Review Article **CODEN: IJRPJK** **ISSN: 2319 – 9563**

International Journal of Research in Pharmaceutical and Nano Sciences

Journal homepage: **www.ijrpns.com**

A REVIEW ON BIOSIMILAR DRUGS

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ABSTRACT

It seems biological medicines are set to play a major part in the pharmaceutical industry's future and they already play a major part in its current growth. At the moment, biologicals account for 10 -15% of the pharmaceutical market. More than one-fifth of new medicines launched on the world market each year are now biotechnology derived. The objective of this article is to facilitate regulatory requirements for the approval process of Biosimilars and the need for Biosimilar product class-specific guidelines in Regulated and emerging markets. Biosimilars are biological products that are the replicas of their innovator biopharmaceuticals. Specified regulations, and approval process of generic version of biologicals exists depending on the country. Each class of biologic varies in its benefit / 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 biological products like monoclonal antibodies (mAbs), interferon beta and insulin.

KEYWORDS

Biosimilars, Generics, Recombinant technology, EMA, WHO and FDA.

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INTRODUCTION

Biosimilars also known as follow on biological and biologic medical products whose active drug substances are made by a living organism or derived from a living organism by means of recombinant DNA or controlled gene expression methods[1].

Biosimilars (or follow-on biologics) are terms used to describe officially approved subsequent versions of innovator biopharmaceutical products made by a different sponsor following patent and exclusivity expiry on the innovator product[2]. Biosimilars are

also referred to as subsequent entry biologics (SEBs) in Canada[3]. Reference to the innovator product is an integral component of the approval.

Unlike the more common small molecule drugs, biologics generally exhibit high molecular complexity, and may be quite sensitive to changes in manufacturing processes. Follow-on manufacturers do not have access to the originator's molecular clone and original cell bank, nor to the exact fermentation and purification process, nor to the active drug substance. They do have access to the commercialized innovator product. Differences in impurities and/or breakdown products can have serious health implications.

The biggest challenges facing biosimilar drug developers is proving the equivalence or similarity of their biological drug to the reference product because of great variation in properties and even small alterations can lead to unacceptable changes in safety and efficacy. So there is a need of class-specific guidelines for various complex molecules of biological. The EMA has developed product class-specific guidelines for erythropoietin's, insulin's, growth hormones, Alfa interferon, granulocyte-colony stimulating factors and low-molecular weight heparins (LMWH), with three more (beta interferon's, follicle stimulation hormone, monoclonal antibodies) currently being drafted.

The Biosimilars Playing Field

Over the next 10 to 15 years, the biologics market is expected to grow rapidly and continues to gain share relative to small molecules, while simultaneously, the biosimilars industry is expected to explode, as the patents on branded biologics begin to expire. Analysts agree that biosimilar market size will be fairly significant in the next few years, ranging between $2-3 billion by 2015[11,12].

Forces driving the rapid expansion of the biosimilars industry are an ever-increasing pressure

To reduce healthcare costs, expectations for booming market growth due to patent expiry of high-value innovator biologics, and better-defined regulatory pathways.

REGULATORY REQUIREMENTS

World Health Organisation[4] (WHO)

As an increasingly wide range of SBPs are under development or are already licensed in many countries, WHO formally recognized the need for the guidance for their evaluation and overall regulation in 2007. "Guidelines on Evaluation of Similar Bio therapeutic Products (SBPs)" was developed and adopted by the 60th meeting of the WHO Expert Committee on Biological Standardization in 2009. WHO Guideline issued April 2010. Scope (4): Well-established and well-characterized biotherapeutic products such as recombinant DNA therapeutic proteins, vaccines and plasma derived products and their recombinant analogues are out of scope. Key principles for evaluation of SBPs are basis for setting national requirements. In these guidelines WHO covered the regulatory requirements for quality, safety and efficacy of SBPs quality as a prerequisite for the reduction of the non-clinical and clinical data set requirement for licensure. The intention of the guidelines is to provide globally acceptable principles for licensing biotherapeutic products that claim to be similar to that of the reference products which have been licensed based on a full sale licensing dossier. The WHO has not issued product specific nonclinical or clinical guidelines.

European Union (EU)

Biosimilars were first introduced in Europe today; the continent has the largest biosimilars market in the world. In 2010, the European biosimilars market generated revenues of approximately $172 million. As on 31st December, 2010 14 biosimilar drugs have been approved in Europe. EU has an approached route of thought and which is also an evidence-based approach, established a well-documented legal and regulatory pathway for the approval of biosimilar products which is distinct from the generic pathway. In order to grant a biosimilar product, the EMA requires comprehensive and justified comparability studies between the biosimilar and the reference products in the quality, nonclinical, and clinical level, which are explained in detail in the EMA guidelines[5]. The

approval pathway of biosimilar products in the EU is based on case-by-case reviews, owing to the complexity and diversity of the biologic products. Therefore, besides the three general guidelines, EMA also developed additional product class specific guidelines on non-clinical and clinical studies.

- Quality Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Quality issues (EMEA/CHMP/BWP/49348/2005).
- The Guideline on development, production, characterisation and specifications for monoclonal antibodies and related substances (EMEA/CHMP/BWP/157653/2007).
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical, clinical issues in (EMEA/CPMP/42832/2005).

Specific Guidelines[6]

Each class of biologic varies in its benefit / risk profile, the nature and frequency of adverse events, the breadth of clinical indications, and whether surrogate markers for efficacy are available and validated. Accordingly, the EMA has developed product class specific guidelines that define the nature of comparative studies. So far, guidance for the development of biosimilar products has been developed for six different product classes, including erythropoietins, insulins, growth hormones, Alfa interferons, granulocyte-colony stimulating factors and low-molecular weight heparins (LMWH), with three more (beta interferons, follicle stimulation hormone, monoclonal antibodies) currently being drafted[7]. This approval pathway is now held as one of the golden standards for authorizing biosimilar products.

- In 2011 the overarching guideline the quality issues and the nonclinical and clinical issues guidelines plus the erythropoietin and insulin-specific guidelines are under revision. The first draft guideline for recombinant follicle stimulation hormone is released.
- In 2010 the long-awaited draft guideline for monoclonal antibodies is released for consultation.
- In 2008 the draft guideline for low-molecular-weight heparins is issued (adopted in 2009).
- In 2007 the draft guideline for interferon beta is issued (adopted 2009).
- In 2005 the EMEA releases the general guideline drafts for “quality issues” and “non-clinical and clinical issues” and a little later, it releases draft guidelines for erythropoietin, growth hormone, G-CSF and insulin. All are adopted in 2006.

United States of America (USFDA)

The market[8] in the United States for Biosimilar reached $507 million in 2010 and $1.1 billion in 2011. The market is expected to reach $1.3 billion by 2016, a CAGR of 4.1%. In US in the past, some of the biopharmaceuticals have got approved as 505(b) (2) generic drugs and entered the market. In March 2009, the “Promoting Innovation and Access to life-saving Medicines Act” as introduced to the US Congress, authorized US Food and Drug Administration (FDA) to approve follow-on biologics/biosimilars in an abbreviated manner. The approval of abbreviated biosimilar/biologics license applications (bBLAs) or 351(k) filings is based largely on the sponsors proving structural, composition and clinical similarities with a reference product. The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was enacted as part of the Patient Protection and Affordable Care Act on 23rd March, 2010. The BPCI Act has created an abbreviated licensure pathway for biological products demonstrated to be biosimilar to, or interchangeable with, a reference product. In the US, no products have been approved yet under a biosimilar pathway, but two have been approved under the 505(b)(2) regulatory pathway of the Federal Food, Drug, and Cosmetics Act Enoxaparin (Lovenox), a low-molecular heparin; and Omnitrope (Genotropin), a generic of the growth hormone. Since March 2010, the US provisions for biosimilars have been defined via the Patient Protection and Affordable Care Act

(PPACA). They are set out in PPACA[9] Sections 3139 and 7001 to 7003. The latter sections are the Biologics Price Competition and Innovation Act of 2009 (BPCIA), which inserts Sections 351(k), 351(l), and 351(m) into the Public Health Service Act (PHSA), introducing the approval pathway for biosimilars. On 9 th February, 2012, the FDA published three draft guidance[10] documents on biosimilar product development.

Interchangeability of Biosimilar

Another important issue raised by the BPCI Act is the interchangeability of biosimilars. Once approved, standard generic drugs can be automatically substituted for the reference product without the intervention of the healthcare provider in many states. However, the automatic interchangeability cannot be applied to all biosimilars. In order to meet the higher standard of interchangeability, a sponsor must demonstrate that the biosimilar products can be expected to produce the same clinical result as the reference product in any given patient. Similar to the requirement of the WHO and EMA, a number of factors are considered important by the FDA when assessing applications for biosimilars, including the robustness of the manufacturing process, the demonstrated structural similarity, the extent to which mechanism of action was understood, the existence of valid, mechanistically related Pharmacodynamic assays, comparative pharmacokinetics and immunogenicity and the amount of clinical data and experience available with the original products in Figure No.1.

INDIA (CDSCO)

In India, apart from Central Drugs Standard Control Organization (CDSCO), the office of Drug Controller General of India (DCGI) the apex regulatory body under Government of India (GoI), two other competent authorities are involved in the approval process of biosimilars or Similar Biologics products (SBPs). These include: Review Committee on Genetic Manipulation (RCGM), which works under Department of Biotechnology (DBT), Ministry of Science and Technology. RCGM regulates import, export, carrying out research, preclinical permission, No objection certificate for clinical trial (CT) and other related activities involving genetically modified organism (GMO), as per the DBT guidelines. Genetic Engineering Approval Committee (GEAC), which functions under the Department of Environment (DoE) as a statutory body for review and approval of activities involving large scale use of genetically engineered organisms (Living Modified Organism - LMO) and their products in research and development, industrial production, environmental release and field applications. As far as the products are concerned, various biosimilar products being marketed currently include Erythropoietin, Human Growth Hormone, Recombinant Human Insulin, G-CSF, and Interferon. Industry statistics indicate that in 2010, Epoetinalfa (Erythropoietin Biosimilar) occupied more than 40% of the market share, followed by Filgrastim (G-CSF Biosimilar) with 33% market share, and Somatropin (Human Growth Hormone Biosimilar) with 25% market share.

The Indian Biosimilar industry is estimated to be a US$ 338 million industry that has been growing at a compounded Annual Growth Rate (CAFR) of 30% since 2008. This growth rate is expected to continue till 2012. There are around 25 Indian companies operating in the Biosimilar space, marketing close to 50 products in the Indian market and few of these products in some of the unregulated markets. India had approved approximately 50 Biosimilar products up until December 2011 in Figure No.2.

ICH Harmonization

Though the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has not yet formulated any guidelines specific to biosimilars, some of its guidelines (Q5) on biotechnology products are relevant to this area. Fundamental basic information we would have to submit for biosimilars are the following:

- Information of authenticity of the active substance and medicinal drug (biosimilar) production process in comparison with the production processes of the active substance and reference biological medicinal product.

- Proofs of structural similarity with the biological medicinal product and composition identity.
- Reports on pre-clinical (non-clinical) comparative studies aimed at detection of differences in pharmacotoxicological properties of the biosimilar and reference biological medicinal product.
- Reports on clinical studies containing the established equivalent quality and safety, safety and immunogenicity information presented on the basis of the study of a certain number of Patients sufficient for determination of the biosimilar adverse reactions nature, and comparison of the nature, frequency and severity of adverse reactions of the biosimilar with reference biological medicinal product.
- Instructions on medical application with specification that the medical product is a biosimilar.
- The clinical safety of biosimilar products should be followed and monitored on an on-going basis during post-marketing surveillance. Although there are still differences, the authorities are in contact to further harmonize them.

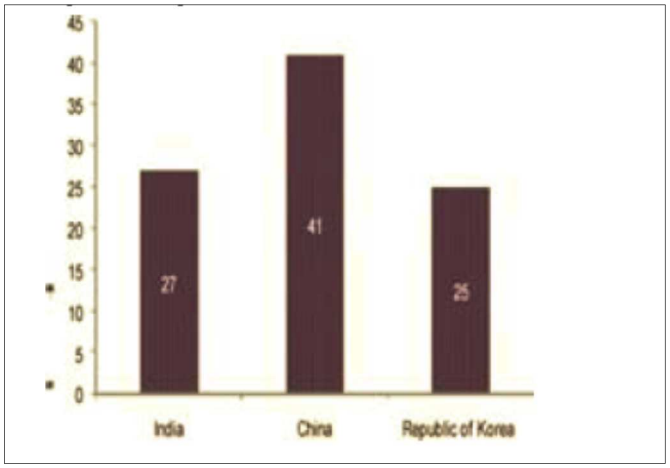

Figure No.1: Bio-Pharmaceutical companies actively engaged in Biosimilar by country, 2011-2012 [11]

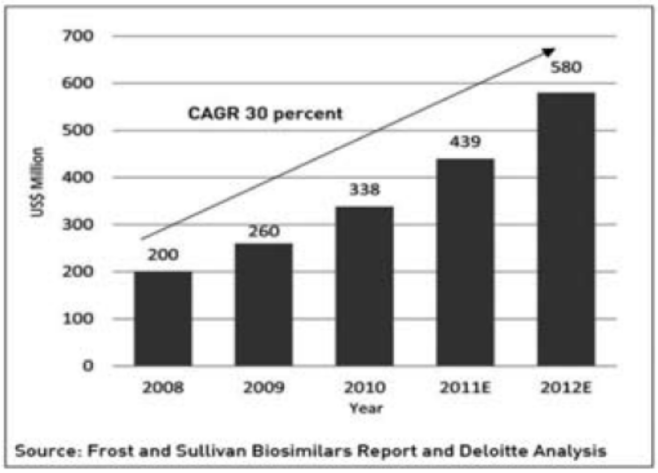

Figure No.2: Market overview of India

CONCLUSION

Biopharmaceuticals are different from small molecule chemical drugs. Generic drug approval approach is not appropriate. Establishing a high degree of similarity in quality between the Biosimilar product and the original product is a crucial key in the regulatory approval process, because biologicals vary greatly in properties and where even small alterations can lead to unacceptable changes in safety and efficacy. The efficacy and safety of biosimilars are in most cases highly species specific, which makes performing nonclinical studies more difficult and potentially expensive. So, there is a need for class-specific guidelines for various complex molecules (erythropoietin's, insulin's, Alfa interferons, and monoclonal antibodies etc.) of biologicals. Even though WHO have not issued product specific nonclinical or clinical guidelines, majority of ROW countries are following these guidelines. The EMA has developed product class-specific guidelines for various therapeutic classes of biologicals. So, by considering EU, regulated and regulating market country regulatory authorities come forward to draft product specific guidelines for biosimilars to overcome these problems.

ACKNOWLEDGEMENT

The authors are thankful to Krishnateja Pharmacy College, Tirupati, for providing necessary facilities and support to carry out the review work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

REFERENCES

1. www.ebe-biopharm a.org/index.php? option= com _content and task= view and id= 2 6 and Item id= 1 02.
2. Nick C. The US Biosimilars Act: Challenges Facing Regulatory Approval, *Pharm Med*, 26(3), 2001, 145–152.
3. Blanchard A. Helene D Iorio and Robert Ford. What you need to know to succeed, Key trends in Canada's biotech industry, *Insights*, *spring*, 2010.
4. http://www.gabionline.net/Reports/WHO-guidelines-on-biosimilarscase-studies-and-discussion-highlights.
5. http://www.ema.europa.eu/ema/index.jsp?curl= pages/regulation/general/general_content_000408.jsp and mid.
6. http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pd.
7. https://www.pharmatching.com/inforena/pharma-outsourcingpractice- bio similars-guidelines-players.
8. http://www.google.co.in/#hl=en and spell=1 and q=Recent+Regulations+of+Biosimilars+in+Japan and sa=X and ei=o3NULe5FsztrQe_yoGQDQ and ved=0CBwQvwUoAA and bav=on.2, or.r_gc.r_pw.r_qf. and fp.
9. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/default.html.
10. http://www.expresspharmaonline.com/20120215/market04.shtml.
11. Data Monitor, Pharmaceutical Key Trends, Biosimilar Market Overview, 2011.
12. IMS Institute for Healthcare Informatics, the Global Use of Medicines, Outlook Through, 2015.

Please cite this article in press as: Vamseedhar Naik B. *et al*. A review on biosimilar drugs, *International Journal of Research in Pharmaceutical and Nano Sciences*, 3(2), 2014, 153-158.