical specialists' attitudes to prescribing biosimilars. Pharmacoepidemiol Drug Saf 2017,26(5):570-577.
5. Remuzat C, Kapusniak A, Caban A, Ionescu D, Radiere G, Mendoza C, Toumi M: Supply-side and demand-side policies for biosimilars: an overview in 10 European member states. J Mark Access Health Policy 2017
6. Leader B, Baca QJ, Golan DE. Protein therapeutics: a summary and pharmacological classification. Nat Reviews Drug Discov. 2008; 7: 21–39.
7. Genentech Inc. Corporate Chronology. 1982.
7. http://www.gene.com/gene/about/corporate/history/timeline.html.
8. Global Biopharmaceutical Market Report (2010–2015) IMARC October 29, 2010:234 Pages. Pub ID: IMRC2849563.

9. http://www.icis.com/Articles/2010/02/15/9333235/follobw-on-biologics-presentopportunity-to-big-pharma.htm