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BIOSIMILAR: AN OVERVIEW

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ABSTRACT: Biosimilars are defined as officially approved new version of innovator bio-therapeutic products for which the patent has expired. Biosimilars the 'generic' versions of biopharmaceuticals, continue to enter Indian pharmaceutical market, to treat a variety of diseases. Biosimilars available in India include monoclonal antibodies for treating various malignant and immunological disorders, growth factors like erythropoietin and granulocyte colony stimulating factor (G-CSF), human insulins for treating diabetes mellitus etc. In the recent scenario, there is an increasing demand for biological drugs. The development and production of biosimilars are boosted by existing manufacturing technology. Due to no investment in phase I-II of clinical trials, biosimilars are available at cheaper prices than the reference products, so that it has low market risk. The main goal of this review is that the phase I-II trials are typically not required for biosimilar approval unless it is found necessary in special cases. Phase III trials with a minimum of 100 patients are mandatory for establishing bioequivalence. Therefore, the total cost to develop a biosimilar in India can range from $10 – 20 million, which helps Indian companies to offer their products at a 25-40% cheaper price than the innovator biologics.

INTRODUCTION: Biogenerics are biological products manufactured after expiry of the patent of innovator biopharmaceuticals and these are also called as Biosimilars, Similar biologics, Follow-on biologics [1], follow-on protein products and Subsequent entry biologics in different countries, intended to have the same mechanism of action for the same diseases as the innovator biopharmaceutical drugs. The term "bio-generic" is misleading, as no two biopharmaceutical products could possibly be exactly identical, because of their nature and the complexity of their manufacturing process.

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Thus, the common terminologies used to describe such products are "Biosimilars" and "Follow-on biologics". Biosimilars the 'generic' versions of biopharmaceuticals, continue to enter Indian pharmaceutical market, to treat a variety of diseases.

Biosimilars available in India include monoclonal antibodies for treating various malignant and immunological disorders, growth factors like erythropoietin and granulocyte colony stimulating factor (G-CSF), human insulins for treating diabetes mellitus etc. The global biosimilars market [2] is expected to be worth $19.4 billion by 2014, growing at a Compound Annual Growth Rate (CAGR) of 89.1% from 2009 to 2014. Biological products worth $25 billion are going to be off patent by 2016 and this will open a pathway for the drug manufacturers to increase their market share, profit margins and reduce the medical expenditure of biosimilar

products [3]. Even though cost-savings with biosimilars is appealing for patients, physicians, insurance providers and governments, still there are concerns about the safety, efficacy and quality of these products due to the absence of stringent guidelines for evaluating these products in our regulatory system [4].

Definition: Biosimilars are defined as officially approved new version of innovator bio-therapeutic products for which the patent has expired.

- **Biosimilars** – A biosimilar, similar biological medicinal product, follow-on biologic[5], or biogeneric**:** This is a copy drug that is similar to a biological drug that has already been authorized (the biological reference medicine). Its active substance is shown by appropriate testing to have similar physicochemical, preclinical and clinical properties to an originator therapeutic protein[6].

Scope [7, 8]: There is large market needs and growing affordability for biosimilars. They offer competitive pricing advantage over the reference product in global market. The focus within the biopharmaceutical sector in India is directed more towards development of biosimilars because of much lower developmental costs and risks reduce spending on research and development, reduced time to market and expertise in reverse engineering drug development process.

In India Phase I-II trials are typically not required for biosimilar approval unless it is found necessary in special cases. Phase III trials with a minimum of 100 patients are mandatory for establishing bioequivalence. Therefore, the total cost to develop a biosimilar in India can range from $10 – 20 million, which helps Indian companies to offer their products at a 25-40% cheaper price than the innovator biologics. Due to the sophisticated nature of these biomolecules and their 3-D structure it's a new area of research for pharmaceutical scientists and drug.

In recent scenario there is increasing understanding and applicability to biological drugs i.e. biosimilars. In India apart from Biogenerics a host of molecules especially have Biosimilar copies of compounds especially in endocrinology namely insulin, Exenatide, growth hormone, teriperatide like peptides are made in India.

There exist new types of co-operation between Pharma, Biotech or Generics through biosimilars. Number of innovator biopharmaceutical products are going off patent, urgent attention is required to regulate the increasing number of biosimilars which are available at lower price to economically compromised patients. Clinicians prescribing biosimilars immediately after their launch, indicating that the biosimilars have established a good reputation among healthcare professionals.

Advantages:

1. There is large market needs and growing affordability for biosimilars in global and domestic market.
2. Development and production of biosimilars are boosted by existing manufacturing technology.
3. In the recent scenario, there is increasing demand for biological drugs.
4. Due to competitive pricing advantages biosimilars are available at affordable prices on global market and they are typically sold at the discount up to 85 %.
5. Due to no investment in phase I-II of clinical trials, biosimilars are available at cheaper prices than the reference products, so that it has low market risk.

Biosimilar Comparison with Bioequivalent:

Generics: A drug with the same active ingredients and equivalence as the original small-molecule pharmaceutical produced by using chemical synthesis.

Bioequivalence: FDA Official statement (1997), two formulations are said to be bioequivalent, if "The rate and extent of absorption of the test drug do not show a significant difference from the rate and extent of absorption of the reference drug, when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either single dose or multiple doses".

Biologics: A complex biopharmaceutical, produced using biotechnology (i.e. rDNA, controlled gene expression or antibody technologies etc.)

Biosimilars: An approved drug, produced by using biotechnology, referencing an originator biologic. Biosimilars are sometimes *mistakenly* called "generic" versions of the original biologic drugs. However, unlike generics, which are virtually identical copies of traditional drugs, biosimilars are not the same as the original biologic medicine. This is an inevitable outcome because biologics are made of living cells – as opposed to the chemical composition of traditional drugs. As you can imagine when dealing with living organisms, even the slightest variation in the cell line or raw materials or even in the laboratory conditions can impact the way these medicines are created (**table 1**).

TABLE 1: COMPARISON OF GENERICS, BIOSIMILAR AND BIOLOGICS

Sr. no.	Particulars	Generics [9]	Biosimilar	Biologics
1.	Manufacturing	• Mostly smaller chemical molecules - less sensitive to production process changes • Produced by using chemical synthesis • Reproducibility easy to establish	• Sensitive to production process • changes - expensive and specialized production facilities handling living cells (mammalian, yeast, bacteria) • Highly sensitive to manufacturing changes • Reproducibility difficult to establish	• Sensitive to production process changes - expensive and specialized production facilities handling living cells (mammalian, yeast, bacteria) • Highly sensitive to manufacturing changes • Reproducibility difficult to establish
2.	Clinical Development	• Limited clinical activities, often only • Phase I studies • Short timeline for approval • Development costs up to 5 m$ • Enrolment of around 20 - 100 subjects	• Extensive clinical trial activities, • including Phase I and III studies • Pharmacovigilance and periodic safety updates after launch needed • Development costs around 80-120 m $ • Timeline of 6 – 10 years • Enrolment of around 100 – 1500 patients/ subjects	• Extensive clinical trial activities, • including Phase I - III studies • Pharmacovigilance and periodic • safety updates after launch needed • Development costs around 350 – 800 m $ • Timeline of 6 – 15 years • Enrolment of > 1.000 patients/ • Subjects
3.	Regulation	• Needs to show bioequivalence • Abbreviated registration procedures in Europe and US • •Automatic substitution allowed	• Regulatory pathway defined for • Europe (EMEA); not yet in US (BLA) • Needs to demonstrate • "comparability"; currently no • automatic substitution intended	• Highly regulated like all innovator drugs

History: Overview and Background: On March 23, 2010, President Obama signed the law of Patient Protection and Affordable Care Act [10]. The Affordable Care Act contains the BPCI Act that establishes an abbreviated approval pathway for biological products that are shown to be "biosimilar" to, or further shown to be "interchangeable" with, an FDA-licensed biological product. The BPCI Act states that in order for a biologic product to be considered biosimilar to a reference product, the biological product must be proven to be biosimilar to a reference product based on data derived from analytical, animal, and clinical studies. The BPCI Act1 defines "biosimilar" or "biosimilarity" as a 2-part demonstration that 1) the proposed biosimilar product is "highly similar to the reference product not withstanding minor differences in clinically inactive components," and 2) "no clinically meaningful differences" exist between the proposed similar product and the reference product in terms of "safety, purity, and potency." Additionally, it must be proven that the proposed biosimilar product have the same route of administration, dosage form, and strength as the reference product.

The BPCI Act amends Section 351 the Public Health Service Act (PHSA) to add subsection (k), which establishes an abbreviated approval pathway for biosimilars. This creation of an abbreviated approval pathway under the PHSA largely aligns with the Hatch-Waxman concept of permitting reliance for approval, at least partly, on an appropriate previously approved drug as the reference product, with the potential of saving time and resources and avoiding unnecessary duplication of human or animal testing. The policy issues surrounding biosimilars has been required to be discussed because of biosimilars' potential to reduce health care costs.

The FDA has not released any guidance for industry, creates questions about what will be necessary to gain FDA approval. The development of biosimilars is anticipated to have a major impact on the management of cancer. The use of biologics is widespread and has become an essential component in cancer treatment and supportive care management. Patents for older cancer biologics will soon expire, removing one of the barriers to commercialization of biosimilars. The potential to provide wider access to more affordable cancer biologics may be realized through the BPCI Act [11]; however, the regulatory process for the approval of biosimilars is under development by the FDA.

For biologics that are administered more than once to a patient, the risks in terms of safety and efficacy of alternating or switching between use of the reference product and biosimilar must be equal to the risk of using only the reference product. Celltrion got approval for Remsima (infliximab) the south Korean company proclaim remsima as world's first official biosimilar antibody to get approved, but it's copy of Johnson & Johnson's Remicade is considered a regulatory milestone in biologics world, because it was one of the first monoclonal antibody (MAb) TNF inhibitors approved for the treatment of rheumatoid arthritis.

Dr. Reddy's laboratory did not get approval from Indian authorities for reditux way back in 2007 a full five years before celltrion's Remsima. Celltrion can claim that Remsima is the world's first official biosimilar antibody with the operative word being "official". At the time Reditux was up for approval, the European Medical Agency [EMA] was sole global regulator to have released guidelines for biosimilars which it had released in 2005. In 2007, India like most countries, did not have a separate approval process for biosimilars, so Reditux was approved using an abbreviated version of the pathway for small molecule generics.

Reditux was launched at half the price of the originators & it looks like the regulators in India. By the time celltrion's Remsima ,came up for approval five years later, the Korean Food and Drug Administration had in place a biosimilar pathway based on globally accepted guidelines like the EMA and WHO. Thus, Celltrion can claim that Remsima is the world's first official biosimilar monoclonal antibody. From this September, India's biosimilar guidelines will in place and this time, they too are modelled on global norms, Government and regulators are aware that biosimilars are key to keep the healthcare cost down. India released the draft guidelines for manufacturing and marketing of biosimilar drugs in India this July 2012.

Biosimilars Current Status in World [12, 13]: In 2010, global pharma market reached $830 B. Biologics drugs market exceeded $116 B (14%). Biosimilars drug sales $380 M & large number of biological drug patent are expiring in recent times. Biosimilars are follow-on versions of highly complex biopharmaceuticals that are no longer patent protected. This complexity means that development requires a much larger financial investment than other generic products. Sandoz was the first company to bring one to the market – human growth hormone Omnitrope® in 2006. The first truly complex biosimilar Binocrit®/ Epoetin alfa Hexal followed in 2007 and then Zarzio®/Filgrastim Hexal® was launched in several EU countries in 2009 (**table 2**).

TABLE 2: NAME OF COUNTRY AND BIOSIMILAR GUIDELINES APPROVAL

Sr. no	Name of country	Biosimilar guidelines approval
1.	Canada	First Biosimilar Omnitrope 2009
2.	Australia	Following EU , Omnitrope since 2005
3.	Japan	First Biosimilar Omnitrope 2009
4.	EU	World Leader
5.	FDA	Not Yet
6.	India	Guidelines in place
7.	BRAZIL	Final guideline, 2005
8.	VENEZUELA	Final guideline 2000
9.	TURKEY	Final Guideline 2008
10.	MALAYSIA	Final Guideline 2008

Current status of Biosimilars in India [14, 15]: India released the draft guidelines for manufacturing and marketing of biosimilar drugs in India this July. There are around 25 Indian players in the space with around 40-50 products already being sold in the Indian market costing about-$200 million-2008 &-$580 million-2012.

With such a huge market opportunity opening up, it is no wonder that regulation for biosimilars across the world is keeping pace. Up to now the regulatory process for biosimilars in India was on a case basis, using an abbreviated version of the pathway followed for small molecules, involving the Drug Controller General (India)'s office under the Central Drug Standard Control Organization (CDSCO) and DBT.

While the CDSCO evaluated the safety, efficacy and quality aspect, the DBT through the Review Committee was responsible for overseeing the development and preclinical evaluation of recombinant biologics.

India's new draft guidelines have made the pathway much clearer which believes will lead to reduction in approval time lines, but adds an important caveat; provided the government infrastructure is in place to support requisite approval processes. Most of the biologics and the process to make them between 1990 -2005 were never patented in India. The draft guidelines thus open prospects to bring more Biosimilar brands in market at perhaps the lowest cost.

While ensuring product safety, quality and efficacy, points out that "extremely onerous clinically trials are obviated, thereby enabling biosimilars to be launched in a faster time frame at a competitive cost in relation to other context. More than 20 biologics have been approved in India by this process. But now with more biologics going off patent, the Indian regulators clearly felt the need, if more formalized approach, in line with global norms. They seem to be based on current global guidances like that of European Union; they are tailored to need the local Indian market and the players in the Indian market. It is very clear that government is creating a level playing field for Indian biosimilar players to compete globally.

Draft guideline once implemented they will evolve further with feedback from industry. Draft guidelines as an excellent attempt to streamline the regulation of the biosimilars but while keep pace with other regulatory bodies like the United states-Food &Drug Adminitsration and EMEA, we should not blindly at what they are following, and we should have our own identity. The Indian biosimilar draft guidelines do reflect their own identity, going by the key differences from the global biosimilar guidelines. Firstly in addition to the DCGI/CDSCO and RCGM /DBT, the draft biosimilar guideline have added a third the Genetic Engineering Appraisal Committee (GEAC) which functions under the Ministry of Environment and Forests (MoEF) as the statutory body for review and approval of activities involving large scale use of genetically engineered organisms. The involvement of three authorities, fewer than three ministries is the most obvious differentiating factor.

Single-window procedure of obtaining marketing approval would make the process similar to the developed world's approval frame work. In fact, in addition to being dependent on multiple regulatory agencies, the draft biosimilar guidelines lean on other guidelines (like Recombinant DNA Safety Guidelines, 1990; CDSCO guideline for industry, 2008; Guidelines and handbook institutional biosafety committees, 2011etc.) and other Acts.

The Legasis team cautions that this situation may cause procedural delays for approval. Another key difference is that India's drat regulations have not defined the time lines in the approval process unlike the biosimilar guidelines in the EMEA, while have well define timelines for each part of approval process [16]. The focus of biopharmaceutical sector in India is projected towards the development of biosimilars due to much lower development costs and risks, reduce the spending on research and development, reduce the time to market and expertise in the reverse engineering drug development process.

In these present days, there are 16 brands of erythropoietin (EPO) and 14 brands of Granulocyte Colony Stimulating Factor (G-CSF) are available in Indian market which shows the intensity of competition among the biopharmaceutical companies.

In India phase I-II trials are not required for biosimilar approval unless in special cases, phase-III trials with minimum of 100 patients are mandatory for establishing bioequivalence (**table 3**).

Therefore, total cost of development of biosimilars in India ranges from $ 10-20 millions, which helps the Indian companies to offer their product at 25-40% cheaper price than innovator biologics [17, 18, 19].

TABLE 3: BIOSIMILAR PRODUCTS IN INDIA

Sr. no.	Biosimilar	Company	Product Name	Year of Launch
1.	Insulin	Wockhardt Biocon Shreya Life Sciences	Wosulin Insugen Recosulin	2003 2004 2004
2.	Erythropoietin	Hindustan Antibiotics Emcure Wockhardt Ranbaxy Intas Pharmaceuticals Shantha Biotechnics	Hemax Epofer Wepox Ceriton Epofit & Erykine Shanpoietin	2000 2001 2001 2003 2005 2005
3.	Hepatitis B vaccine	Shantha Biotechnics Bharat Biotech Panacea Biotec Wockhardt Serum Institute of India Biological E	Shanvac B Revac B Enivac HB Biovac-B Gene Vac-B Bevac	1997 1998 2000 2000 2001 2004
4.	Granulocyte colony stimulating factor	Dr. Reddy‟s Laboratories Intas Pharmaceuticals	Grastim Neukine	2001 2004
5.	Streptokinase	Bharat Biotech Shantha Biotechnics Cadila Pharmaceuticals	Indikinase Shankinase STPase	2003 2004 2004
6.	Interferon alpha-2b Rituximab (MAb)	Shantha Biotechnics Dr Reddy‟s Laboratories	Shanferon Reditux	2002 2007
7.	Anti- Epidermal Growth Factor (MAb)	Biocon	BioMAB-EGFR	2006

Development of Biosimilars [20, 21]: There are four stages in the development of a biosimilar:

1) Product development and comparative analysis
2) Process development, scale up and validation
3) Clinical trials
4) Regulatory (EMA, WHO and FDA) review and approval. All stages come with varying requirements and take varying amounts of time contributing to the overall cost of developing a biosimilar.

1. **Product development and comparative analysis:** This stage involves the production of protein of interest from cell culture and validates their stability. The product must also demonstrate that it is biosimilar to the innovator product.
2. **Process development, scale up and validation:** During this stage, scale up of manufacturing process can be carried out to improve the product yield. This process should be carried out under good manufacturing practices and reproducibility of the manufacturing process needs to be demonstrated.
3. **Clinical trials** [22]: Clinical trials will be required for almost all biosimilar products in order to demonstrate bioequivalence to innovator product.
4. **Regulatory review and approval:** In Europe, the Committee for Medicinal Products for Human Use (CHMP), the European Medicines Agency (EMEA) led the way for biosimilars, by issuing its first specific regulatory guidance in October 2005. Two general guidance documents

addressing quality and nonclinical and clinical perspectives (Feb 2006), five product specific annexes on nonclinical and clinical issues (June-July 2006) and a manufacturing change comparability guideline (Nov 2007) are now available.

Patient Safety & Biosimilars [23, 24, 25]: Because of the complexities of biologics, we believe that patient safety must be paramount when evaluating the approval of biosimilars. The introduction of biosimilars into the marketplace must ensure the current purity, potency, and safety standards established for innovator products by FDA. In addition, because the manufacturing process can have a significant impact on a biologic's structure and activity; a regulatory pathway should ensure a rigorous inspection and control process for the manufacture of biosimilars that is similar to the innovator product standards. We believe that all biosimilars applicants should be required to conduct clinical trials that demonstrate sufficiently similar product safety, efficacy and immunogenicity relative to the innovator product. Non-clinical methods of characterizing complex biotechnology drugs have not matured to the point where they can substitute for clinical studies.

Therefore, to ensure patient safety, it is essential for biosimilar sponsors to demonstrate product safety and efficacy by testing their product in adequate and well-controlled clinical studies. Furthermore, immunogenicity testing in human subjects, an integral part of biologics drug development, is critical to help measure potential adverse immune response to the biosimilar product. Immunogenicity has been associated with allergic or anaphylactic reactions, as well as reduction in efficacy or autoimmunity. We believe the FDA should issue moleculeby- molecule guidance for clinical trials required for biosimilars to account for the particular characteristics of the product.

Biosimilars in Market:

Omnitrope®:

- It is First approved biosimilars in Europe, which is manufactured by Sandoz. The application for approval had been submitted on 1/7/04 and got approval in 12/4/06 and also got FDA approval after litigation against the FDA.

The Omnitrope® story [26, 27, 28]:

- 2001: First attempt to obtain EU approval: The application had been filed to have the product considered for generic authorization based on a detailed scientific bibliography, which is accompanied by studies aimed at showing comparability with the reference product.

- 06/2003: CHMP issued a positive opinion: CHMP had improperly accepted Sandoz' application as a bibliographical application based on the well-established use of the medicine, while at the same time it had accepted/required comparability studies to be performed, but European Commission (EC) decided not to follow the opinion

- 03/2004: After legal action by Sandoz, EC publication:

- Sandoz appealed the EC decision with the ECJ:- In that appeal Sandoz contests that the performance of comparability studies implied that the legal conditions for the application of the bibliographical application procedure were not met.

- Second attempt after new regulatory framework. Sandoz submitted new application on 01/07/04 and after verification by CHMP it gave positive opinion on 26/01/06. On getting positive opinion from CHMP, EC also gave approval to Sandoz's submission on 12/04/06.

- Clear example of a need for a regulatory pathway. In the case of Omnitrope, Sandoz relied on the data submitted for the prior approval of Pfizer's Genotropin.

  In addition, they provided clinical data in support of Omnitrope's pharmacokinetic, pharmaco-dynamic, physiochemical, and bioavailability similarity to Genotropin, as well as new pharmacology, toxicology, and safety data specific to Omnitrope. Documentation was not as extensive as required for a new drug but, it still represented a significant investment of time and resources by Sandoz. Even with such extensive documentation, Omnitrope got approval after years of consultation and a court-case between Sandoz and the FDA. Since its

approval, no additional biosimilars had been submitted to the FDA, as the approval pathway is complex and limiting. The FDA has yet to issue a biosimilar specific protocol for future applicants.

Economics of Biosimilars [29, 30]**:** About 20 Indian companies are engaged in production biosimilars,among them Dr. Reddy's Laboratories, Ranbaxy, Biocon, Shantha Biotech, Reliance Life Sciences, Panacea Biotech and Intas Biopharmaceuticals are actively take part in this field. But several other well-known companies have recently entered the field, including Glenmark, Cipla and Lupin Pharma. In June 2010, Cipla announced that it was spending $65 million in two biotechnology companies – MabPharm and BioMab, based in India and Hong Kong, respectively – to bolster its presence in the global biosimilars market. Nearly about 50 biosimilars have already reached the Indian market, and they are typically sold at discounts of as much as 85%, thus make them available at lower cost.

In 2009/10, domestic sales of erythropoietin & interferons rose to $22 million while sales of c-GCSF rose to $11 million, and sales of streptokinase rose to $15 million. Moreover, demand is likely to grow considerably, as India becomes the part of core market. US investment bank Goldman Sachs estimates that the number of Indians with annual incomes of between $6,000 and $30,000 (measured in terms of purchasing power parity) will increase by 250-300 million during the next decade alone. The global biosimilars market has even more potential for the most efficient Indian biosimilars manufacturers, since the market will be characterised by price competition, though only a very limited number of rival products.

The manufacturers of branded products are likely to use second-generation products with more convenient administration schedules as a means of defending their territory. Some of these manufacturers may also try to crowd out the competition by producing their own biosimilars. So the competition is likely to be intense. Biosimilar opportunities promises to give better margins, even after patent expiry, as the cost and complexity of biosimilar development and manufacturing prevents the entry of too many players in competition, thus it is no wonder that the share of biologics in the global biopharma-market is projected to rise 28.9 per cent in 2015, from a base of 4.5 per cent in 1990. Similarly, the share of biosimilars in biologics is projected to raise from 0.1 per cent in 2009 to 6.4 per cent in 2017. Remicade (i & i's infliximab) serves a good example of biosilmilar boom around the corner and is the top selling branded antibody with $8.5 billion in sales in 2011 and analyst predicts that the brand could well turn out to be the top selling branded drug in 2012. Many biosimilar manufactures are waiting for Remicade to fall off the patent cliff in 2013. In fact various reports predict that biologic patent expiries worth more than $ 40 billion are expected by 2016 (**figure 1**).

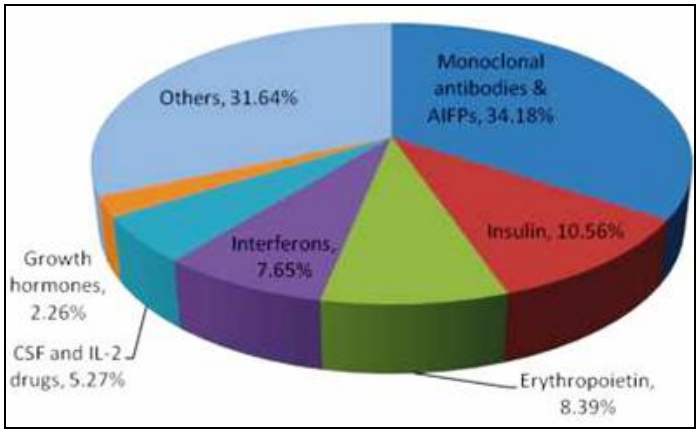

FIGURE 1: SHARE OF THE TOTAL BIOLOGICS MARKET BY DRUG TYPE IN 2009 (%)
Source: visiongain

The global market for biosimilars was around $378 million till 2011& according to analysis this likely to rise around $2.5 billion by 2015 [31,32]. The contribution of monoclonal antibodies & AIFS to total sales was found to be 34.18 %, Insulin 10.56%, erythropoietin 8.39 %, Interferons 7.65 %, CSF and IL-2 drugs 5.27%, Growth hormones 2.26 % & others 31.64 %. Tapping the biosimilars opportunity will require staying power as these drugs of high molecular complexity and are unstable.

There mode of delivery needs to be intravenous and all these factors results in a high capital requirement of around $10-$15 millions, which may scale up to $400 millions .All these factors mean that in medium term , there will be challenges in gaining acess to regulated markets, but emerging ones will have better potential for Indian players. As with small molecule drugs , the US will be the key global market for biosimilars (worth around $25 billions) and represent a 10 % share of the total biologic market.

The overall sale of biosimilars within the off–patent biological market is forecast to reach around 50 per cent by 2020. The Indian biologics market consists primarily of vaccines, monoclonal antibodies, recombinant proteins and diagnostics. In the 2009/10 financial year, it was worth $1.9 billion – 62% of the $3 billion generated by the biotechnology industry as a whole (i.e., including bioagricultural and bioindustrial products, bioinformatics and bioservices). India already has a strong pharmaceutical manufacturing base.

It is thus well positioned to capitalise on the opportunities arising from the "patent cliff" and growing demand for biosimilars. But the domestic market will remain relatively small in the near term, so India's efforts should be directed towards becoming a global manufacturing hub. If India captures 10% of the global biosimilars market by 2020 – the goal for which we believe it should aim – the private sector will have to invest a considerable amount of capital in building the necessary manufacturing capacity and skills. The government of India will also need to provide the environment required to enable that expansion. This article covers the infrastructure improvements, fiscal incentives, regulatory changes and policy initiatives that we believe will be crucial.

We estimate that they will require an investment of at least $1 billion over the next five years. We have divided our recommendations into six sections: R&D; manufacturing and commercialization; human capital; the regulatory framework; innovation; and intellectual property. The global biosimilars market is expected to be worth $19.4 billion by 2014, growing at a Compound Annual Growth Rate (CAGR) of 89.1% from 2009 to 2014.

The American market (including North America and Latin America) is expected to account for nearly 35.3% of the total revenues in 2014. Biological products worth $25 billion are going to be off patent by 2016 and this will open a pathway for the drug manufacturers to increase their market share, profit margins and reduce the medical expenditure of biosimilar products (**figure 2**).

The Biosimilar Market currently sits at $235 Million: Moving Closer To Patent Clifnn

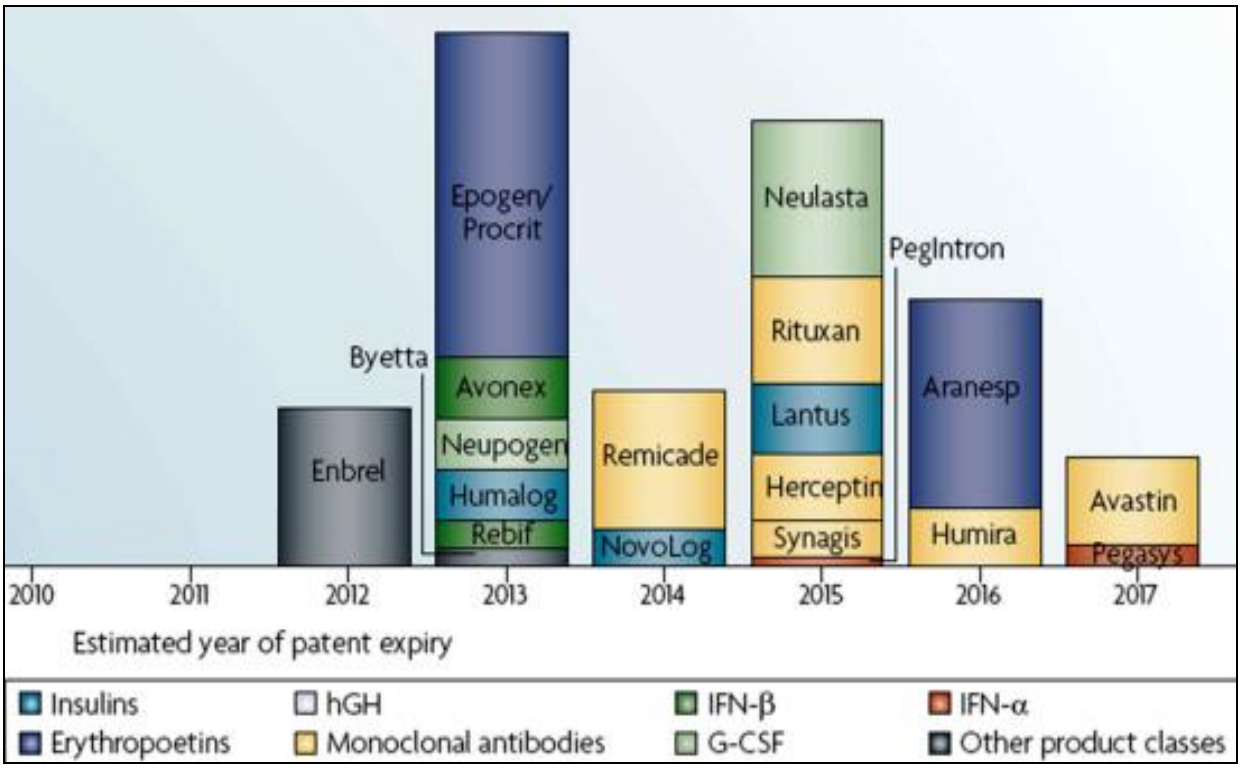

FIGURE 2: MOVING CLOSER TO PATENT CLIFNN. Ref-: Nature reviews| Drug Discovery Volume 7 |September 2008 |725

Biosimilars Market [33]: Significant Biopharmaceuticals that go off-patent in the near future: (**table 4**)

TABLE 4: BIOPHARMACEUTICALS THAT GO OFF-PATENT IN THE NEAR FUTURE

Sr. no.	Product	Generic name	Company	Therapeuti Sub-Category	2009 Sales ($)	Patent Expiry
1.	Neupogen	Fligrastim	Amgen	Immunostimulants	1,288	12-03-2013
2.	Humalog	Insulin Lispro	Eli Lilly	Anti-Diabetics	1,959	07-05-2013
3.	Avonex	Interferon beta- 1a	Biogen	IdecMS Therapies	2,323	30-05-2013
4.	Epogen	Epoetin elfa	Amgen	Anti-anaemics	2,569	20-08-2013
5.	Procit/Eprex	Epoetin elfa	Johnson & Johnson	Anti-anaemics	2,245	20-08-2013
6.	Rituxan	Rituximab	Roche	Anti-neoplastic Mabs	5,620	31-12-2014
7.	Procrit/Eprex	Epoetin alfa	Johnson & Johnson	Anti-anaemics	2,245	20-08-2013
8.	Cerezyme	Imiglucerase	Genzyme	Other therapeutic products	793	27-08-2013
9.	Rebif	interferon beta-1a	Merc	k KGaA MS Therapies	2,142	31-12-2013
10.	NovoMix	Insulin & Insulin as part Novo	Nordisk	Anti-diabetics	1,216	06-06-2014
11.	NovoRapid/ NovoLog	Insulin aspart Novo	Nordisk	Anti-diabetics	1,825	07-12-2014
12.	Rituxan	Rituximab	Roche	Anti-neoplastic	5,620	31-12-2014
13.	Kogenate	Octocog alfa	Bayer	Anti-fibrinolytics	1,238	31-12-2014
14.	Prevnar	Pneumococcal vaccine	Pfizer	Vaccines	287	01-01-2015
15.	Lantus	insulin glargine	Sanofi-Aventis	Anti-diabetics	4,293	12-02-2015
16.	Actemra	Tocilizumab	Roche	Other antirheumatics	44	07-06-2015
17.	Gonal-F/ Gonalef	Follitropin alfa	Merck	KGaA Fertility agents	678	16-06-2015
18.	Neulasta	Pegfilgrastim	Amgen	Immunostimulants	3,355	20-10-2015
19.	Nimotuzumab	Nimotuzumab YM	BioSciences	Anti-neoplastic Mabs		17-11-2015
20.	Norditropin SimpleXx	Somatropin	Novo Nordisk	Growth hormones	824	15-12-2015
21.	Helixate	Octocog alfa	CSL	Anti-fibrinolytics	563	31-12-2015

Disadvantages of Biosimilars:

1) The development and manufacturing process of biosimilars is more complex than that for small molecule drugs.

2) Manufacture of biosimilars requires growing and harvesting of the product from living cells which is very costly & time consuming process.

3) The development of biosimilars is lengthy process & can take many months to produce.

4) As compared to chemical drugs, Biologics are often dozens to thousands of times larger, so that development process is very critical.

5) Traditional generic drugs must be shown to be the same as the reference drug; however, with modern science, follow-on biologics or biosimilars can only be similar to the reference or innovator biologic.

6) In comparison with reference products, the research and development for biologics is long, costly and risky.

7) A regulatory approval pathway for biosimilars must include adequate measures for assuring patient safety.

8) At least 14 years of data exclusivity or data protection must be part of any biosimilars legislation to provide the certainty necessary for continued R&D investment leading to needed medical advances [34, 35].

9) The development of biosimilars require clinical trials to demonstrate safety and efficacy and for each indication unless otherwise scientifically justified.

10) The major problem in the development of biosimilars is that current science does not permit automatic substitution of one biologic product for another.

11) Different biologics may have different clinical and therapeutic effects in patients and their switching should be a conscious decision made by physicians in consultation with their patients.

12) Patent protection in the context of biosimilars is less certain than for traditional small molecule drugs.

13) Competitors may be able to get around patents while relying on the innovator company's data for FDA approval, which is big disadvantage of biosimilar competition.

14) Economic analysis of the time required for the development of biologics to break-even on their R&D investment indicates data protection for biologics should between 12.9 and 16.2 years [36].

FUTURE PERSPECTIVES [37, 38]:

2020 outlook: Within the three main geographic clusters, a number of differentiating factors will impact the value generation opportunity for biosimilars, including ease of access in the short term, speed of uptake, clarity of regulation and, particularly, the role of public and private stakeholders. Accordingly, most of the immediate value will be sourced from the pharma emerging markets, spurred by the anticipated flow of new patients.

However, in the long-run, the US will be the cornerstone of the global biosimilars market, powering a sector worth between US$11 billion and US$ 25 billion in 2020 representing a 4% and 10% share respectively of the total biologics market. The overall penetration of biosimilars within the off-patent biological market is forecast to reach up to 50% by 2020, assuming a price discount in the range of 20-30% (or 40-50% with tender discounts included).

Underlying this forecast are six core drivers with the potential to spur or curb future growth of the biosimilars market: the US uptake, the spread of biosimilars in pharmerging markets, the continued pattern of evolution in Europe, technology and the second wave of biosimilars, volume effect and the competitive landscape.

Challenges [39, 40]: Economics of introduction has to be a fraction of the cost of biological drug near patent expiry Production cost, clinical development cost and market access costs have to be comparatively less. Ambiguous regulatory pathway adds significantly to introduction cost.

1) **High Development Costs:** Developing a biosimilar is not a simple process but one that requires significant investment, technical capability and clinical trial expertise. Average cost estimates ranges from US$100-250 million (various industry sources) if plant development is included (or US$20-100 million for non-plant cost). While lower than the costs of developing a small molecule NCE, they are nevertheless orders of magnitude higher than the costs associated with developing traditional generics, which are typically around US$1-4 million.

2) **Fledgling Regulatory Framework:** In most markets apart from Europe, the regulatory framework for biosimilars is generally still very new compared to the well-established approval process for NCEs and small-molecule generics; in some cases it is non-existent, making global investments risky.

3) **Manufacturing issues:** Barriers to developing a biosimilars manufacturing capability are not prohibitive, but the development of biosimilars involves complicated analytical sophisticated technologies and processes, raising the risk of the investment. In specific areas such as insulins, there are strict requirements for compatibility with existing devices. Manufacture process is complex and expensive to achieve "similar" quality, safety, and efficacy profile.

4) **Branded mentality:** Winning the trust of stakeholders will call for many of the skills, resources and branded mentality of a conventional innovative pharmaceutical company – potentially involving changes to commercial models. Initiatives to allay safety concerns among physicians and patients will be particularly important, supported by sales teams

with deeper medical and technical knowledge. There is no interchangeability, hence brand marketing is required.

5) **Guideline issue:** In the recent scenario, there is lack of clear regulatory guidance for approval of biosimilars in many countries (US, China), there are no universally accepted guidelines for the biosimilars. WHO and FDA guidelines for biosimilar approval are not yet available.

6) **Balanced legislation:** The balanced legislation between biologics and innovator drugs is required to protect and promote innovative drugs.

7) **Market risk:** The marketing of biosimilars is very risky because competition against innovative drugs and other competitors.

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