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Review Article

Biosimilars: Fundamentals and authorization as per U.S. perspective

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ABSTRACT

Biosimilars are biological products that are the replicas of their innovator biopharmaceuticals. At the moment, biological products account for 10 -15% of the total pharmaceutical market. More than one-fifth of new medicines launched on the world market each year are now biotechnology derived. These are developed after patent expiration of innovator biopharmaceuticals and are submitted for separate marketing approval. In view of the structural and manufacturing complexities of biopharmaceuticals, biosimilars should not be considered as biological generics. Each class of biologic varies in its benefit and risk profile, the nature and frequency of adverse events, the breadth of clinical indications and whether surrogate markers for efficacy are available and validated. But most of the countries do not have specific guidelines for potential market of biological products. Following the legislation that allowed the FDA to approve biosimilars in the United States, biological products that are similar to the reference product in terms of safety, purity and potency are gradually entering into the market. To date, only five biosimilars have been approved in the U. S. although many agents are currently undergoing trials and may soon become available. This article will address the differences between biosimilars and generics, issues concern with the approval process, use of biosimilars and need.

1. Introduction

Biologics are medicines that generally come from living organisms, which can include humans, animals and microorganisms such as yeast and bacteria. They are different from conventional medications, which are generally made from chemicals or chemically synthesized and therefore their structure can be relatively easily defined. Biologics are big and very complex molecules often 200 to 1,000 times the size of more common small-molecule drugs. For example, aspirin, a small-molecule drug is made up of only 21 atoms. While the biologic drug Enbrel, which is used to treat rheumatoid arthritis and plaque psoriasis consists of more than 20,000 atoms. As a result of their complex makeup, biologics are highly sensitive to manufacturing and handling condition and many of those production details are highly-guarded intellectual property of the company that develops the initial drug. Creating imitations is therefore very difficult. Producing generic small-molecule drugs is relatively simple it's like following a recipe with standard ingredients.[1] Biologic drugs are made using living cells that treat disease usually by genetically modifying cells through highly complex manufacturing processes. They must be handled and administered under carefully monitored conditions. They are used to prevent, treat, diagnose or cure a variety of serious and chronic illnesses including cancer, chronic kidney disease, autoimmune disorders and infectious diseases. The differences between generics and biosimilars data is given in Table 1.[2,3]

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A biosimilar is exactly what its name implies it is a biologic that is "similar" to another biologic drug already approved by the Food and Drug Administration (FDA). Under U.S. law, a biosimilar is approved based on a showing that it is "highly similar" to an FDA-approved biological product, known as a reference product.[4] It may not have any clinically meaningful differences in terms of safety and effectiveness from the reference product. Only minor differences in clinically inactive components are allowable in biosimilar products. Biosimilars are less costly imitations of drugs known as biologics, which are used to treat a range of diseases including cancer, rheumatoid arthritis, diabetes and anemia. But they are different from generics in that they are not exact copies. These are much more challenging because living cells are highly sensitive to their environments and manufacturers have to create their own unique process to attract these cells to produce an identical outcome to an existing treatment. Biosimilars. The molecular makeup of each biosimilar treatment will look unique like individual snowflakes, even though they all have similar outcomes. This is the result of differing manufacturing processes and that makes drug approvals challenging. Generics are approved based on matching chemical structure, but that doesn't work for biosimilars. Each new biosimilar has to run clinical trials to prove the outcome matches that of the biologic it's imitating even though it looks structurally different, according to recently announced guidelines from the FDA. A biosimilar product can only be approved by the FDA if it has the same mechanism of action, route of administration, dosage form and strength as the reference product and only for the indication and condition of use that have been approved for the reference product. The facilities where biosimilars are manufactured must also meet the FDA's standards.[5–7]

The opportunities for biosimilars are huge for both manufacturers and consumers. Many leading biologic medicines, worth more than $81 billion global annual sales, will lose their patent protections by 2020. Much like generics, biosimilars can help cut drug costs, though the savings are smaller because of their complexity as well as regulatory challenges of getting FDA approvals. Biosimilars cost about $75 million to $250 million to reach the approval stage, versus around $2 million to $3 million for a generic small-molecule medicine. Biosimilars can only be authorized for use once the period of data exclusivity on the original 'reference' biological medicine has expired. In general, this means that the biological reference medicine must have been authorized for at least 10 years before a similar biological medicine can be made available by another company.[8,9]

2. Authorization of Biosimilars

For the authorization of biosimilar products studies should be carried out to know the products i.e., it is similar to the reference medicine, it does not have any meaningful differences from the reference medicine in terms of quality, safety or efficacy. If the information of the reference medicine is already available, the amount of information needed to recommend a biosimilar for authorization is usually less. An *interchangeable* biological product is biosimilar to an FDA-approved reference product and meets additional standards for interchangeability. An interchangeable biological product may be substituted for the reference product by a pharmacist without the intervention of the health care provider who prescribed the reference product. FDA requires licensed biosimilar and interchangeable biological products to meet the Agency's rigorous standards of safety and efficacy. That means patients and health care professionals will be able to rely upon the safety and effectiveness of the biosimilar or interchangeable product, just as they would the reference product.[10] In 2010, Congress approved the Biologics Price Competition and Innovation Act (BPCIA), creating an abbreviated approval pathway for biosimilars, while maintaining incentives for continued medical advances. The legislative intent was to balance the desire for increased competition among biologics from biosimilar products with the need for incentives to support future medical innovation. Congress achieved this balance by providing biopharmaceutical innovators with 12 years of data protection for biologic medicines. To date, the FDA has issued several draft and final guidance documents to assist biosimilar sponsors in generating data to support biosimilar applications. FDA guidance and regulations provide insight into the agency's current thinking regarding how it will evaluate biosimilar biological products. Biologic medicines are often the only lifesaving treatments for the most severe diseases, but their high price tag can keep them out of reach for many patients. The cost of biologics is increasing at a faster annual pace than any other component in health care. As proven with chemical prescription drugs, biosimilar competition is expected to be the most important opportunity to hold down the cost of biologic medicines. Generic pharmaceutical association (GPhA) is working with the FDA to ensure the approval process is workable and provides for timely availability of FDA-approved safe, effective and less-costly biosimilar medicines.[11–13] The approval process is shown in Figure 1.

The approval process for biosimilars varies from areas of distinction. In the United States, Europe, Japan, Canada and Australia regulatory authorities will require developers to meet high quality, safety and efficacy standards between a biosimilar and the reference product. More specifically, they will require robust analytical, non-clinical and clinical studies. Together, the studies form the "totality of evidence" on which many regulatory authorities will base an approval decision. Therefore, they are important to the regulation of biosimilars. This is depicted in Figure 2. The analytical

data that proves critical quality attributes of a biosimilar have been matched to the reference product needs to be reviewed along with the non-clinical and targeted clinical data package. Regulators will use the total data package to make two key decisions. They are

1. Whether to approve the biosimilar for patient use in the disease indications studied for the biosimilar
2. Whether to approve the biosimilar with extrapolation to the specific set of disease indications listed in the full label of the reference product, including one or more disease indications not clinically studied for the biosimilar
3. FDA has outlined a stepwise approach, which includes a comparison of the candidate biosimilar to the reference biologic in the domains of structure, which is depicted in Figure 3. The physiochemical and biological characteristics and bioequivalence, safety and efficacy are compared.[14,15]

3. Switching to a Biosimilar

Switching typically refers to a physician-guided exchange of one medicine for another with the same therapeutic intent in patients who are undergoing treatment. If a biosimilar has adequately demonstrated that patients can be transitioned or switched from a reference medicine to its biosimilar with no additional risk introduced and similar efficacy maintained, it may be appropriate to switch a patient with the consent of a treating physician. However, repeated switching between different biologic medicines, including biosimilars of the same product that are not designated as interchangeable (US only) should be avoided.[16]

3.1. Substitution of interchangeable biosimilars in the United States:

Substitution is a practice wherein a pharmacist may dispense an alternative biologic medicine for a prescribed biologic medicine without the prior approval of the prescriber. Certain state US law specifies that in order to be eligible for substitution, the biosimilar must be designated as "interchangeable". The US biosimilars pathway offers the opportunity for a drug manufacturer to demonstrate "interchangeability", which is a separate standard than "biosimilarity" and requires additional evidence to achieve.[17–19]

1. An interchangeable biologic is a biosimilar that the FDA has determined is safe for a pharmacist to substitute for the reference biologic product without the intervention of the prescriber
2. To obtain an interchangeability designation, a biosimilar must be expected to produce the same clinical result as the reference product in any given patient
3. According to US regulators, obtaining a designation of interchangeability will include, among other things, successfully conducting switching studies in which patients alternate between the reference and biosimilar products with no loss in efficacy, safety, or immunogenicity versus continued use of the reference product
4. As a general rule, automatic substitution is usually permitted with generic small molecules where the FDA has determined the two products to be therapeutically equivalent
5. Unlike the US, the European Medicines Agency (EMA) has the ability to approve a product as biosimilar, but does not evaluate biosimilars for interchangeability designation. In Europe, the term "interchangeable" typically refers to physician-directed changing of medicines for another medicine in the same class, also commonly referred to as switching. Although European countries are exploring measures to facilitate pharmacy-level substitution of biologics, most European nations currently prohibit that use of biosimilars.[20,21]

3.2. USFDA approved biosimilars

The FDA approved the first biosimilar product, Zarxio (filgrastim-sndz) by Sandoz; a Novartis company is based in Princeton, New Jersey for marketing in the United States in March 2015. This is the biosimilar of biologic Neupogen, is marketed by Amgen, based in Thousand Oaks, California. The approval is based on review of evidence that included structural and functional characterization, animal study data, human pharmacokinetic and pharmacodynamics data, clinical immunogenicity data and other clinical safety and effectiveness data that demonstrates Zarxio is biosimilar to Neupogen.[22–25] It can be prescribed by a health care professional for:

1. Patients with cancer receiving myelo suppressive chemotherapy
2. Patients with acute myeloid leukemia receiving induction or consolidation chemotherapy
3. Patients with cancer undergoing bone marrow transplantation
4. Patients undergoing autologous peripheral blood progenitor cell collection and therapy
5. Patients with severe chronic neutropenia

FDA approved the second biosimilar product Inflectra (Infliximab-dyyb), a biosimilar to Remicade (infliximab) in April 2016. The FDA's approval of Inflectra is based on review of evidence that included structural and functional characterization, animal study data, human pharmacokinetic and pharmacodynamics data, clinical immunogenicity data and other clinical safety and effectiveness data that demonstrates Inflectra is biosimilar to Remicade. Inflectra

is manufactured by Celltrion, Inc, based in Yeonsugu, Incheon, Republic of Korea, for Hospira, of Lake Forest, Illinois. Remicade is marketed by Janssen Biotech, Inc., based in Horsham, Pennsylvania.[26,27] Inflectra can be prescribed by a health care professional for the treatment of:

1. Adult patients and pediatric patients (ages six years and older) with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy
2. Adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response to conventional therapy;
3. Patients with moderately to severely active rheumatoid arthritis in combination with methotrexate;
4. Patients with active ankylosing spondylitis (arthritis of the spine
5. Patients with active psoriatic arthritis
6. Adult patients with chronic severe plaque psoriasis

The most common expected side effects of Inflectra include respiratory infections, such as sinus infections and sore throat, headache, coughing and stomach pain. Infusion reactions can happen up to two hours after an infusion. Symptoms of infusion reactions may include fever, chills, chest pain, low blood pressure or high blood pressure, shortness of breath, rash and itching. Inflectra contains a Boxed Warning to alert health care professionals and patients about an increased risk of serious infections leading to hospitalization or death, including tuberculosis, bacterial sepsis, invasive fungal infections (such as histoplasmosis) and others. The Boxed Warning also notes that lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with tumor necrosis factor blockers, including infliximab products such as Inflectra. Other serious side effects may include liver injury, blood problems, lupuslike syndrome, psoriasis, and in rare cases nervous system disorders.

The FDA approved 3^{rd} biosimilar, a version of Enbrel, the blockbuster arthritis drug made by Amgen that brought in $5 billion in sales in 2015. The newly approved drug, made by Novartis' Sandoz division, with the marketed name Erelzi (August 30, 2016).[28,29] This newest biosimilar is now approved to treat, according to the FDA, the same conditions that Enbrel is approved to treat:

1. Moderate to severe rheumatoid arthritis
2. Moderate to severe polyarticular juvenile idiopathic arthritis
3. Active psoriatic arthritis
4. Active ankylosing spondylitis
5. Chronic moderate to severe plaque psoriasis in adults

FDA approved the 4^{th} biosimilar Amgen's Amjevita on September 23, 2016.[30–33] This is biosimilar to AbbVie's Humira for multiple inflammatory diseases. Humira was approved by the FDA in 2008, is the brand name of a monoclonal antibody (adalimumab) used to treat rheumatoid arthritis, plaque psoriasis, crohn's disease, ulcerative colitis, psoriatic arthritis and hidradenitis supporativa. This drug has appeared as a miraculous shot when no other treatments have appeared to relieve pain and other symptoms of people who have to deal with those diseases every single day. Humira is AbbVie's top selling product. It has been so successful that in the first six months of fiscal 2016, Humira generated 62.3% of AbbVie's total sales and the revenues generated from the drug are close to ten times higher than any of the company's other products. Humira revenues accounted for over $14 billion of its total sales ($22.8 billion) in 2015. In 2014, Humira was even recognized by IMH Health as the "world's best selling drug". But serious infections are observed in people taking Humira. They are tuberculosis (TB) and infections caused by viruses, fungi, or bacteria that have spread throughout the body. Some people have died from these infections. Amjevita is approved for the following indications in adult patients:

1. Moderately to severely active rheumatoid arthritis
2. Active psoriatic arthritis
3. Active ankylosing spondylitis (an arthritis that affects the spine
4. Moderately to severely active Crohn's disease
5. Moderately to severely active ulcerative colitis
6. Moderate to severe plaque psoriasis

The FDA recently approved a fifth biosimilar product, Renflexis (infliximababda; Samsung Bioepis) on April 21, 2017. This is the first US approved treatment developed by Samsung Bioepis. It is a biosimilar copy of the popular rheumatoid arthritis drug, Remicade (infliximab, Johnson & Johnson). Renflexis can be used for multiple indications, including Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis. It has been reported that Remicade is the biggest selling drug for Janssen, with US sales of roughly $5 billion a year, or 9.7% of the company's revenue for fiscal year 2016. However, with two recent biosimilar approvals, the shift in cost for Remicade is still unknown, but Janssen is projecting the competition will reduce sales. Renflexis is a tumor necrosis factor blocker that is administered by 100mg intravenous infusion. It has been reported that the most common adverse reactions include infections, infusion related reactions, headache, and abdominal pain—all similar adverse events that have been observed with Remicade in patients. Renflexis will also have a boxed warning noting that the treatment increases the risk for serious infections that include tuberculosis.[34,35]

Table 1: Differences between biosimilars and generics

Properties	Generics	Biosimilars
Size	Small	Large
Molecular weight	~150 daltons	~150,000 daltons
Structure	Simple and well-defined	Complex with potential structural variations
Manufacturing	Predictable chemical process to make identical copy	Specialized biological process to make similar copy
Complexity	Easy to fully characterize	Difficult to characterize
Stability	Relatively stable	Sensitive to storage and handling conditions
Adverse immune reaction	Lower potential	Higher potential
Manufacturing quality tests	≤ 50	≥ 250
Approval requirements	Small clinical trials in healthy volunteers	Large clinical trials in patients

Table 2: Biosimilars under investigation

Reference product	Estimated patent expiry	Indication	Biosimilar	Manufacturer	Published data
Adalimumab (Humira, AbbVie)	2022	Rheumatoid, psoriatic arthritis, crohn's disease	GP2017	Sandoz	Phase III under way
			PF06410293	Pfizer	Phase I trail underway
			BCD057	Biocad	Phase III
Bevacizumab	2019	Colorectal, lung and renal cancer	BCD-021	Biocard	Phase III trails completed
			PF-06439535	Pfizer	Preclinical/ Phase I trails completed
Cetumimab (Erbitux, Eli Lilly)	Expired (2016)	Colorectal, head and neck cancers	ABP 215	Amgen	Phase III trail under way
			ABP 494	Amgen	Phase III trail under way
Darbepoetin alfa (Aranesp, Amgen)	2018	Anemia due to CKD or chemotherapy	BCD-066	Biocad	Phase III trail under way (2017)
Enoxaparin (Lovenox, Sanofi-Aventis)	Expired (2010)	DVT, VTE	BCD-080	Biocad	Phase III trails under way (2016)
Epoetin alfa (Epogen, Amgen)	Expired (2015)	Anemia due to CKD or chemotherapy	HX575	Sandoz	Phase III trail completed
Glatiramer acetate (Copaxone, Teva)	Expired (2014)	Multiple sclerosis	BDC-063	Biocad	Phase III trails under way (2016)
Infliximab (Remicade, Janssen Biotech)	September 2018	Autoimmune diseases including RA, psoriasis, UC, Crohn's disease	GP 1111	Sandoz	Phase III trails under way
			PF-06438179	Pfizer	Phase III trails under way
			ABP 710	AMGEN	No data available
			BCD-055	Biocad	Phase III (2017)
Pegfilgrastim-(Neulasta,-Amgen)	Expired (Oct 2015)	Chemotherapy induced neutropenia	LA-2006	Sandoz	File accepted by FDA at the end of 2015
Rituximab (Rituxan, Genentech)	September 2016	Lymphoma	GP2013	Sandoz	Phase II and III trails under way
			BCD-020	Biocad	Phase III trails completed
			PF-05280586	Pfizer	Preclinical/ phase I trials completed
			CT-P10	Celltrion	Phase III trials completed
			RTXM83	mAbxience	Phase III trails completed
Trastuzumab (Herceptin, Genentech)	June 2019	Breast cancer	ABP 798	Amgen	No data available
			BCD-022	Biocad	Successful Phase I trails
			PF-05280014	Pfizer	Preclinical/ phase I trials completed
			ABP 980	Amgen	Phase III trails under way
			CT-P10	Celltrion	Phase III trials completed

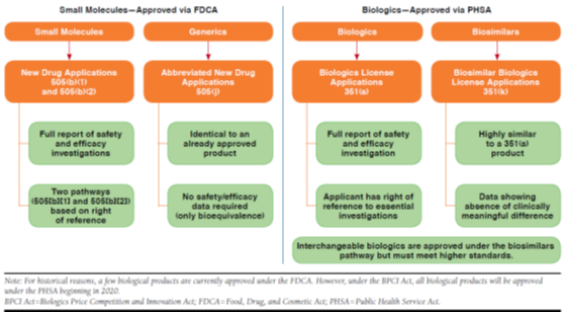

Fig. 1: Approval pathways for biosimilars

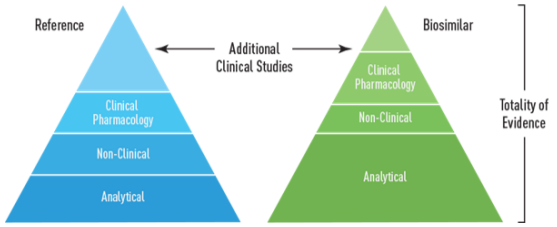

Fig. 2: FDA proposed "Totality of evidence" to demonstrate biosimilarity

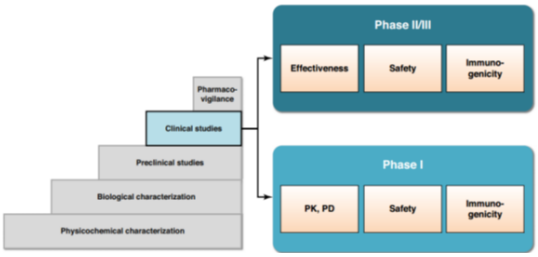

Fig. 3: The stepwise development approach for abiosimilars

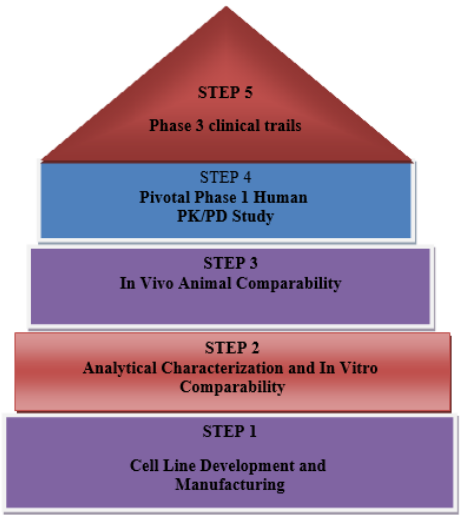

Fig. 4: Five step process to demonstrate bio-similarity

3.3. Process to demonstrate biosimilarity

To earn the confidence of regulators, health insurers, physicians and patients, the manufacturer must show that their biosimilar products are in fact highly similar to the branded products. The five step process (depicted in Figure 4) describes the clinical designs, product development and regulatory strategies of biosimilars. In step 1 process, the amino acid sequence of the candidate biosimilar molecule was validated prior to developing clones. All the clones are expected to produce proteins with the same primary structure, it is essential to select clones that produce proteins which closely matches the glycosylation profile of the originator, if glycosylated since such product quality characteristics impact pharmacokinetics and pharmacodynamics properties as well as safety and efficacy of the molecule. A process to manufacture the desired product must be developed, scale-up and implemented in a GMP facility in order to be used in human clinical trials. In step 2, the analysts determine the chemical and physical similarity of the biosimilar candidate and the original product. The biological activity of the biosimilar was tested by using in vitro pharmacological assays which demonstrate the binding characteristics, functionality and mechanism of action. During Step 3, animal models are using to compare the biosimilar product with original product means pivotal Phase I study. In step 4, clinical studies are done in human subjects to establish PK/PD similarity. The US and European regulatory agencies established requirements for bioequivalence with respect to three prospectively defined parameters as C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. Finally, in step 5, Phase 3 confirmatory safety and efficacy study is carried for approval process.[36]

3.4. Biosimilars are good or bad for patients

The profit of biosimilars is that consumers can get biologics for cheaper. By some estimates, that could save the $250 billion over the next decade. That is good for everyone, provided that biosimilars work as well as the more expensive ones. But there is a downside i.e. Drug companies are investing in biologics and biosimilars because they think they can keep their patents for longer. Since biologics are made from living cells, it takes more work for drug companies to prove to the FDA these drugs are safe and effective. Drug companies invest in biologics because they perceive that biosimilars will not be developed even after the patent expires, because competitors would have to make a relatively large investment to develop a biosimilar and get it approved by the FDA. The biosimilars seems to treat some conditions, such as cancer and autoimmune disorders better than small molecules. Hence, the biosimilars provide clear advantage overall.[37,38]

3.5. Future biosimilars

A number of biological products are soon to lose patent protection and more biosimilars are expected to enter the market. Table 2 lists some of the trials being conducted on biosimilars. If the trails are successfully completed, these products may become available in market in near future.[39]

4. Conclusion

Biotechnological medicines become an important part of future healthcare panorama. The introduction of biosimilars into the U.S. market is an opportunity to moderate costs related to traditionally expensive medications. With patent expiration of innovator products, the biosimilars will increasingly become available. Experience in Europe indicates that these products are therapeutically equivalent to their reference products and confer moderate savings. Awareness of the deviations between biosimilars and innovator products in terms of efficacy, safety and immunogenicity is essential for proper prescription and safety of the patients. Some policy issues remain unresolved in the United States, such as naming, interchangeability and reimbursement. Additionally, pharmacists will have responsibility for substituting biosimilars and incorporating them into the medication use process within their practice. Further, survey studies indicate that more education is needed about biosimilars. Till now, USFDA approved five biosimilars for marketing in US and more number of biosimilars may enter into the market in less time period.

5. Source of Funding

None.

6. Conflict of Interest

None.

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