

Biosimilars: Challenges and the Regulatory Framework

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Abstract

Biosimilars are the successor to a biologic medicine. They represent a niche but a great opportunity in the global biopharmaceutical industry and are currently one of the fastest growing pharmaceutical segments. Their expansion is certain as they address many areas of unmet clinical needs that include many cancers and genetic diseases. They have already hit the market in Europe, though the United States lags significantly and has recently seen its first biosimilar entry into the market. The process of developing a biosimilar is far more complex than the relatively straightforward process of introducing a generic. Biologics are large complex molecules produced by cells in culture or whole organisms and are inherently much more variable. Therefore they present challenges at every level, right from manufacturing, development, testing, reproducibility, nomenclature, labeling, post-marketing surveillance, market entry, physician and patient acceptability. The aim of this article is to provide a brief overview of the scientific and regulatory challenges faced in developing and evaluating similar bio-therapeutic products for global use. The article further details the opportunities involved, which make the biologic drug market entry very attractive though risky.

Keywords: Biosimilars; biological; Pharmaceutical; Regulatory challenges; Regulatory framework; Bio-therapeutics; Labelling; Zarxio; Humira; Monoclonal antibodies

Abbreviations: EU: European Union; US: United States; DNA: Deoxy ribonucleic acid; BPCI Act: Biologics Price Competition and Innovation Act; PHS Act: Public Health Service Act; FDA: Food and Drug Administration; EMA: European Medicines Agency; CHMP: Committee for Medicinal Products for Human Use; MABs: Monoclonal Antibodies; MAA: Marketing Authorization Application.

Introduction

Biological therapeutics market presence is traced back to 1980s when the first recombinant DNA products, insulin and somatropin were approved by the regulatory agencies in EU and USFDA. Subsequent biosimilar entry had been locked until early 2000s in EU while US is yet to see a biosimilar in the market. Regulatory pathways for the approval of biosimilars were not established until 2000s.

The biopharmaceutical (biologics drugs) sector has been one of the best performing sectors over the past few years. This performance has been due to the facts that biologics address areas of unmet clinical needs that include many cancers and genetic diseases, are able to command a premium price and unlike other pharmaceuticals, have not been facing the generic competition. This de-facto monopoly of the innovators/branded biologics have been due to the wide exclusivity periods covering these biologics and the lack of firm regulatory framework to bring cheaper follow-on copy products to the market. Biosimilars are the high investment, high risk and high return sector with complex mechanisms and processes involved for both manufacturers and the healthcare authorities. This article would focus on the potential challenge areas for the biosimilars, the current regulatory pathway comparing US and EU regions and future modeling of the regulatory framework.

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Current Market Trends and Future Potential

Biosimilars are gaining focus as twelve biological products with global sales of more than US \$ 67 billion will be exposed to bio-similar competition by 2020 due to the patent expiry. Namely, Enbrel (etanercept, global sales of US\$7.3 billion), Humira (adalimumab, global sales of US\$7.9 billion) and many others. According to a published study by Allied Market Research, Global Biosimilars Market is expected to reach US\$35.032 Billion by 2020 as new products penetrate the market in North America, Europe and Asia. With the recent regulatory scenario changes, technology advancements and soaring cost of healthcare, biosimilars are being looked upon as mechanism of cost reduction. In the recent news from New York Times, an expert panel recommended on approving the drug EP2006, which is a close copy of Amgen’s Neupogen (filgrastim). EP2006 is already approved in EU as Zarzio. Introduction of EP2006 is anticipated to save \$ 5.7 billion in drug cost in next 10 years [1].

The recombinant glycosylated proteins segment is the largest segment and accounts for a share of 40% of the global biosimilars market in 2013. By application, oncology is the largest and fastest-growing segment and accounts for a share of 25% of the global biosimilars market.

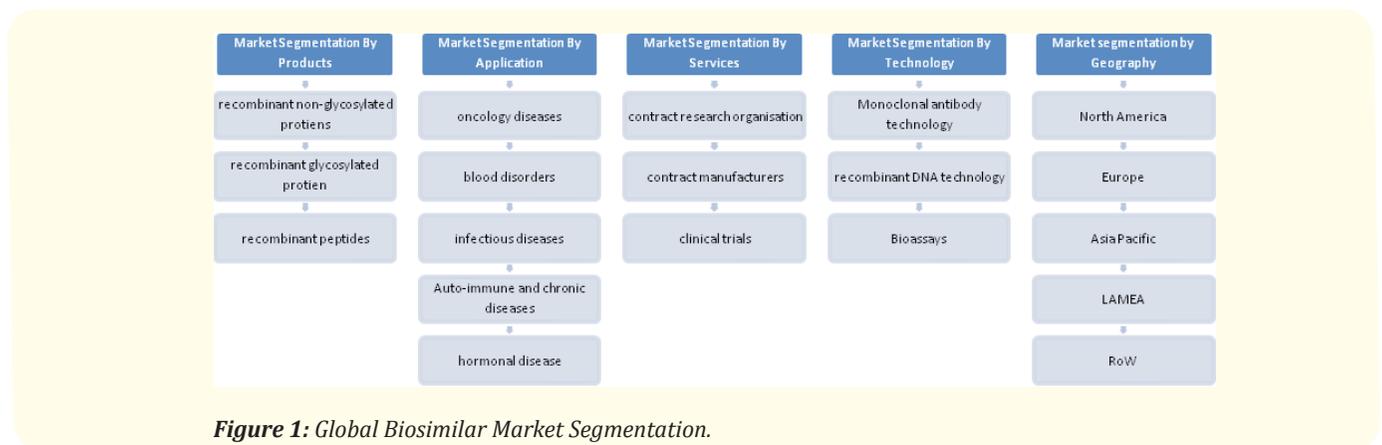


Figure 1: Global Biosimilar Market Segmentation.

Europe dominates the global biosimilars market with around 40% share in 2013. The factors driving the European market are its well-defined regulatory guidelines; presence of various biosimilar drugs such as omnitrope, tepegastim, and binocrits; numerous pipeline products; and more than 15 biologics going off-patent in the coming years. The U.S., on the other hand, has a very restricted biosimilars market owing to the stringent regulatory environment in North America. The Asia-Pacific market is estimated to be the fastest-growing with an overall share of 29% of the global biosimilars market.

The factors restricting the growth of the market are high manufacturing complexities and costs, costly purification processes, stringent regulatory environment in U.S. and Europe and innovative strategies used by biologic drug manufacturers to protect their intellectual property. This is further elaborated later in the article [2].

Regulatory Framework in US and EU

The regulations, both in the United States and Europe, are still in a very early, formative stage. This presents an opportunity for commentary and an exploration of comparative advantage. Regulatory pathway for the abbreviated approval of the biosimilars was defined by US FDA recently through affordable care act, 2010. The BPCI Act was enacted as part of the Affordable Care Act on March 23, 2010. Europe has had an established pathway for biosimilars since 2005.

EMA published guidance documents in 2003, to outline the quality, clinical and non-clinical issues related to comparability of medicinal products containing biotechnology-derived proteins as active substance and in 2005, The Committee for Medicinal Products for Human Use (CHMP) issued specific guidelines concerning the scientific data to be provided to substantiate the claim of similarity used

as the basis for a Marketing Authorization Application (MAA) for any biological medicinal product. Recently there has been revision of the overarching guidance document from EMA in 2014.



Figure 2.

As per Art. 10(4) of Directive 2001/83/EC	As per section 351(i)(2) of the PHS Act
A similar biological or 'biosimilar' medicine is a biological medicine that is similar to another biological medicine that has already been authorized for use.	The biological product is highly similar to the reference product with no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product notwithstanding minor differences in clinically inactive components.

TABLE 1: BIOSIMILAR DEFINED BY EMA (EUROPEAN MEDICINE AGENCY AND USFDA).

The EMA evaluates biosimilar medicines for authorization purposes. The Agency’s evaluations do not include recommendations on whether a biosimilar should be used interchangeably with its reference medicine. For questions related to switching from one biological medicine to another, patients should speak to their doctor and pharmacist. EU Agency’s stand for not defining criteria for establishing interchangeability is a critical point when it comes to define the future of biosimilars. This shall be discussed later in the article along with the other challenges.

The BPCI Act creates an abbreviated licensure pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product. However, there are many follow-on biologics which have been approved in US though 505 (b)(2) route before effect of BPCI act. Omnitrope was approved based largely on comparisons with Genotropin from Pfizer derived from Hatch-Waxman Act–505(b)(2) regulations. The European Union approved Omnitrope and another recombinant E. coli-expressed somatotropin (Valtropin) under its biosimilar regulations based on comparisons with Genotropin and Humatrope (from Eli Lilly), respectively. Others recombinant peptides approved through 505 (b)(2) routes include Calcitonin (Forical), Glucagon (GlucaGen), Hyaluronidase (Hylenex). Although these products were approved to be marketed but it is interesting to note that with this route of approval, equivalence/substitutability is not established for these products and the products are sold under the brand name.

The application/dossier must contain information demonstrating that the biological product is biosimilar to a reference product based upon data derived from analytical studies, animal studies, and a clinical study or studies. Both regulatory agencies have similar requirements for sourcing of the reference product for analytical, non-clinical (*in vitro* and/or *in vivo*), as well as Phase I comparability studies. Both agencies require the reference product to be sourced from the country/region of interest- i.e., for a biosimilar product to be

approved in the US, the reference product has to be sourced from the US, even though the product may have the same name as the one being marketed in the EU. This implicates need of multiple repetitive clinical studies for the applicant which might not even provide any additional information [3].

FDA also defines the conditions for interchangeability. To meet the higher standard of “interchangeability,” an applicant must provide sufficient information to demonstrate biosimilarity, and that the biological product can be expected to produce the same clinical result as the reference product in any given patient and, if the biological product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch (section 351(k)(4) of the PHS Act). It is yet not precisely described that to demonstrate interchangeability, should FDA require the same multi-year span of data that the pioneer originally used to convince the FDA to approve the product in the first place. Interchangeable products may be substituted for the reference product without the intervention of the prescribing healthcare provider (see section 351(i) (3) of the PHS Act).

Also, FDA has a requirement for a transition study in order to garner approval as a biosimilar product in the US. This is one time transition for patients who are on the reference product to be switched to the biosimilar product in development to show that there are no increases in safety events between the pre- and post- switch population. A transition study is not required by EMA.

Biosimilar parameters	European Union	United States
Exclusivity for first interchangeable drug	None	1 year
Regulatory application must show:	Efficacy and safety	Patient benefit
Decisions related to “biosimilarity” determined on case-by-case basis	Yes	Likely
Exclusivity period	10 years	12 years
Postmarketing requirements	Same as pioneer drug	Not yet determined

TABLE 2: BIOSIMILAR DIFFERENCES: EUROPEAN UNION VERSUS UNITED STATES.

Although both EU and USFDA define the biosimilarity very precisely, but practically for the manufacturers to translate this definition in terms of the information details and the analytical data required is a tactical task.

Challenges and Opportunities

There are a number of issues that make approval of biosimilars much more complicated than the approval of generic equivalents of conventional pharmaceuticals. These issues arise due to constitutional complexity of biopharmaceutical agents. The biologicals cannot be replicated to be identical and hence, health authorities have defined similarity. The very first question that arises is “similar to what extent”. Similarity has to be shown in terms of quality, efficacy and safety in head-to-head comparative studies. The products that have been approved and been on market in EU were relatively simple proteins and assessing similarity through comparative analysis was less complicated than what it would be for the large molecules like monoclonal antibodies (mAbs) [4].

Biopharmaceuticals are complex proteins that require multifaceted manufacturing processes and there is a strong relationship between the manufacturing processes of biopharmaceuticals and the characteristics of the final product. Even a minor change in manufacturing processes, protein source and extraction/purification processes may result in heterogeneity of the resulting biopharmaceuticals. Manufacturing process used by the innovator is proprietary information and Biosimilar manufacturers will not have knowledge about the exact process being followed by the innovator. It is to ponder that even when the exact same manufacturing process is replicated, still it is expected to have batch to batch variability in biological product. Therefore it is impossible for a biosimilar manufacturer to produce exact copy of the protein. This makes it all the more important to have extensive analytical data generated to gain confidence and prove similarity between the follow on biologic and the innovator.

A systematic approach with extensive testing and maintenance of strict control on critical process parameters is required. FDA's guidance for industry document "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product" outlines 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. FDA relies on the totality-of-the-evidence approach to review applications for biosimilar products.

Both the regulatory agencies more or less rely on same principles for assessing similarity and do not expect a stand-alone development to support a full Marketing Authorization Application. Preliminary recommended step is a comprehensive physicochemical and biological characterization and a comparative structural and functional characterization. Higher the capability of these studies to identify (qualitatively or quantitatively) the differences in relevant product attributes between the biosimilar and the innovator, the more useful such characterization will be in determining the additional studies/data that may be required [5].

The extent and nature of the nonclinical *in vivo* studies and clinical studies to be performed depend on the level of evidence obtained in the previous step. Generally, the aim of clinical data is to address slight differences shown at previous steps and to confirm comparable clinical performance of the biosimilar and the reference product. Clinical data cannot be used to justify substantial differences in quality attributes. The ultimate goal of the biosimilar comparability exercise is to exclude any relevant differences between the biosimilar and the reference medicinal product. Therefore, studies should be sensitive enough with regard to design, conduct, endpoints and/or population to detect such differences. Analytical techniques that are available currently are not sensitive enough for detecting or predicting all the biological and clinical properties of proteins and hence, differences between biopharmaceutical products can easily remain undetected. For biosimilars, most of which have long half-lives, a crossover study would be ineffective and unethical due to the fact that the wash-out period would be quite long. The patient is not allowed to take the drug during this wash-out period, and hence, will have no treatment for their condition. Therefore, parallel-group studies are required, but these studies do not provide an estimate of within-subject variation. Another barrier is the difficulty in attracting patients to clinical trials of biosimilars. Patients may be reluctant to participate in the trials, especially for serious diseases, because only some of them will receive the biosimilar rather than being confident of receiving the branded biologic outside of a clinical trial [6].

A key element in the demonstration of biosimilarity is establishing that there are no clinically meaningful differences in immune response between a proposed product and the reference product. Structural, functional, and animal data are generally not adequate to predict immunogenicity in humans. Therefore, at least one clinical study that includes a comparison of the immunogenicity of the proposed product to that of the reference product will generally be expected [7].

However, Immunogenicity assays are generally non-quantitative (qualitative) and proving similarity/comparability based on qualitative assays can be very challenging.

In addition to immunogenicity testing, an extensive pharmacovigilance programs is required to monitor the efficacy and safety of biosimilar products post-approval. The importance of immunogenicity testing and pharmacovigilance is illustrated by an incidence associated with biosimilar growth hormone Omnitrope. During development, production of this product was transferred from one facility to another. While qualitative testing demonstrated no notable differences between the end products of these facilities, a difference was observed with respect to immunogenicity, which was subsequently resolved by the manufacturer prior to approval. Both, FDA and EMA focus on post-marketing safety programs and to detect possible differences between reference and biosimilar products, a comparison of frequency and severity of the known side effects of the reference product shall be observed with any differences or new side effects not yet observed with the reference product [8].

Biosimilars to establish on market, a key factor is customer and consumer acceptance. Biosimilars incur a higher research and development costs and hence, the cost of bringing a biosimilar to market is many folds higher than small molecule generic drugs. While a generic drug is 70-80% cheaper than the innovator brand, the differences in the price between a biosimilar and the originator brand in

the region of 15-30% have been suggested in the literature. These numbers don't look lucrative that too with the risk of inherent variability associated with the class of therapeutic in question. However, this price differential can be substantial when applied to expensive biopharmaceuticals and chronic disease management [9].

In addition to all the well-known big challenges, there are some ground level challenges that can be expected. When biosimilars are approved in EU, they are considered 'comparable' and not 'interchangeable' to the reference product. This does not ensure therapeutic equivalence. Inherent differences between biosimilars may produce dissimilarities in clinical efficacy, safety, and immunogenicity. Switching biosimilars should be considered a change in clinical management. This fact may impact user acceptance negatively, when it is about critical care conditions. Consider a patient who has been on a biological medicine for management of cancer or some genetic disorder and the treatment has been working positive for him/her. What would make a physician or patient to alter the therapy and switch to biosimilar, when they are not even assured of therapeutic equivalence? Will cost alone promote acceptance for biosimilars in the market. It's been decades generic products are on market and the market is already matured, still it's not uncommon to hear that patient consider generics to sub-standard and cheap quality medication. To this a medical information officer has a legal/scientific basis to answer that the generic drug has proven therapeutic equivalence to the brand. However, if same question is asked for biosimilars, it would be difficult to convince a patient in a simple language [10].

USFDA has though defined interchangeability criteria but it would be interesting to follow how it is actually implemented. How labeling would differ for biosimilar and interchangeable?

Regulatory agencies have not yet adequately addressed the naming of biosimilars, but this could have a significant impact on patients and providers. Some have suggested that biosimilars and their reference products need distinct names for recognition purposes and for the monitoring of product-specific safety and immunogenicity concerns. Others have argued that distinct naming would help improve the accuracy of patient records. It could also aid in avoiding unintentional substitutions, help physicians properly differentiate among brands, aid patients in identifying which products are branded and which are biosimilars, and increase confidence in biosimilars [11].

The European Commission's proposal for improving the EU pharmacovigilance system stresses the importance of being able to precisely trace a biological product. Specifically, the Commission suggests that marketing authorization holders should advise those completing adverse event reports to provide "the (invented) name and the batch number". Also, in order to improve the pharmacovigilance of biological products including biosimilars, the Commission has proposed that Member States ensure that biological medicinal products that are the subject of adverse reaction reports be identifiable i.e. traceable [12].

The information provided on the labels of biosimilars will be a strong determinant of physician comfort with the products. Although guidelines about packaging and labeling of biosimilars have not yet been set, but it is clear that labels should include clear, informative, and unique information. For physician ease and patient comfort, labels should include information about how clinical data for a biosimilar were obtained (e.g., how many trials were conducted and what information was extrapolated from the reference product), whether the biosimilar is interchangeable (and a warning against substitution if it is not), and whether data were extrapolated from other indications. Moreover, a biosimilar should be clearly labeled with tracing information to facilitate adverse event reporting [13].

The reference product companies have not sat idly by, and have responded in different ways to the potential entry of biosimilars. They have followed strategies such as "improvements to the first-generation products, reducing the frequency of dosing schedules, and providing more convenient administration technologies [that] may extend patent protection" or achieve new exclusivity. Other strategies include price decreases, patent defenses, and extensions, as well as the use of trade secrets.

Discussion

At this point in time, biosimilar market/development and manufacturing is in a formative phase. Biosimilars development presents challenges at every level, from selection of a manufacturing platform, to analytical assays demonstrating comparability, to in vivo testing and clinical testing, market access, and post marketing surveillance. Though there are challenges, but the sponsors can minimize roadblocks while streamlining biosimilar development by frontloading analytical methods that demonstrate comparability with the reference molecule, selecting animal studies judiciously, and preparing to maintain a Phase IV drug registry. Companies that navigate these activities successfully may be rewarded with an expedited regulatory review.

Conclusion

As the market matures and the manufacturer gain experience with biosimilar developments and production, technology advancement will happen. Health authorities through their combined experience of approval process from original biologics as well as biosimilar will gain more confidence with this product segments and during the course there will be regulatory changes based on these experiences. With more products in market and if strong pharmacovigilance plans are in place, biosimilars will acquire market in due course of time. Once the product segment is established total cost of bringing the product to market is expected to decrease and so would be the healthcare cost. All in all, future looks brighter for the biosimilars.

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