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BIOAVAILABILITY AND BIOEQUIVALENCE OF BIOSIMILARS

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ABSTRACT: Biosimilars are the most promising medicines for treating complex diseases. The first biosimilar was approved in India in 2000, and since then, there is no looking back. CDSCO in collaboration with DBT has developed new guidelines in 2012, which were revised in 2016 for pre and post-marketing approval of biosimilars in India. India is one of the leading manufacturers of biosimilars catering to domestic and international market. Soon it will have a vast opportunity to develop more similar biologics as the patent of many biologics is scheduled to expire by the year 2020. India has emerged well in global market of biosimilars. India started its journey with near about US$ 250 million biosimilar market in 2015 and it is estimated to reach around US$ 40 billion in India while US$ 240 billion in world by 2030. Biosimilars are the boon in treating patients.

INTRODUCTION: Biosimilars are the products that are extremely similar to an already existing original biologic, which can be an innovator or brand name product. But unlike a generic product, they are not identical. Biologics are highly effective and very specific medicines made by living cells. These are used to improve health in complex conditions like diabetes, cancer, growth deficiencies etc. Few examples of biologics include hormones, vaccines, growth factors, blood products etc. Biologics are delivered to patients through injections either by subcutaneous or intravenous route. Biologics cannot be administered orally as they become ineffective during the process of digestion. Biosimilar is a biologic product, which is very similar to approved biological product known as reference product with no clinically significant differences in terms of safety and efficacy [1]. The aim of biosimilar development is to demonstrate biosimilarity that is highly similar in terms of biological activity, structure, safety, efficacy, and immunogenic profile [2].

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Difference between Generics, Biologics and Biosimilars:

Generics: Generic medication is created similar to an already marketed brand name in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use. Once the patent expires, other companies can reproduce the same active pharmaceutical ingredient as the original product. After approval from the regulatory bodies like FDA, they can sell this product into the market as a generic product. The innovator product and the generic products are considered to be bioequivalent due to the same API [3].

Biologics: These are very large and complex molecular structures. These are produced by living cells through complex biotechnological processes

using highly specialized ingredients [2]. Biological products include a wide range of products such as vaccines, blood & blood components, allergenic, somatic cells, tissues, and recombinant therapeutic proteins [4]. Biologics are currently preferred specialized products useful in treating critical illnesses, but the major drawback of high cost makes them unaffordable to many patients, especially in developing countries [5].

Biosimilars: A biosimilar or similar biologic can be defined as a biological product that is formed by genetic engineering techniques and is "similar" in terms of safety, efficacy, and quality to the reference biologic [6] but available at a much lower cost. There are inherent variations from batch to batch of a biologic; these changes are secondary and tightly controlled by the manufacturing process within a definite range, so quality is not affected. This is not the same as the differences between the biologic and biosimilar. Because the cell cultures (starting material) and production steps are the exclusive knowledge of the originator, it is not possible for a biosimilar company to accurately replicate the original manufacturing process [7]. It is believed that biosimilars will have a positive impact on drug pricing. This will reduce the overall cost of treatment and enhance accessibility to these life-saving drugs [8]. A research study in the United States of America predicted that over the upcoming ten years, replacing biologics by biosimilars would reduce the cost burden by 54 billion US dollars [1].

The biosimilar must have the same mechanisms of action, routes of administration, dosage forms, strengths and indications as that of reference drug [9].

Comparison of Biologic, Biosimilar and Generic Drugs:

Parameter	Biologic	Biosimilar	Generics
Immunity	Immunogenic	More immunogenic than biosimilar	Negligible immunogenicity
Treatment	Use in cancer, arthiritis, Psoriasis, Anovulation, *etc*.	Use in cancer, arthiritis, Psoriasis, Anovulation, *etc*.	Covers almost all areas of treatment
Cost	Extremely costly	Less costlier than biologic	Affordable
Route of administration	Injection	Injection	Orally (usually)
Preparation	From living cells	From living cells	From chemicals
Structure	Complex	Complex	Defined structure
Cost of development	Extremely high	Lesser than biologic	Extremely low
Stability	Variable - sensitive to temperature and light	Variable - sensitive to temperature and light	Relatively stable
Characterization	Difficult	Difficult	Easy

Status/History: Europe was the first in the world to lay down the guidelines for the approval of biological products [10]. In Europe, the first biologic - NUTROPIN AQ was approved in 2001, manufactured by Ipsen's Pharma used for turner's syndrome, long-term kidney disorders, and as growth hormone. Later in 2006, Sandoz-Novartis got approval for first biosimilar in Europe named OMNITROPE by Europe Medicinal Agency (EMA) [11, 12]. In 1991, United States got its first biologic - filgrastim manufactured by Neupogem used as a granulocyte agent approved by USFDA. The biosimilar of filgrastim was approved in 2015 named filgrastim-sndz manufactured by Sandoz-Novartis [9]. Afterward, USFDA approved a number of biosimilars till date for the treatment of cancer and many other conditions.

Indian System: 'Similar biologics' is the term used by Indian regulatory agencies for biosimilar. Indian companies are taking numerous steps to get involved in global biosimilar market. India got its first biosimilar Biovac-B approved in 2000 and marketed by Wockhardt for hepatitis B although no guidelines were present at that time, it did not get credit of being first [13]. More than 100 Indian biopharmaceutical companies are engaged in the manufacturing and marketing of biosimilars. India has a very flourishing biosmiliar domain in comparison to other countries as Indian Pharmaceutical companies are growing and glowing worldwide.

The approval process of biosimilar requires more data than generic drugs. To address the challenges associated with the development of biosimilars, Central Drugs Standard Control Organization (CDSCO) collaborated with the Department of Biotechnology (DBT) to form the guidelines for the manufacturing, approval and marketing of biosimilars in 2012 and revised them in 2016.

These guidelines address the regulatory requirements, principles for the development of biosimilars, data requirements for preclinical studies, clinical trials application, marketing authorization application and post-marketing surveillance for biosimilars [14]. Principles for the development of biosimilars include the selection of reference biologics, proper manufacturing process and quality comparability studies of biosimilars.

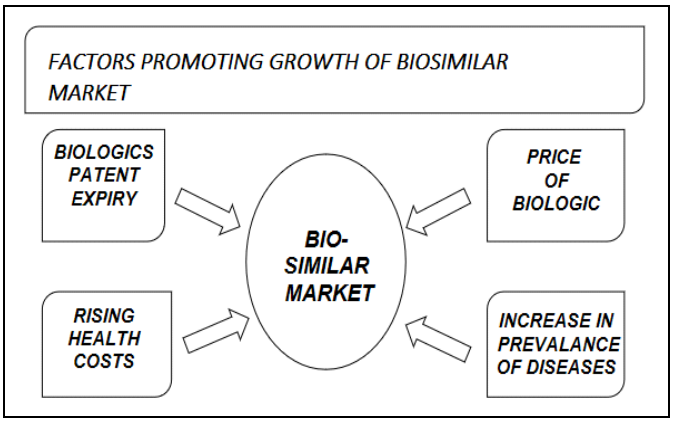

FIG. 1: FACTORS PROMOTING GROWTH OF BIOSIMILAR MARKET

These guidelines also focus upon the regulations related to the quality, efficacy, and safety of biosimilars. CDSCO brought some major changes in its 2012 guidance which is revised in 2016 like [a] Now biologics can be approved either in India or any other international council for harmonization countries (*i.e.*, European Union, Japan, United States, Canada, and Switzerland) but earlier it was important for the reference biologic to be approved in India for manufacturing of its biosimilar in India. It is also align with other international agencies like EMA and WHO. [b] Emphasis on post-marketing studies, CDSCO says, to further reduce the residual risk of biosimilar, phase IV studies must be conducted on minimum 200 patients within 2 years of getting the marketing approval [14].

Switching and Interchangeability: If a patient has a small molecule medication in his prescription, then a pharmacist have the right to substitute a generic version without consulting to the patient's Physician, this is known as interchangeability. Whereas, biosimilars are not interchangeable with the original biologic. Physicians may switch the medication from original biologic to the biosimilar for the economic benefit of patients using available clinical evidence during a consultation. One-time switch of original biologic to biosimilar or reverse is known as switching. This process is reversible if the desired effect with substituted biosimilar is not observed. The switching should be made by the patient during consulting with the physician by using the available clinical evidence [15].

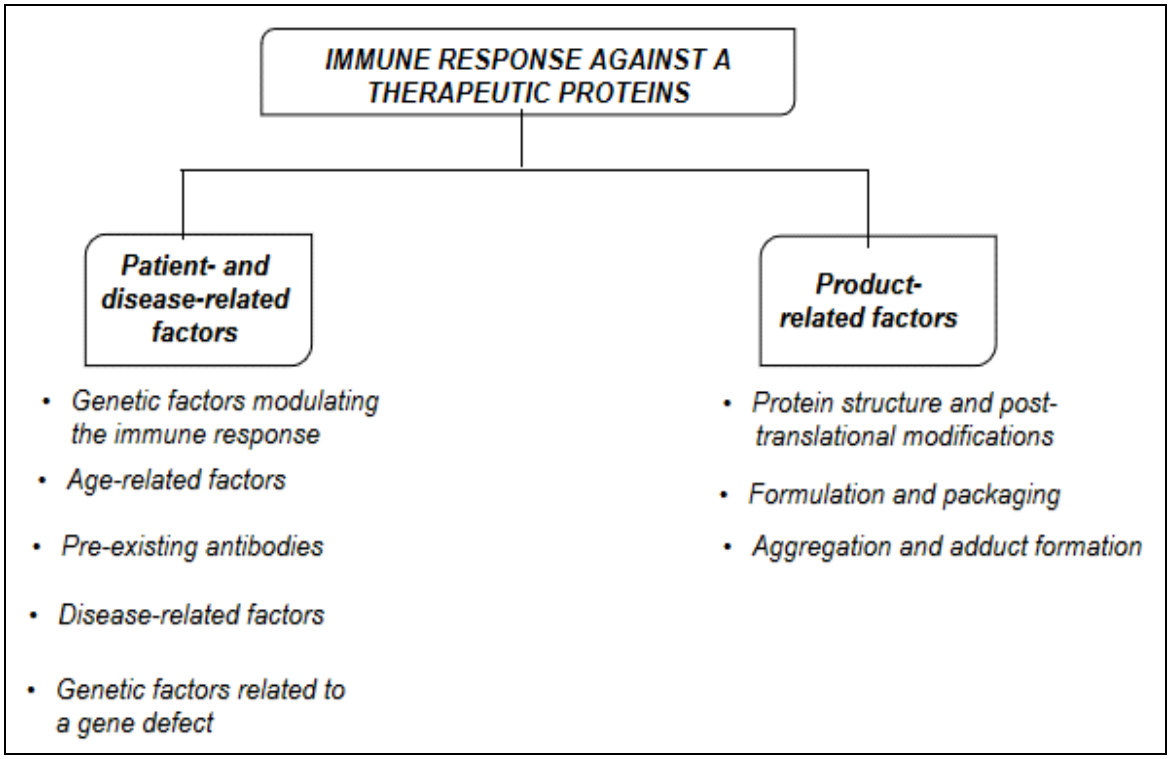

FIG. 2: IMMUNE RESPONSE AGAINST THERAPEUTIC PROTEINS

Immunogenicity: Therapeutic proteins are recognized by the human immune system. Immunogenicity refers to the ability of a drug to induce an immune response in the body. This potentially harmful immune response is complex and, in addition to ADA (Anti-Drug Antibodies) formation, involves T cell activation and innate immune responses [15]. As biosimilars are proteins, they may induce immunogenic reactions in the body. Many patients, disease, and product-related factors may influence the immunogenicity of therapeutic proteins The possibility of these reactions must be discussed before starting the therapy and switching from original biologic to biosimilar or reverse.

Bioavailability: Bioavailability of a drug is defined as the extent and rate to which the active drug ingredient from the drug product is absorbed and becomes available at the site of drug action [16]. Any alteration in the bioavailability of a drug is reflected in its pharmacological effects. The rate and extent of drug absorption are commonly measured by the maximum concentration (C_{max}) and area under the blood or plasma concentration-time curve (AUC). A slower rate of absorption is desired when the aim is to prolong the duration of action or to avoid the side effects. A comparative bioavailability study refers to the comparison of bioavailabilities of different formulations of the same drug or different drug products [17].

Fig. 3 shows that bioavailability depends upon 3 factors -

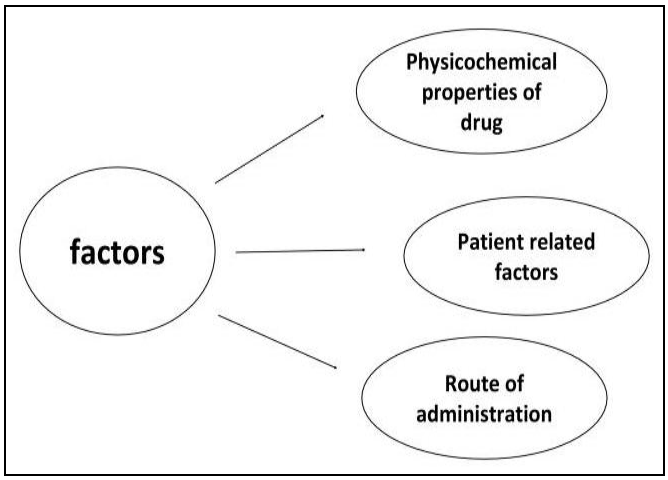

FIG. 3: FACTORS AFFECTING BIOAVAILABILITY

The bioavailability through the parenteral route is maximum as this route bypasses various metabolic processes. The dose available at the site of action is called the bioavailable dose or systemic availability. Bioavailability of drugs depends upon the route of administration. The bioavailability as per route of administration can be -

Parenteral > Oral > Rectal > Topical

The term bioavailable fraction (F), refers to the fraction of administered dose that enters the systemic circulation[18].

F = Bioavailable dose / Administered dose

Bioequivalence: This term denotes that the drug substance in two or more identical dosage forms reaches the systemic circulation at the same relative rate and to the same relative extent, *i.e.*, their plasma concentration-time profiles will be identical without significant statistical differences.

Bio-inequivalence: When statistically significant differences are observed in the bioavailability of two or more drug products [18].

Generic molecule before approval by FDA needs to prove bioequivalence by pharmacokinetic parameters such as area under plasma-concentration time curve (AUC) and peak concentration (C_{max}) which can be provided through bioequivalence studies.

Types of Bioequivalence Studies -

1. *In-vivo* bioequivalence studies
2. *In-vitro* bioequivalence studies

The purpose of establishing bioequivalence is to demonstrate equivalence in quality between the proposed and existing drug product (*e.g.*, generic versus brand, post-change versus pre-change product). Therefore, bioequivalence testing typically eliminates the need for preclinical tests and clinical trials.

Table 1 - 5 threw light on the status of biologics and biosimilars discovered and launched in INDIA, CANADA, JAPAN, the USA, and EUROPE from 2014-2019. All these biosimilars are approved by respective regulatory authorities like USFDA after proving the bioequivalence and toxicity studies.

Table 1- India: Central Drugs Standard Control Organization (CDSCO) and Food and Drug

Administration (FDA) are the drug regulatory bodies of India. In 2012, the guidelines were made by CDSCO in collaboration with the Department of Biotechnology (DBT). According to the guidelines, it was essential that the reference biologic must be approved in India for manufacturing of its biosimilar in India. But these guidelines were further revised in 2016, which state that for manufacturing the biosimilars in India, the biologics can be approved either in India or in any country included in International Council for Harmonization (*i.e.*, European Union, Japan, United States, Canada, and Switzerland) [14]. **Table 1** elaborates the bioavailability, product name, company, year of approval, prices, and therapeutic uses of biologics and biosimilars marketed in India in the span of five years from 2014 to 2019.

Table 2- Canada: Health Canada is a drug regulatory body of Canada. As per Health Canada, biosimilar can enter the market after the expiry of the reference biologic drug's patents and data protection. Health Canada authorizes biosimilars for sale using the same rigorous regulatory standards of quality, efficacy and safety adopted for biologic drugs [15]. **Table 2** elaborates the biovailability, product name, company, year of approval and therapeutic uses of biologics and biosimilars marketed in Canada in the span of five years from 2014 to 2019.

Table 3- Japan: Ministry of Health, Labor and Welfare (MHLW) is a healthcare regulatory body of Japan. The Japanese guideline states that for the development of a biosimilar product, a reference product must be approved in Japan and a single reference product should be used during the development of the biosimilar product [39]. **Table 3** elaborates the biovailability, product name, company, year of approval and therapeutic uses of biologics and biosimilars marketed in Japan in the span of five years from 2014 to 2019.

Table 4- USA: United States Food and Drug Administration (USFDA) is the regulatory body of United States of America. It is the requirement of the USFDA that a manufacturer has to demonstrate the equivalence of the biosimilar with the reference biologic by characterizing the structure and establishing the efficacy. The tests such as purity, chemical identity, and bioactivity are performed to prove the similarity between the biosimilar and reference product. Minor differences like change in buffer or stabilizer between reference product and biosimilar are acceptable if they are not interfering in biological activity [47]. **Table 4** elaborates the biovailability, product name, company, year of approval and therapeutic uses of biologics and biosimilars marketed in USA in the span of five years from 2014 to 2019.

Table 5- Europe: A biosimilar is a biological medicine highly similar to another already approved biological medicine (the 'reference medicine'). Biosimilars are approved according to the same standards of pharmaceutical quality, safety and efficacy that apply to all biological medicines. The European Medicines Agency (EMA) is responsible for evaluating the majority of applications to market biosimilars in the European Union (EU) [49]. **Table 5** elaborates the bio-vailability, product name, company, year of approval and therapeutic uses of biologics and biosimilars marketed in Europe in the span of five years from 2014 to 2019.

Facts and Figures of Biosimilars and its Future: India got its first biosimilar approval in 2000. Indian biosimilar market catering to domestic population was about US $250 million, and export to other countries was about US $50 million in 2015. The compound annual growth rate was about 14% [1]. With the support of legislation and the Indian Government, the Indian biosimilar market continued to grow and reached a value of $2.2bn in 2017. India has strongly established itself in the global biosimilar market as well [59]. In 2018 Reliance Lifesciences topped the global pecking order, followed by Intas and Biocon. According to the Associated Chambers of Commerce of India's 2017 report and based on the analysis of the currently approved biologic drugs, drugs in clinical pipeline, expectations around price erosion, and market penetration, 'Assocham and Sathguru' estimated that the global market for biosimilars would be about $240 billion by 2030 and the Indian domestic market could be about $40 billion [60, 61]. The above facts and the figures exhibit that the biosimilar market would grow multifold in a span of about 10 years. The future of biosimilars is bright, and it is expected to enter the mainstream of therapy.

TABLE 1: BIOLOGICS WITH BIOSIMILARS APPROVED IN INDIA FROM 2014-19 [19-33]

Drugs	Bioavailability and references	Biologic and *references*				Biosimilar and *references*[13]				Therapeutic area [13]
		Brand name	Manu-facturing company	Year of approval	Cost	Brand name	Manufacturing company	Year of approval	Cost	
Rituximab	100 IV[19]	Mabthera/ Rituxan	Roche	November 1997- USFDA[20]	500 mg - Rs 80,000 50 ml inj [21]	Maball	Hetero Group	2015	500 mg- Rs 30,285 for 50 ml inj	Non-Hodgkin lymphoma, Chronic B-cell lymphocytic leukaemia
						Rituxirel	Reliance Lifesciences	2015	500 mg - Rs 38,541	
						Acellbia	Biocad	2017	-	
Infliximab	92 IV[22]	Remicade	Janssen Biotech	August 1998- USFDA [23]	Powder for inj - Rs 41,039	Infimab	Epirus Biopcentical	2014	Powder for inj - Rs 32,000	Ankylosing spondylitis, Crohn's disease, Psoriasis, Psoriatic arthritis, Rheumatoid arthritis, Ulcerative colitis
Etanercept	76 SC[24]	Enbrel	Amgen and Wyeth Pharmaceuticals	November 1998- USFDA[25]	50 mg - Rs 17170 for 10 ml	Intacept	Intas Pharmaceuticals	2015	50 mg - Rs 10390 for 1 ml	Ankylosing spondylitis, Juvenile idiopathic arthritis Psoriasis, Psoriatic arthritis, Rheumatoid arthritis
Darbepo-etinalfa	47 SC[26]	Aranesp	Amgen	2001 USFDA [27]	-	Darbatitor	Torrent pharmaceuticals	2014	60 mcg - Rs 4505 for 1 ml inj	Anaemia, Cancer, Chronic kidney failure
						Actorise	Cipla/Hetero	2014	60 mcg - Rs 3500 for 1 ml inj	
Adalimumab	64 SC[28]	Humira	AbbVie	December 2002 USFDA[29]		Exemptia	Zydus Cadila	2014	40 mg/ 0.8 ml - Rs 25000	Ankylosing spondylitis, Plaque psoriasis, Psoriatic arthritis, Rheumatoid arthritis, Ulcerative colitis
						Adfrar	Torrent Pharmaceuticals	2016	40 mg/ 0.8 ml - Rs 25000	
Ranibizumab	50-60 ITV INJ[30]	Lucentis	Novartis	2006 USFDA[31]	0.5 mg/1 ml - Rs 70160	Razumab	Intas Pharmaceuticals	2015	2.3 mg / 1 vial - Rs 17000	Wet macular degeneration, Macular edema, Degenerative myopia, Diabetes complications
Bevacizumab	50-100 SC[3]	Avastin	Roche	February 2004 - USFDA[33]	400 mg/16 ml - Rs 1,16,000	Bevacirel	Reliance Lifesciences	2016	400 mg/16 ml - Rs 38,856	Colorectal cancer

TABLE 2: BIOLOGICS AND BIOSIMILARS APPROVED IN CANADA FROM 2014-19 [34-38]

Drug	Bioavailability (%)	Biologic and reference			Biosimilar and reference [34]			Therapeutic Area [34]
		Product	Company	Year of approval	Product	Company	Year of approval	
Infliximab	92 IV[22]	Remicade	Janseen biotech	August 1998- USFDA[23]	Remsima	Celltrion	2014	Ankylosing spondylitis, Crohn's disease, Psoriatic arthritis, Psoriasis, Rheumatoid arthritis, Ulcerative colitis
					Inflectra	Hospira	2014	
					Renflexis	Samsung Bioepis	2018	
Filgrastim	69.1 IV[35]	Neupogen	Amgen	1991 USFDA [36]	Grastofil	Apotex	2015	Neutropenia
Etanercept	76 SC[24]	Enbrel	Amgen and Wyeth Pharmaceuticals	November 1998- USFDA [25]	Brenzys	Merck Canada	2016	Ankylosing spondylitis
					Erezi	Sandoz	2017	Rheumatoid arthritis
Pegfilgrastim	80 SC[37]	Neulasta	Amgen	January 2002-	Lapelga	Apotex	2018	Neutropenia

				USFDA [38]				
Adalimumab	64 SC[28]	Humira	AbbVie	December 2002 USFDA [29]	Hadlima	Samsung Bioepis	2018	Rheumatoid arthritis
Bevacizumab	50-100 SC[32]	Avastin	Roche	February 2004 USFDA[33]	Mvasi	Avastin	Roche	Colorectal cancer

TABLE 3: BIOLOGICS AND BIOSIMILARS APPROVED IN JAPAN FROM 2014-19 [40-46]

Drug	Bioavailability and references	Biologic and references			Biosimilar and references [40]			Therapeutic area[40]
		Product	Company	Year of approval	Product	Company	Year of approval	
Infliximab	92 IV[22]	Remicade	Janssen Biotech	August 1998-USFDA[23]	Remsina [Infliximab biosimilar 1]	Celltrion/Nippon Kayaku	2014	Ankylosing spondylitis, Crohn's disease, Psoriatic arthritis, Psoriasis, Rheumatoid arthritis, Ulcerative colitis
					Remsina [infliximab biosimilar 2]	Nichi-Iko Pharmaceutical/ Yakuhan Pharmaceutical	2017	
					Remsina [infliximab biosimilar 3]	Pfizer Japan	2018	
Filgrastim	69.1 IV[35]	Neupogen	Amgen	1998 USFDA[36]	Filgrastim BS [filgrastim biosimilar 3]	Pfizer Japan	2018	Neutropenia
Etanercept	76 SC[24]	Enbrel	Amgen & Wyeth Pharmaceuticals	November 1998USFDA[25]	Etanercept BS [etanercept biosimilar 1]	Mochida Pharmaceutical	2018	Ankylosing spondylitis, Rheumatoid arthritis
Rituximab	100 IV[19]	MabThera/Rituxan	Roche[20]	November1997 USFDA[21]	Rituximab BS [rituximab biosimilar 1]	Sandoz	2017	B-cell non-Hodgkin's lymphoma, B-cell lymphoproliferative disorder, Microscopic polyangiitis, Wegener's granulomatosis
Insulin glargine	73 SC[41]	Lantus	Sanofi-Aventis	April 2000-USFDA[42]	Insulin glargine BS [insulin glargine biosimilar 1]	Eli Lilly/ Boehringer Ingelheim	2014	Diabetes
					Insulin glargine BS [insulin glargine biosimilar 2]	Biocon/Fujifilm Pharmav	2016	
Trastuzumab	77 SC[43]	Herceptin	Roche	September 1998- USFDA[44]	Trastuzumab BS [trastuzumab biosimilar 1]	Celltrion	2018	HER2+ gastric cancer HER2+ breast cancer
					Trastuzumab BS [trastuzumab biosimilar 2]	Daiichi Sankyo	2018	
Darbepoetin alfa	47 SC[26]	Aranesp	Amgen	September 2001 USFDA [27]	Darbepoetin alfa injection syringe [KKF]	Kyowa Hakko Kirin	2018	Anaemia
					Darbepoetin alfa (CKD11101)	Chong Kun Dang Pharmaceutical	2018	
Agalsidase beta	100 IV infusion [45]	Fabrazyme	Sanofi	April 2003-USFDA [46]	Agalsidase Beta BS [JCR]	JCR Pharmaceuticals	2018	disease

TABLE 4: BIOLOGICS AND BIOSIMILARS APPROVED IN USA FROM 2014-19 [48]

Drug	Bioavailability and references	Biologic			Biosimilar and references [48]			Therapeutic area[48]
		Product	Company	Year of approval	Product	Company	Year of approval	
Infliximab	92 IV[23]	Remicade	Janssen Biotech	August 1998- USFDA[23]	Inflectra	Celltrion	2016	Ankylosing spondylitis, Crohn's disease, Psoriatic arthritis, Psoriasis, Rheumatoid arthritis, Ulcerative colitis
					Renflexis	Samsung Bioepis	2017	
					Ixifi	Pfizer	2017	
Pegfilgrastim	59 SC[37]	Neulasta	Amgen	January2002- USFDA[38]	Udenyca	Coherus BioSciences	2018	Febrile neutropenia
Filgrastim	89 IV[35]	Neupogen	Amgen	1998 USFDA[36]	Zarxio	Sandoz	2015	Autologous peripheral blood progenitor cell collection and therapy, Bone marrow transplantation, Cancer, Myeloid leukaemia Neutropenia
					Nivestym	Pfizer	2018	
Rituximab	100IV[19]	MabThera/ Rituxan	Roche[20]	November 1997- USFDA[21]	Truxima	Celltrion	2018	Non-Hodgkin lymphoma
					Ruxience	Pfizer	2019	
Etanercept	76 SC[24]	Enbrel	Amgen and Wyeth Pharmaceuticals	November 1998-USFDA[25]	Erelzi	Sandoz	2016	Juvenile idiopathic arthritis Rheumatoid arthritis
					Eticovo	Samsung Bioepis	2019	
Trastuzumab	77 SC[43]	Herceptin	Roche	September 1998- USFDA[44]	Ogivri	Mylan GmbH	2017	HER2 breast cancer HER2 metastatic gastric or gastroesophageal junction adenocarcinoma
					Herzuma	Celltrion	2018	
					Ontruzant	Samsung Bioepis	2019	
					Trazimera	Pfizer	2019	
					Kanjinti	Amgen	2019	
Adalimumab	64 SC[28]	Humira	AbbVie	December 2002- USFDA[29]	Hyrimoz	Sandoz	2018	Ankylosing spondylitis, Crohn's disease, Juvenile arthritis, Psoriatic arthritis, Psoriasis, Rheumatoid arthritis, Ulcerative colitis
					Cyltezo	Boehringer Ingelheim Pharmaceuticals	2017	
					Hadlima	Samsung Bioepis	2019	
					Amjevita	Amgen	2016	
Bevacizumab	93 IV[32]	Avastin	Roche	February 2004-USFDA[33]	Mvasi	Amgen	2017	Cancers of lung, colon, rectum, cervix, ovary, or fallopian tube, metastatic breast cancer, kidney and brain (glioblastoma) cancers
					Zirabev	Pfizer	2019	

TABLE 5: BIOLOGICS AND BIOSIMILARS APPROVED IN EUROPE FROM 2014-19 [50-58]

Drug	Bioavailability & Reference	Biologic And reference			Biosimilar and reference[50]			Therapeutic Area [50]
		Product	Company	Year of approval	Product	Company	Year of approval	
Infliximab	92 IV[22]	Remicade	Johnson & Johnson and Merck	August 1998- USFDA[23]	Flixabi	Samsung Bioepis	2016	Ankylosing spondylitis, Crohn's disease, Psoriatic arthritis, Psoriasis, Rheumatoid arthritis, Ulcerative colitis
					Zessly	Sandoz	2018	
Pegfilgrastim	80 SC[35]	Neulasta	Amgen	January 2001	Ziextenzo	Sandoz	2018	Neutropenia

				USFDA[36]				
Follitropin alfa	66-76 [51]	Gonal-F	Serono	May 2004 USFDA[52]	Bemfola	Finox	2014	Anovulation (IVF)
Teriparatide	95 [53]	Forteo/ Forsteo	Eli Lilly	November 2002- USFDA[54]	Terrosa	Gedeon Richter	2017	Osteoporosis
					Movymia	STADA Arzneimittel	2017	
Rituximab	100 IV[19]	MabThera/ Rituxan	Roche[20]	November 1997- USFDA[21]	Rixathon	Sandoz	2017	Non-Hodgkin lymphoma
					Truxima	Celltrion	2017	
					Riximyo	Sandoz	2017	
Etanercept	76 SC[24]	Enbrel	Amgen and Wyeth Pharmaceuticals	November 1998 USFDA[25]	Erelzi	Sandoz	2017	Juvenile idiopathic arthritis, Rheumatoid arthritis
					Benepali	Samsung Bioepis	2016	
Trastuzumab	77 SC[43]	Herceptin	Roche	September 1998 USFDA[44]	Ontruzant	Samsung Bioepis	2017	HER2 breast cancer
					Herzuma	Celltrion Healthcare	2018	HER2 metastatic gastric or gastroesophageal junction adenocarcinoma
					Kanjinti	Amgen	2018	
					Ogivri	Biocon	2018	
					Trazimera	Pfixer	2018	
Adalimumab	64 SC[28]	Humira	AbbVie	December 2002 USFDA[29]	Cyltezo	Boehringer Inglheim	2017	Ankylosing spondylitis, Crohn's disease, Juvenile arthritis, Psoriatic arthritis, Psoriasis, Rheumatoid arthritis, Ulcerative colitis
					Imraldi	Samsung Bioepis	2017	
					Amgevita	Amgen	2017	
					Solymbic			
					Halimatoz	Sandoz	2018	
					Hefiya	Sandoz	2018	
					Hulio	Mylan	2018	
					Hyrimoz	Sandoz	2018	
					Kromeya	Fresenius kabi	2019	
Bevacizumab	93 IV[32]	Avastin	Roche	February 2004 USFDA[33]	Mvasi	Amgen	2018	Cancers of lung, colon, rectum, cervix, ovary, or fallopian tube, metastatic breast cancer, kidney and brain (glioblastoma) cancers
					Zirabev	Pfizer	2019	
Pegfilgrastim	80 SC[37]	Neulasta	Amgen	January2002 USFDA[38]	Udenyca	ERA Consulting	2018	Neutropenia
					Pelmeg	Mundipharma	2018	
					Pelgraz	Accord Healthcare	2018	
Insulin lispro	55-77 SC [55]	Humalog	Eli Lilly	USFDA [56]	Insulin Lispro Sanofi	Sanofi	2017	Diabetes mellitus
Insulin glargine	73 SC[24]	Lantus	Sanofi	April 2000 USFDA[42]	Abasaglar	Eli Lilly	2014	Diabetes
					Lasduna	Merck	2017	
Enoxaparin sodium	90 SC[57]	Clexane	Aventis	Janurary 2008 MHLW[58]	Inhixa	Techdow Europe AB	2016	Venous thromboembolism
					Thorinane	Pharmathen S.A	2016	

CONCLUSION: Biosimilars are the low-cost, highly effective, genetically engineered versions of biologics used for treating complex diseases like diabetes and cancer. Biosimilars are the order of the day all over the world and are developing at a fast pace to ensure high efficacy with clinical safety while treating complex disorders. Governments all over the world are supporting them for the benefit of mankind.

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