Original Research Paper

Volume - 7 | Issue - 6 | June - 2017 | ISSN - 2249-555X | IF : 4.894 | IC Value : 79.96

Management

# Tapping the Regulatory Hurdles of Biosimilars: Marketing Authorization across European Union

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**ABSTRACT**

**Background:** The European Medicines Agency (EMA) has led the way in the development of regulatory guidelines for the development and assessment of biosimilars by providing an overarching regulatory approval framework for biosimilars and subsequently approving its first biosimilar the following year in 2006. The complexity of establishing bio-similarity with reference biological product lies in the way of developing biosimilars in compliance with regulatory path.

**Objective:** The objective of the study is to assess the Regulatory aspects of Biosimilars in the European Union.

**Methods:** Researcher has adopted an exploratory design with the Dual approach system to establish the objectivity of the research study.

**Findings:** Through the totality of evidence approach in alignment with the ABCE of biosimilars and ascertaining the evidence data points in the registration dossier for marketing authorization, streamlines the regulatory challenges buckled for the marketing approval of biosimilars in the European Union.

**Conclusion:** Tapping the regulatory hurdles relies on the deployment of totality-of-evidence approach to establish biosimilarity in line with reference biologic.

**KEYWORDS :** Biosimilars, Reference Biologic, European Union, EMA, Marketing Authorization.

## BACKGROUND

Biologics are therapeutic proteins, derived from genetically modified living sources such as bacteria, yeast or mammalian cells.[1] Since the cell lines in a given source are unique and generate drug products via complex biological systems and production methods, the biopharmaceuticals manufactured by various companies other than the original biologic innovator are not considered to be as identical molecular copies, so the term biosimilars was created for the products that are similar, but not identical to the reference biologic molecules.

A **Biosimilar** is a biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product (reference medicinal product). A biosimilar demonstrates similarity to the reference product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise.[2]

The **European Medicines Agency** (EMA) has led the way in the development of regulatory guidelines for the development and assessment of biosimilars by providing an overarching regulatory approval framework for biosimilars and subsequently approving its first biosimilar the following year in 2006.[3] Since then, the European Union (EU) has led the world in biosimilar development, having approved 29 different biosimilar products as of February 2017 and these EU guidelines on biosimilars are updated in 2014.[3]

In 2009, World Health Organisation (WHO) developed a set of globally accepted standards to ensure the safety, efficacy and quality of similar biotherapeutic products (SBPs). These were mainly targeted to aid and ensure regulatory authorities of all the nations to adhere to the international standards. Ever since there has been a rapid evolution of guidelines and most of the countries have adopted the general framework of either EMA or WHO, while others have established their individual national guidelines based on either of these templates. For instance, Australia adopted the EU guidelines without any changes, while Singapore and Malaysia amended their guidelines mainly in accordance with the EMA guidelines.[4]

The US FDA was a late entrant in formulating the biosimilars regulatory pathway. On March 23, 2010, the Biologics Price Competition and Innovation Act (BPCIA) were signed as part of the Patient Protection and Affordable Care Act, which created a new licensure pathway for biosimilars within the domain of US FDA. Biosimilar applications are to be submitted under section 351(k) of the Public Health Service Act and the FDA has issued 3 draft guidance documents in 2012, recommending a stepwise approach to demonstrate biosimilarity by laying importance on totality of evidence.[4] In March 2015, FDA approves the first biosimilar in the U.S, Zarxio (Filgrastim-sndz) by Sandoz.[5]

### Biosimilars scenario in Europe

In fact, biologics have transformed the clinical outcomes for patients across Europe but their high cost factor has put a heavy strain on European healthcare systems. Biosimilars improves patient access to treatment and are economical for European healthcare systems. This is for two main reasons; firstly, the development of biosimilar medicines builds on the scientific knowledge obtained with the reference biological medicine and not all the phases of clinical studies carried out with the reference biologic need to be repeated. Secondly, after launching in the market, biosimilars competes with the reference biologic for sustainability and as a result, they are offered at economical price value.

A company chooses to develop a biological medicinal product claimed to be "similar" to the reference biological medicinal product, which has been granted a marketing authorisation in the European Economic Area (EEA) on the basis of a complete dossier in accordance with the provisions of Article 8 of Directive 2001/83/EC, as amended. For this scenario, the legal basis of Article 10(4) of Directive 2001/83/EC and Section 4, Part II, Annex I to the said Directive lays down the requirements for the Marketing Authorisation Applications (MAAs) based on the demonstration of the similar nature of the two biological medicinal products. Comparability studies are required to generate evidence substantiating the similar nature in terms of quality, safety and efficacy of the similar biological medicinal product and the chosen reference biological medicinal product authorised in the EEA.[6]

The Committee for Medicinal Products for Human Use (CHMP) issues specific guidelines concerning the scientific data to be provided to substantiate the claim of similarity used as the basis for a Marketing Authorisation Application (MAA) for any biological medicinal product and is defined in Section 3.2.1.1, Part I, Annex I to Directive

2001/83/EC, as amended. The legal basis for similar biological applications are found in Article 6 of Regulation (EC) No 726/2004 and Article 10(4) of Directive 2001/83/EC, as amended. The dossier requirements for similar biological medicinal products are found in Part II, Section 4 of the Annex I of Directive 2001/83/EC, as amended. In addition to these, Guidelines on similar biological medicinal products containing biotechnology-derived proteins as active substance: Quality issues (EMA/CHMP/BWP/247713/2012) and the Guidelines on similar biological medicinal products containing biotechnology-derived proteins as active substance: Non-Clinical and Clinical issues EMEA/CHMP/BMWP/42832/2005 Rev) are to be focused for biosimilar approach.[6] Biosimilars Regulatory Pathway of EMA is depicted as below (Figure-1).

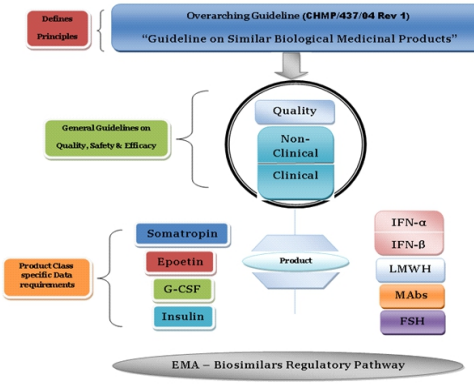


**Figure 1: EMA – Biosimilars Regulatory Pathway**

Omnitrope (Somatropin) by Sandoz was the first product approved in the EU as biosimilar in 2006 and till date, EMA has approved 29 biosimilars within the product classes of Human growth hormone, Granulocyte colony stimulating factor, Erythropoiesis stimulating agent, Insulin, Follicle stimulating hormone (FSH), Parathyroid hormone and Tumor necrosis factor (TNF) inhibitor, for use in the EU nations. Two biosimilar approvals have been withdrawn; One for Filgrastim in April 2011 and other for Somatropin in May 2012, leaving a total of 27 biosimilars approved for use in Europe by February 2017.[7]

Between 2006 and 2014, biosimilar medicines have increased patient access by 44% overall within in the EU-5 countries.[8] Global biosimilars sales in 2015 reached only $1.7 billion, but by 2020 biosimilars penetration is expected to have delivered from $11 billion to $33 billion in savings across the EU.[9]

## OBJECTIVE OF THE STUDY

The objective of the study is to assess the,

1) Regulatory challenges and apt strategies for marketing authorization
2) Impact of regulations on commercialization of Biosimilars in the European Market.

## RESEARCH METHODOLOGY

The researcher adopted an exploratory study with the Dual approach system to establish the objectivity of the research study. The first step, involves the retrieval of entropy of the information from various data sources and the second step implies the Discussion-Framework technique, with the panel of experts of the domain to have a qualitative content emphasis and is transcribed to objective insight.

## FINDINGS & DISCUSSION

### Regulatory Challenges

The biosimilars poses substantial challenges to the companies for regulatory authorisation. These include the following;

#### *Establishing Biosimilarity in line with Reference Biologic*

Biosimilarity is to be established to denote the comparability between a biosimilar and its reference biologic. The marketing authorisation of a biosimilar is based upon a regulatory assessment that the applicant has demonstrated the product's similarity to the reference biologic as outlined in the Committee for Medicinal Products for Human Use (CHMP) of EMA - Scientific Guidelines on Biosimilar Medicines. **Comparability** is the core principle of a biosimilar development.[10]

Extrapolation of clinical efficacy studies to other indications of the reference biologic, which are not specifically studied during the clinical development of the biosimilar product is achievable based on the overall evidence of comparability rendered with suffice scientific justification (European Commission, 2013). The comparability exercise with reference to innovator biologic is executed in 3 steps to ensure biosimilarity.[6]

a) First step: Quality comparability studies
b) Second step: Non-Clinical comparability studies
c) Third step: Clinical comparability studies.

#### *Assessment of Immunogenicity*

All the biologics demonstrate a greater capacity to elicit an immune response as they are protein derived compounds and therefore might be recognized by the human immune system as antigens. **Immunogenicity** is the capability of a specific product to elicit an unwanted immune response that is triggered by more than one single factor. The immunological response is complex as it triggers antibody formation and leads to events such as T-cell activation thereby contributing to loss of effect of the biologic medicine and any potential adverse effect in the patients. However, in many patients, an immune response does not lead to any clinical consequences. Immunogenicity may be influenced by factors relating to the biologic development process, the individual susceptibility of a patient and further immunogenic studies are required after marketing authorisation too. So, the assessment of immunogenicity is also a part of Post-approval Risk Management Plan (RMP) i.e. Pharmacovigilance activities.[11]

These challenges are to be figured out to attain the marketing authorization for biosimilars in the respective market.

### Strategies to Counter the Regulatory Challenges

The **totality-of-evidence** approach has to be deployed for establishing the biosimilarity to the reference biologic, as to obtain the regulatory approval for market authorization. The approach involves the streamlining of clinical development process by endearing **ABCE** of biosimilars and ascertaining the totality of evidence in the **registration Dossier** of marketing authorization.

The totality of evidence establishes the analytical and biological relation data points and adhere data extrapolation in line with the reference biologic[12] by endearing the ABCE path.[13](Table-1)

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| A - Accuracy of Analytics (Analytical demonstration and Biological characterization) |
| B - Bridging of Clinical data points |
| C - Curb the expectation of Clinical trials in every indication |
| E - Embrace Extrapolation. |

**Table 1: ABCE of Biosimilars**

The approach exploits the variations by analytical demonstration and justifies the biosimilarity via the clinical development process as a whole. The analytical characterization and clinical trial process is imbibed as the comparability studies as a whole in line with reference biologic.

Every biosimilar product application will be assessed on the individual basis and the EMA has released both the general and product specific guidelines in terms of quality, non-clinical and clinical issues and immunogenicity for every biosimilar product category.[3]

Besides it, the clinical development strategies should focus on patient selection, recruitment and appropriate clinical endpoints. The patient and sample size selection and recruitment is accelerated on case to case basis and incorporating appropriate clinical endpoints including validated biomarkers of efficacy and any surrogates on case basis with an integrated protocol design as a part of clinical trial design is a requisite to establish biosimilarity with the reference biologic.[14]

The registration dossier for a biosimilar comprises of a data package based on the scientific guidelines as per EMA. The dossier filed is accessed via the centralized procedure involving the two independent assessment teams from two member states and scientific experts from all the other member states.[11] The data package imbibed in the dossier (Table-2) should ensure the biosimilarity and then the biosimilar receives the marketing authorization from the European Commission.

| | |
|---|---|
| Quality Data | Data points on manufacturing process, process controls, analytical tests and stability data i.e. analytical demonstration data. |
| Non-Clinical Data | Data on In-Vitro studies and in case of exceptionality, it implies PK & PD studies along with tolerability case models. |
| Clinical Data | Data of both positive and negative results of clinical trials and also postulates the data on Immunogenicity. |
| Pharmacovigilance | Data on the Risk Management Plan (RMP) and Pharmacovigilance system postulating the Periodic Safety Update Reports (PSURs). |

**Table 2: Data Package imbibed in Dossier for Marketing Authorization by EMA**

A summary pertaining to the biosimilar data and its assessment is made accessible in the public domain as European Public Assessment Report (EPAR) by EMA, after issuance of the marketing authorisation by the European Commission. The Risk Management Plan (RMP) is imbibed in the EPAR after authorization of the biosimilar product and is to be updated throughout the lifetime as a part of Pharmacovigilance system.[11]

Through the totality of evidence approach in alignment with the ABCE of biosimilars and ascertaining the evidence data points in the registration dossier for marketing authorization, streamlines the regulatory challenges buckled for the marketing approval of biosimilars in the European Union. As soon as the European Commission has cleared the path for marketing authorization, the companies then should focus on the commercialization strategies to ensure the biosimilar product in the market space.

**Impact of Regulations on Commercialization**

One of the major gray areas is **Interchangeability** in the European Nations. The EMA had announced that the member nations are solely responsible to decide upon the issue and the nations have framed their policies on interchangeability as par with EMA guidelines and the policies differ across the EU.[15] (Table-3)

| Interchangeability Regulatory Landscape |
|---|
| **France**<br>In 2014, the legislation has passed allowing the automatic substitution but with the informed choice of the patient. |
| **Germany**<br>No authorized legislation regarding interchangeability, but the pharmacist can substitute a biosimilar in consultation of physician |
| **UK**<br>Interchangeability is not allowed and the switching depends on the physician based on the case. |
| **Spain**<br>Interchangeability is not allowed and the switching depends on the physician as a part of economic prescribing pattern. |
| **Italy**<br>Interchangeability is not allowed and the AIFA has stated that the physicians can prescribe biosimilars for the patients naive to the therapy case. |

**Table 3: Interchangeability Regulatory Landscape across Eu5**

The **Name Game** has revolved around **INN** (International Non-Proprietary Name) to the biosimilars in Europe, while many industry leaders favor in giving a unique INN to biosimilar versions corresponding to reference biologic, but the EMA in 2009, has stated that the biosimilars are referred by their unique trade/brand names rather than INN system and the INN of a biosimilar is identical to its reference biologic. For instance, the European packaging of Zarzio (Filgrastim Biosimilar) by Sandoz denotes the product by its trade name.[16]

The **Labeling and Public Information** of biosimilars should aims to provide an orbit of information on safety and efficacy and about dosing and administration pattern in line with reference biologic. The innovator biologic companies are of the strong opinion that specific rules should be deployed by EU for the biosimilar companies, to clearly denote their product is a biosimilar to the innovator biologic and also the biosimilar labeling should denote the way in which every indication has been approved by EMA, thereby demonstrating safety and efficacy. In the recent years, these elements are reported in the European Public Assessment Reports (EPARs) by EMA and also to extent, in the product literature of biosimilar. In support to this, the UK Medicines and Healthcare Products Regulatory Agency has announced that biosimilars will carry a **Black Triangle** symbol, as to denote biosimilars and that should be monitored for the emergence of any adverse events. In March 2013, the European Commission adopted the symbol for the biosimilar products.[17]

The aspect of **Pharmacovigilance** is related to Immunogenicity issue of biosimilar and any other adverse events. The risk of immunogenicity is to be monitored by surveillance of biosimilars via patient health records. As the biosimilars are marketed, the companies should prepare reports on regular basis to review the safety data and are called as Periodic safety Update reports (PSURs). Along with this, Post-Authorisation Safety Studies (PASS) are also a requisite and to ascertain the safety profile of biosimilars, the EU Pharmacovigilance legislation has stated that biosimilars should include a Black symbol and a sentence inviting the reporting of adverse effects/events, these are to be included in the summary of product literature as well as patient information leaflet. The identification of adverse reaction with regards to manufacturing is of crucial one for biosimilars, so the EU legislation requisites the name of the biosimilar as well as its batch number to be included in the adverse drug reaction (ADR) report. The **EudraVigilance** system ensures the reporting of adverse reactions to the EMA or National Competent Authorities (NCA) by biosimilar companies, physicians, nurses and patients through the continuous screening and evaluation effective Pharmacovigilance system.[11]

Tapping the regulatory hurdles by overwhelming the impact of challenges on commercialization requisites the Pharmacovigilance surveillance and winning firms will build agile framework that allows them to quickly incorporate real world evidences, translating into insights to enable decisive responses in view of regulatory prospects, thereby ascertaining the successful market authorization phenomenon of Biosimilars across the European Nations.

## CONCLUSION

Biosimilar companies seeking to enter in to the European market are struggling to sweep over the unique challenges at the regulatory level for biosimilars. From navigating the complex EMA regulatory landscape to ascertaining the market authorization, the roadmap for biosimilars is riddled with the regulatory path and its impact on commercialization, to craft a strategy for market authorization.

In order to ascertain the integrated prospects of regulatory approval, the unique challenges of it are to be addressed by streamlining the clinical development process and demonstrating the data of real world evidences. The regulatory strategies must address the specifications pertaining to the product, its indications and the market by deploying the totality-of-evidence approach for establishing the biosimilarity of the product in line with reference biologic, so as to gain the marketing authorization from the European Commission via EMA and overwhelming the impact of challenges of it on commercialization requisites the Pharmacovigilance surveillance.

Utmost, the successful market approval relies on the regulatory roadmap phenomenon by countering the impact of it on commercialization enacts as the winning strategy to gain the authorization across European Union.

## LIMITATION AND FURTHER SCOPE OF STUDY

The researcher has explored and identified the Regulatory considerations of Biosimilars in European Union by thorough research. Due to short of resources like time, materials and funds in this domain, researcher could not study the detailed Pharmacovigilance system of Biosimilars. Future is driven by Biosimilars and there is tremendous scope of study on Pharmacovigilance aspects of the domain across EU.

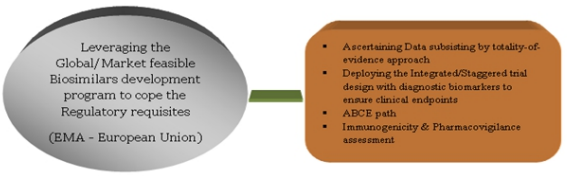
## ACKNOWLEDGEMENT

I express my sincere gratitude to my family members, research supervisor and domain experts for the continuous support, guidance and motivation to complete this research work.

## CONFLICT OF INTEREST

Authors declare no conflict of interest.

## PICTORIAL ABSTRACT




**Biosimilars – EMA Regulatory Requisites**

## SUMMARY

- The Objective of this exploratory research is to study the Regulatory aspects of Biosimilars in the European Union.
- Biosimilars poses substantial challenges for companies to gain marketing authorization from EMA because of their complexity.
- The Dual approach system is deployed for the study to assess the regulatory hurdles and strategies to counter them.
- Based on this study findings, it was identified that through the totality of evidence approach in alignment with the ABCE of biosimilars and ascertaining the evidence data points in the registration dossier for marketing authorization, streamlines the regulatory challenges buckled for the marketing approval of biosimilars in the European Union.
- Ultimately, the research establishes that tapping the regulatory hurdles relies on the deployment of totality-of-evidence approach to establish biosimilarity in line with reference biologic.

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