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Comparison Of Global Regulatory Approvals For Biosimilar Products

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Abstract: Biosimilars is a term used to describe officially-approved subsequent versions of innovator biopharmaceutical products made by a different sponsor following patent and exclusivity expiry on the innovator product. The purpose of this article is that an uncertainty over terminology on 'Biosimilars' has led to concerns about patient safety due to misleading published reports on its apparent ills. Therefore, a comparison is made among the different regulatory approvals globally with intend of achieving harmony in regulations and escalating entree to safe medicines globally. Every country should have a guideline for evaluation of Biosimilars, which should be a very similar approach to that described in the WHO guidelines.

Some instances have occurred:
A case of pure red cell aplasia (PRCA) in later stages of adrenal disease patient associated with stimulation of antibodies to administered erythropoietin (EPO) was seen in India. The patient had taken the EPO product Wepox (Wockhardt Limited, India) that is referred to as a 'follow on' product. However, there is no evidence that this product has been approved using the comparability approach required in the EU for Biosimilarity and described in the WHO and other guidelines. [1] Biosimilar path approval, cleared by the U.S. Supreme Court ruling on June 28, 2012, swept the largest biologics market worldwide to vicious competition. Effective implementation of the Biosimilars pathway will be compared across multiple geographies in selected case studies. The significance of proper analytical data, stepwise approach, exclusivity period and origin of the reference product were discussed in this article. [2]

Key words: Biosimilarity, Comparability, Exclusivity Period, Stepwise Approach, Innovator Product.

INTRODUCTION:

A biological medicine is a medicine whose active ingredient is prepared by or derivative of a living organism. E.g. Insulin is being produced from a living organism such as bacterium or yeast, which has been given the gene that enables it to produce insulin.

A Biosimilar medicine is analogous to a biological medicine that has already been approved (the 'biological reference medicine').The active ingredient of a Biosimilar medicine is analogous to the biological reference medicine. Biosimilar and biological reference medicines are given in general at the same dose to treat the same disease. In view of the fact that Biosimilar and biological reference are similar but not identical, the verdict to treat a patient with a reference or a Biosimilar medicine should be taken according to the opinion of a qualified healthcare professional. [3]

In some cases the term "Biosimilar has been used in an inapt way and consequently it is important to review disparity in definitions of Biosimilar products in different expanse.

The different terminologies used for the term Biosimilars and its definitions were discussed briefly in Table 1.

Based on these different definitions, it was interpret that there are three determinants in the definition of the Biosimilar product:

i. It should be a biologic product;

ii. The reference product should be an previously licensed biologic product;

iii. The demonstration of high similarity in safety, quality, and efficacy is obligatory.

Besides, it is well recognized that the similarity should be confirmed using a set of inclusive comparability exercises at the quality, non-clinical and clinical level. The products which are not authorized by this comparability regulatory pathway cannot be called as Biosimilars. [4], [5]

Table 1: Different terminologies used for the word Biosimilars

Term	By	Definition
Similar Biotherapeutic products	WHO	A Biotherapeutic product to an already licensed reference Biotherapeutic product in terms of quality, safety and efficacy
Follow on protein products or Follow on biologics	USFDA Japan	A product highly similar to the reference product without clinically meaningful differences in safety, purity and potency
Subsequent entry biologics	Canada	A biologic drug that enters the market subsequent to a version previously authorized in Canada with demonstrated similarity to a reference biologic drug
Biosimilars	EMEA Korea India China Australia	Biological products which demonstrated its equivalence to an already approved reference product with regard to quality, safety, and efficacy

DISCUSSION:

Like all other drugs, a Biosimilar medicine requires to receive a marketing authorization before it can be marketed. The marketing authorization is granted by different regulatory authorities in different countries as mentioned in Table 2. [6], [7], [8], [9], [10]

Novel medicines profit from a period of market exclusivity under patent law and from a period of data protection following the pharmaceutical legislation. After expiry of this stretch, companies can obtain a marketing authorization for a Biosimilar medicine. As the biological reference medicine has been authorized for several years, there is available information, which does not need to be replicated. The legislation describes the studies that need to be carried out to illustrate that the Biosimilar medicine is akin and as safe and effective as the biological reference medicine.

Due to the intricate method of manufacture of biological medicines, the active substance may differ a little between the biological reference and the Biosimilar medicine. Hence, studies comparing the two medicines have to be carried out. These studies involve a step-by-step process initially with a comparison of the quality, consistency of the medicinal product and of the manufacturing process. Studies are also done to compare the safety and efficacy of the medicines. The studies conducted should demonstrate that the there are no evocative differences between the Biosimilar and the biological reference medicines in terms of safety or efficacy. When the biological reference medicine is used to treat different diseases the efficacy and safety of the Biosimilar medicine may also have to be considered using specific tests or studies for each disease. [11], [12], [13]

Table 2: Different Regulatory authorities of various countries approving Biosimilars

Country	Regulatory authority
European union	European medical agency (EMEA)
United states	United states food and drug administration (USFDA)
Canada	Health Canada
Australia	Therapeutic goods administration (TGA)
China	China's state food and drug administration
India	Indian ministry of health and family welfare and science and technology.

Biosimilar medicines are produced by following the same quality standards as all other medicines. Regulatory authorities also do the periodic inspections of the manufacturing sites.

- The stepwise approach for demonstrating the Biosimilarity between the developing nations like Europe and US and the under developing nations like India were compared in Table 3.
- The comparison of the origin of the reference product in Europe, US and India was said briefly in Table 4.
- The requirement of safety and efficacy needed for comparative clinical trials studies was contrasted for Europe, US and India in Table 5.
- The exclusivity period is different for different regulations like Europe, US and India as mentioned in the Table 6.[14]

Table 3: Stepwise approach to demonstrating Biosimilarity

EUROPE	U.S.	INDIA
"A stepwise approach should be undertaken to justify any differences in the quality attributes of the similar biological medicina product versus the reference medicinal product in order to make a satisfactory justification of the potential implications with regard to the safety and efficacy of the product." CHMP/BWP/49348/2005 at 5.	A stepwise approach to demonstrating Biosimilarity, which can include a comparison of the proposed product and the reference product with respect to structure , function, animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD), clinical immunogenicity, and clinical safety and effectiveness Guidance "Scientific Considerations" at 2.	Similar biologics are developed through sequential process to demonstrate the similarity by extensive characterization studies revealing the molecular and quality attributes with regard to the reference biologic. Indian Guideline at 5.

Table 4: Origin of the Reference Product

EUROPE	U.S.	INDIA
No provision for non-EMA licensed reference products.	**"**To obtain licensure… a sponsor must demonstrate that the proposed product is Biosimilar to a single reference product that previously has been licensed by FDA… However, under certain circumstances, a sponsor may seek to use data derived from animal or clinical studies comparing a	Licensed in India or in "similar biologic can only be developed against an authorized reference biologic that has been approved using a complete data package in India. In case the reference biologic is not authorized in India, it should have been licensed and marketed for at least 4 years with significant

	proposed product… In such a case, the sponsor should provide adequate data or information to scientifically justify the relevance of this comparative data to an acceptable bridge to the US-licensed reference product." Guidance for industry in Demonstrating Biosimilarity to a Reference Product at 6.	safety and efficacy data."Indian Guidelines at 3. "The products, where the reference biologic is not authorized in India shall be

Table 5: Requirement of safety and efficacy trials

EUROPE	U.S.	INDIA
"Usually comparative clinical trials will be necessary to demonstrate clinical comparability between the similar biological and the reference medicinal product." EMEA/CHMP/BMWP/42832/2005 AT 6.	**"**As a scientific matter, comparative safety and effectiveness data will be necessary to support a demonstration of Biosimilarity if there are residual uncertaininties about the Biosimilarity of the two products based on structural and functional characterization , animal testing human PK and PD data, and clinical immunogenicity assessment. A sponsor may provide a scientific justification if it believes that some or all of these comparisons on clinical safety and effectiveness are not necessary."	Potential for omission of safety and efficacy trials. See quote above.

Table 6: Exclusivity Period

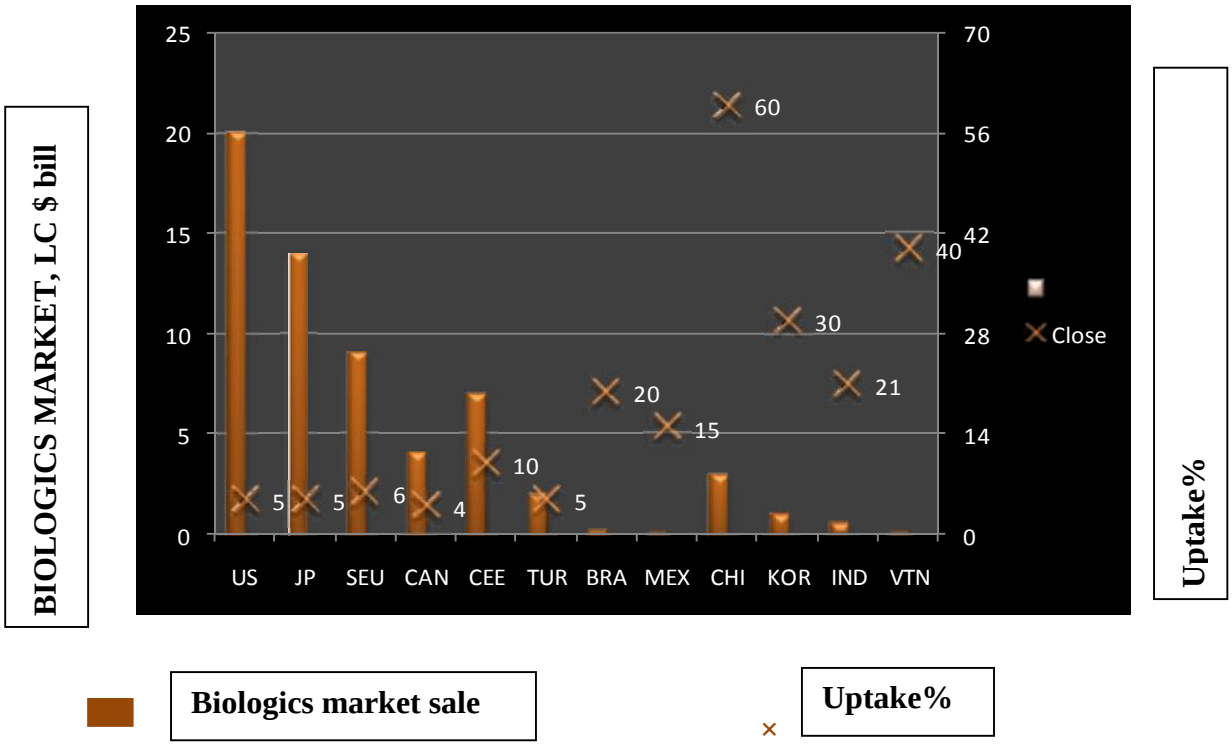
EUROPE	U.S.	INDIA
"8+2+1." A Biosimilar application may not be filed until 8 years after the reference approval. A Biosimilar may not be approved until 10 years after reference approval. The market exclusivity may be extended by an additional year if the reference product sponsor obtains approval for a second significant new indication during the data exclusivity period.	A section (k) application may not be filed until 4 years after reference product approval. A Biosimilar may not be approved until 12 years after reference product approval. 42 USC 262(k)(7).	India provides for no market exclusivity period beyond patent rights.

Market potential of Biosimilars:

The market potential of Biosimilars in different geographical regions was depicted in Graph 1.

Geologically, the market for biologics and Biosimilars falls into three divergent clusters: the US, the other advanced economies (Europe, Japan and Canada) and the pharma-emerging markets. The US accounts for most of the global spending on biologics and will be a key driver of resilient Biosimilars market potential. The progressive economies have the benefit of an established framework for Biosimilars but to date uptake has been deliberate; Europe is the most advanced. Some of the sharp growth rates for biologics are currently observed in the pharmerging markets, and where a large extent of the growth will be found. Biosimilars guidelines in Japan have been recently established and abide by the principles of EU framework. [15]

Graph 1: Market potential of Biosimilars in different geographical regions



Market attractiveness scoring and solutions:

Biosimilars fill an inimitable place depending on whether the market is regulated, semi-regulated or unregulated. In each of these markets, there are a number of issues that companies should consider before endeavor to set up production or market a product and this was clearly differentiated in Table 7.

Market and competitive demands for Biosimilars vary from country to country, but may be broadly categorized according to countries that are:

I. Regulated markets
   - US – 0 approved products
   - EU ~ 14 approved products

II. Semi Regulated markets
   - China ~ 2000 marketed products
   - India ~ 50 approved products [16]

Table 7: Market attractiveness scoring and solutions

Parameter	Regulated markets	Semi-Regulated markets	Un-regulated markets	Market solution
Cost of R&D/ Production	Unfavorable	Favorable	Favorable	As market matures, international companies should shift R&D/ Production to semi- regulated markets
Manufacturing and Clinical Trial Capabilities	Favorable	neutral	Unfavorable	MNCs are pursuing partnerships with firms in low cost locations, for access to low cost manufacturing capabilities
Government Support of Industry	neutral	Favorable	Neutral	Numerous Biosimilars companies are coming up in countries with supportive governments for the sector such as India
Regulatory Rigidity	Unfavorable	neutral	Favorable	Pharmaceutical giants are navigating difficult regulatory paths in developed markets, while smaller companies are targeting developing countries
Attractiveness of Biosimilars to Physician/ Consumers	Favorable	neutral	Unfavorable	Due to the size and market potential of US and Europe, companies are patiently waiting for higher product adoption, while also aggressively marketing to developing countries

Core therapies for biologics:

The constraint to find cost –effective alternative to biologics manifest the growing demand for the complex drugs such as recombinant insulins, human growth harmone (HGH), alteplase, erythropoietins (EPOs), granulocyte colony stimulating factors (G-CSFs) and then monoclonal antibodies (MABs) and it was shown in Graph 2. Currently Biosimilars credit for 16% of global pharmaceutical expenditure and appreciably out- pacing total branded sales; biologics will contribute to smash the global market as more innovative products alternative new treatment options for a growing scope of indications.

Numerous top selling brands, including Herceptin, Humalog, Mabthera, Remicade and Aranesp, are due to the expiry of their product patent protection over the next five years, opening up a wealth of new possibilities for Biosimilar players. Cancer, diabetis and rheumatoid arthritis (RA) are the key therapy areas that will spearhead this new trend of Biosimilars, with contemplation focused on the real cost of anti-TNF MABs, MABs for oncology, and insulins.

Biosimilars market evolution, 2010-2020:

The rise in the market evolution of Biosimilars from 2010 to 2020 was notified in Graph 3. Accordingly the following aspects are expected to happen in the near future

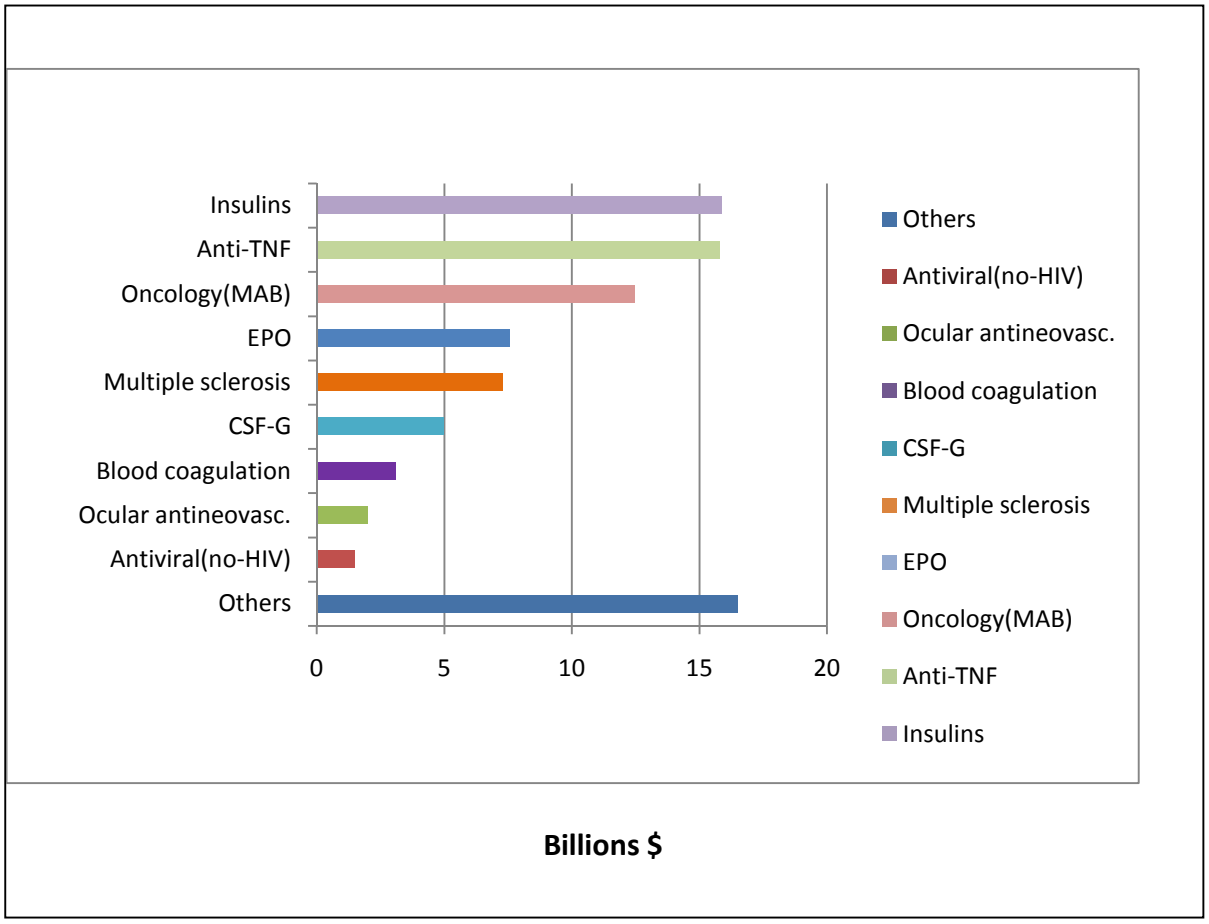
2015 1, 9-2, 6 Bil US$ -

- Gradual uptake in the US due to new legislation enabling innovators to setback the approval process of novel Biosimilars
- Uptake in Europe hasten due to more mature framework
- Emerging countries (Asia specifically) ramping up

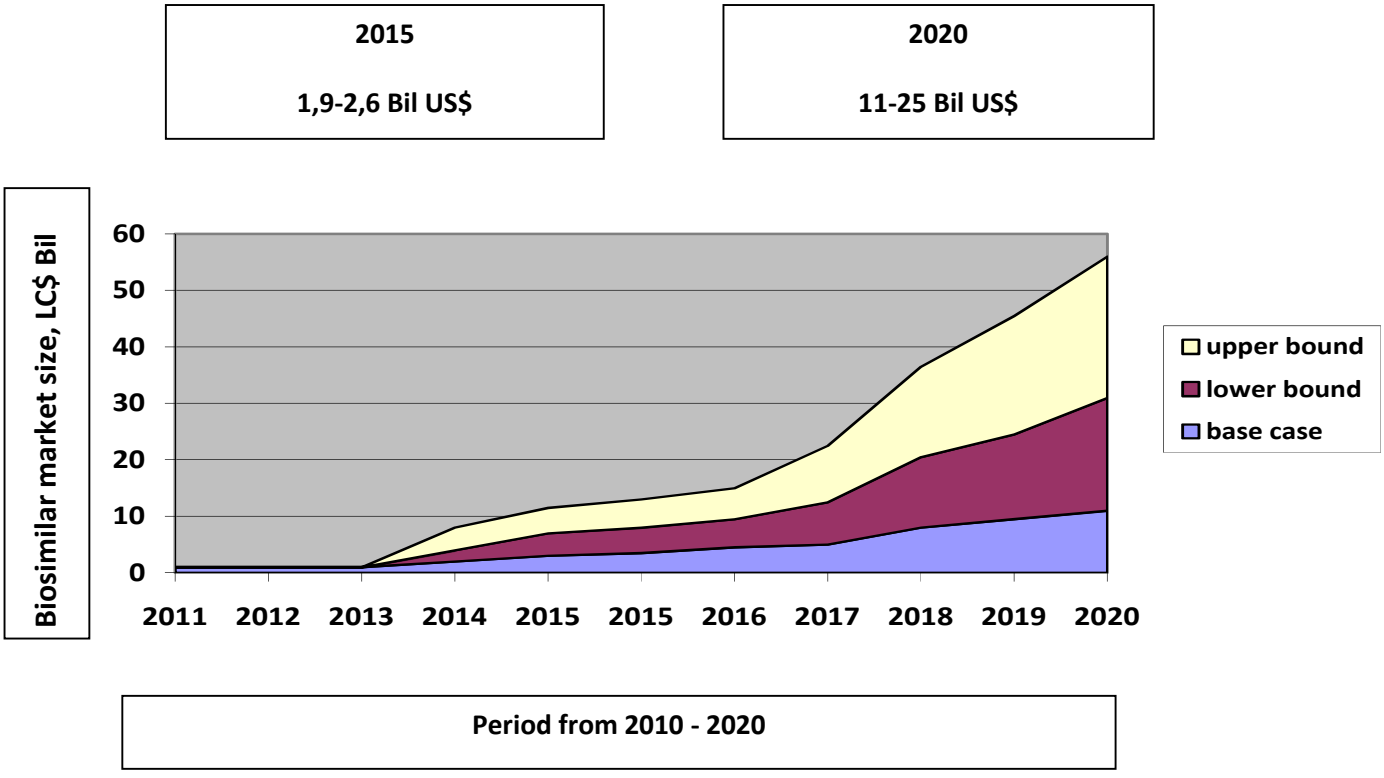
2020 11-25 Bil US$ -

- Key upside drivers epitomize the US market

Graph 2: Core therapy areas for biologics



Graph 3: Biosimilars market evolution 2010-2020



Among the three main geographic clusters, several distinguishing factors will impact the value generation prospect for Biosimilars was compared in the Table 8**,** including ease of usage in the short term, velocity of uptake, transparency of regulation and, particularly, the duty of public and private stakeholders. In view of that, most of the immediate value will be gathered from the pharmerging markets, spurred by the predictable flow of new patients.

Table 8: Distinguishing the market evolution in different geographical clusters

U.S.	EUROPE	PHARMERGING MARKETS
The core upside driver of Biosimilars value in 2020 is uptake in the US long-term (2014-2015), unlocking market potential and economies of scale. Any limitations on this, for example due to regulations favoring innovator companies, will drive down the likelihood of significant growth.	Late-adopting major EU markets suchas Spain and Italy will need to follow Germany in terms of Biosimilars uptake to follow Germany in terms of maximize prospects for growth; it is possible that physician and prayer resistance may impede this, negatively impacting the 2020 outlook.	Growth is also dependent on the pharmerrging countries becoming player in terms of both manufacturing and market size. The more moderate spread of Biosimilars in developing markets and any shortfall in quality standards that prevents these countries from materializing as leading exporters could impact overall potential.

Volume effect:

There is potential for a momentous volume effect on biologics consumption, as pragmatic with G-CSF in the UK and Sweden. Physicians enthused G-CSF back in 1st line cancer treatment owed to lower Biosimilars cost. G-CSF averts hospital readmission owed to infections. This could escalate Biosimilars market growth significantly or equally constrain it should uptake be insufficient to produce a spill-over incentive.

As shown in the Graph 4 by G-CSF granulocyte colony stimulating factor and SU somatotropin uptake the introduction of Biosimilars has generated a spillover effect on off-patent biologic molecules. [15]

Companies of different countries to watch:

There are huge numbers of companies already racing for position and challenging in this space. These companies array in size from petite startups to major generic manufacturers, and most of them are situated in Europe and India. The various companies that are launching the Biosimilar products are given in the Table 9.

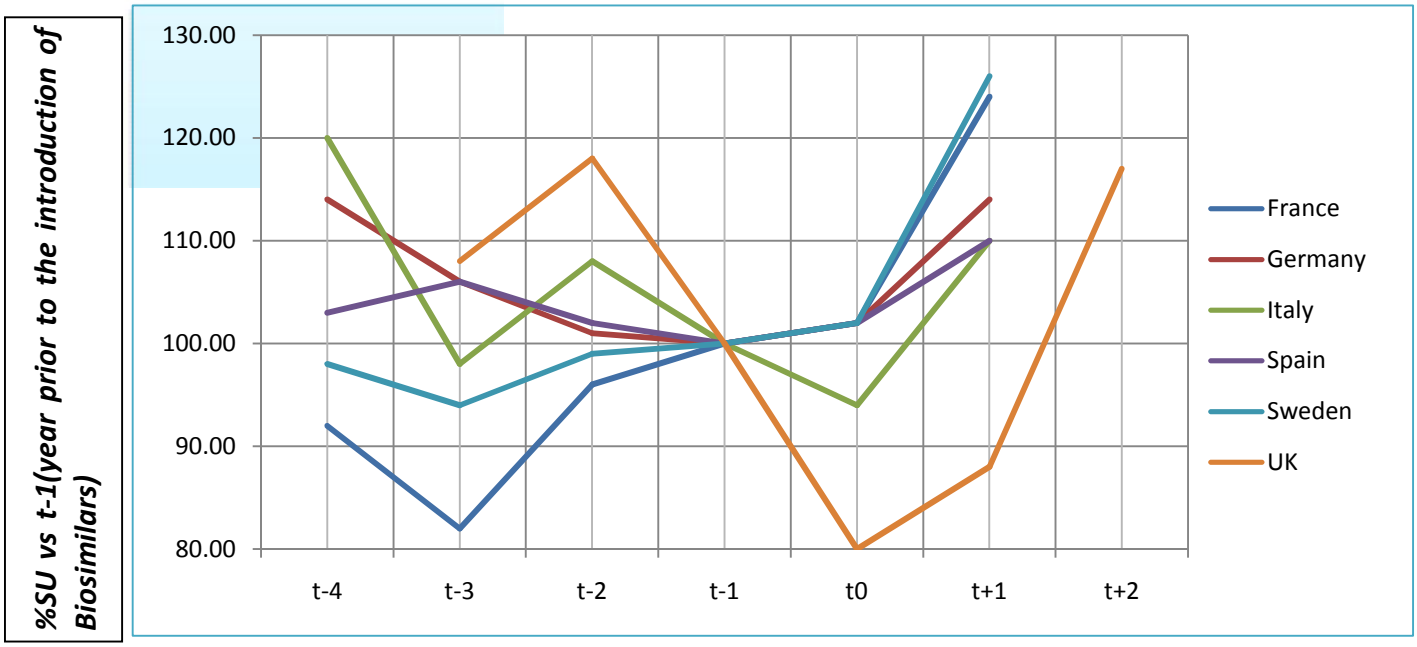
A glance of major companies producing Biosimilar product was given below:

- Switzerland- based Sandoz was the foremost company to come into the Biosimilar market. The company previously approved products in Austarlia, Europe and the United States. Banocrit (epoetin alfa) and Zarzio (filgrastim) have conventional marketing authorization in the EU, and Omnitrope (somatrophin) is accepted in both Europe and the United States (even though Omnitrope, which received FDA approval in 2008, isn't legally considered a Biosimilar).Despite the fact that the company thinks in developing the monoclonal antibodies as it has major opportunities.
- Merck's MBV is a new competitor to the Biosimilar market. Merck's 2006 acquisition Glycofi's humanized yeast platform and its recent purchase of Insmed, a small Richmond, VA-based Biosimilar start-up, provide MBV with the technical qualifications and a product assortment in Biosimilar market. It anticipates in developing as many as 12 FOBs by 2017. While MBV aspires to commercialize its FOBs as rapidly as possible, Merck publicly supports the 12- year exclusivity period will emerge in final U.S Biosimilar legislation.
- Teva was one of the companies to be acquainted with the lucrative business opportunity in Biosimilars. Teva received European approval of a generic translation of filgrastim called Tevafilgrastim in 2008 and also has a number of other products in development. Teva need proficiency in biopharmaceutical

drug development and biomanufacturing. Recognizing this constraint the company is bequeathed into a joint venture with Lonza to develop, manufacture, and market a portfolio of Biosimilars.

- Despite the fact that MBV, Sandoz, and Teva appear to be primitive heads in the emerging Biosimilar/ FOB industry, various smaller European companies like Hexal and Ratiopharm and several Indian companies including Biocon, Dr.Reddy's laboratories, and Ranbaxy, shouldn't be ignored. [17]

Graph 4: Volume effect after the introduction of Biosimilars G-CSF, SU



t0 = year of Biosimilars introduction t0 + (t+1) + (t+2) = Volume effect

G-CSF = Granulocyte colony stimulating factor SU = Somatotropin uptake

Table 9: Various companies launching Biosimilars across the globe

EUROPE	INDIA	U.S.
Biopartners, Hexal, Ratiopharm, Sandoz, Stada Teva as early industry leaders. Other smaller Eurpoean companies include CT Arzeimittel, Hospira, and Medice.	Large companies like Biocon, Dr.Reddy's Laboratories, and Ranbaxy have taken the lead. Several smaller companies like Intas and Zydas Cadila are also developing Biosimilar products.	AstraZeneca and Eli Lilly & Company expressing interest in FOBs and the recent launch of MBV.

Biosimilars approved in different global regions:

1. Europe: In 2003 the EU established a legal framework for approving Biosimilars. This framework purport that Biosimilars can only be approved centrally through EMA and not nationally.

   EMA has built-up guidelines for the approval of Biosimilars by means of an abbreviated registration process during 2005 to 2006.

   In 2006 EU has approved the first Biosimilar product -Omnitrope (somatropin). So far, EMA has approved 14 Biosimilars concerning the product classes of human growth hormone, granulocyte stimulating factor and erythropoietin, for aid in the EU. Filgrastim was one of the Biosimilar whose approval has been withdrawn in April 2011.

   The various products approved in Europe were given in Table 10. [18]

Table 10: Biosimilar products approved in Europe

Product Name	Active Substance	Therapeutic Area	Authorization Date	Manufacturer / Company Name
Binocrit	epoetin alfa	Anaemia Chronic kidney failure	28 Aug 2007	Sandoz GmbH
Biograstim	Filgrastim	Cancer Haematopoietic stem cell transplantation Neutropenia	15 Sep 2008	CT Arzneimittel GmbH
Epoetin alfa Hexal	epoetin alfa	Anaemia Cancer Chronic kidney failure	28 Aug 2007	Hexal AG
Omnitrope	Somatropin	Pituitary dwarfism Prader-Willi syndrome Turner syndrome	12 Apr 2006	Sandoz GmbH
Tevagrastim	Filgrastim	Cancer Haematopoietic stem cell transplantation Neutropenia	15 Sep 2008	Teva Generics GmbH

2. India: Already the guidelines for approving generic versions of small molecule chemical drugs have been established for some time in India. Still, there is no specific guidelines for 'similar biologics', because the Indian regulatory authorities identify these products, have existed in India until a short time ago.

   On 19 June 2012, India publicized the issue of draft regulatory guidelines for 'similar biologics' at the BIO industry conference in Boston, USA. The guidelines summarize a simple abbreviated procedure for evaluation of 'similar biologics' which have been approved and marketed in India, Europe or USA for more than four years

   In India, the Central Drugs Standard Control Organization is accountable for the approval, i.e. marketing authorization of medicinal products, together with these so-called 'similar biologics'.

   In 2000, hepatitis B vaccine was approved and marketed as the first 'similar biologic' in India. About 50 biopharmaceutical products have been approved for marketing in India; with more than half of them being 'similar biologics' recently and some of them are given in Table 11. [19], [20]

Table 11: Biosimilar products approved in India

Product name	Active substance	Therapeutic area	Launch date in India	Company
Basalog	insulin glargine	Diabetes	2009	Biocon
Biovac-B	hepatitis B vaccine	Hepatitis B	2000	Wockhardt
Cresp	darbopoetin alfa	Anaemia Cancer Chronic kidney failure	Aug 2010	Dr Reddy's Laboratories
Epofer	epoetin alfa	Anaemia Cancer Chronic kidney failure	NR	Emcure
Glaritus	insulin glargine	Diabetes mellitus	Mar 2009	Wockhardt
Wepox	epoetin alfa	Anaemia Cancer Chronic kidney failure	Mar 2001	Wockhardt
Wosulin	human insulin	Diabetes mellitus	13 Aug 2003	Wockhardt

CONCLUSION:

To avoid future problems with multiple terminologies used for 'Biosimilars', the definitions provided by EMA for the terms 'Biosimilar' and 'non-innovator biologic' should be adopted for precisely referring to the nature of applicable products.

Considering the current expansion of Biosimilar market world-wide; sophisticated clinical development strategies, effective communication between the regulatory agencies plays a crucial role while foreign clinical data ensures that medicines are evaluated in diverse but representative patient population before approval

For efficient development of Biosimilars and to avoid duplicative clinical studies, manufacturers should seek harmonization of global approval requirements and propose global development programs, using a reliable global reference product, which should be sourced from different regions so that a patient in a given region might receive it without any adverse effects.

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