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The assessment of current regulatory guidelines for Biosimilars - A Global Scenario

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ABSTRACT

Background: With the increasing number and generally high cost of biologic drug products and the impending loss of patent protection by many of them, it seems virtually certain the development of biosimilar drug products will be an increasingly important area in drug regulation and clinical availability. All over the world, countries have been putting regulations in place and are beginning to evaluate biosimilars for marketing approval. The study objectives are to describe the regulatory procedures, quality, safety, efficacy and compare the regulatory aspects of biosimilar guidelines in different countries **Methods:** To attain the desired objectives of the study review of national legislative documents and guidelines were studied. The drift towards harmonization is to promote public health by ensuring quality, safety and efficacy of biosimilars. The bottom line behind a unified framework of guidelines for biosimilars is to prevent duplication of pre clinical studies, clinical trials, comparability studies, demonstration of biosimilarity to reference biological product without compromising on safety and efficacy aspects, which is obligatory for registration and marketing of biosimilars in any country. **Results:** A sure prediction is that regulations governing biosimilars will continue to evolve and will become more detailed and specific as more experience is gained with these products and harmonization can be possible. **Discussion:** Besides, large emerging economies such as China and Brazil, India are currently lagging behind in terms of implementation of regulations and need to act rapidly in developing appropriate regulations for biosimilar product approval. **Conclusion:** A sure prediction is that regulations governing biosimilars will continue to evolve and will become more detailed and specific as more experience is gained with these products and harmonization can be possible.

Keywords: Biosimilar, biologic drug products, biosimilarity, marketing approval, harmonization

INTRODUCTION

'Biologics', considered one of the fastest growing sectors of the pharmaceutical industry, have introduced many new treatments that have revolutionized the treatment of rheumatoid arthritis, cancers, psoriatic arthritis and ankylosing spondylitis and holds promise to expand treatment options for patients with systemic lupus erythematosus or other systemic autoimmune diseases, life-threatening, rare illnesses and have huge market potential. In this way, biosimilars are "similar but not the same" or in other words biosimilars are "the twin but not the clone" to the original biologic innovator product[1]. Therefore the field of biosimilars presents several important challenges, including i) verification of the similarity, ii) the interchange ability of biosimilars and innovator products, iii) the possible need for unique naming to differentiate the various biopharmaceutical products, iv) regulatory framework, v) commercial opportunities as well as guidelines to assist manufacturers in product development, vi) intellectual property rights, and vii) public safety[2]. Guidelines have been issued in different countries for the biosimilars with the European Union being the pioneer in implementation of guidelines for Similar Biological Medicinal Products. This was followed by many other countries in Asia, Middle East, LATAM and also the WHO.

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STRATEGY OF BIOSIMILARS IN THE COUNTRIES CHOSEN FOR THE STUDY[3]

Europe

The European Union (EU) has pioneered in the development of a regulatory system for biosimilar products. The European Medicines Agency (EMA) began formal consideration of scientific issues presented by biosimilar products at least as early as January 2001, when an *ad hoc* working group discussed the comparability of medicinal products containing biotechnology-derived proteins as active substances. In 2003, the European Commission amended the

provisions of the EU secondary legislation governing requirements for marketing authorization applications for medicinal products and established a new category of applications for "similar biological medicinal products". In 2005, the EMA issued a general guideline on similar biological medicinal products, in order to introduce the concept of similar biological medicinal products, to outline the basic principles to be applied, and to provide applicants with a 'user guide', showing where to find relevant scientific information. Since then, 13 biosimilar products have been approved by EMA under the pathway.

North America

For the approval of follow-on biologics in the United States, current regulations depends on whether the biologic product is approved under the United States Food, Drug, and Cosmetic Act (US FD&C) or it is licensed under the United States Public Health Service Act (US PHS). For those biologic drugs marketed under the PHS Act, the BPCI Act passed by the US Congress on March 23, 2010 amends the PHS Act to establish an abbreviated approval pathway for biological products that are highly similar or interchangeable with an FDA-authorized biologic drug, and gives the FDA the authority to approve follow-on biologics under new section 351(k) of the PHS Act. Some early biologic drugs, such as somatropin and insulin were approved under the FD&C Act. In this case, biosimilar versions can receive approval for New Drug Applications (NDAs) under section 505 (b) (2) of the FD&C Act.

Asia Pacific Countries

The APAC biosimilar market accounted for around 27% of the global biosimilar market in 2011. It is expected to grow at a CAGR of 10.3% during the next five years. This market estimation excludes vaccines and blood products and takes into consideration only the product classes that fall under the definition of biosimilars by EMA. Hence, it includes low molecular weight heparins even though their status as a biosimilar is often debated. In fact, 'biosimilar' may not be an appropriate term to refer the copies of biologic drugs sold by APAC companies, since these products are not subjected to stringent regulatory framework comparable to that of EMA. It has to be noted that EPO biosimilar comparison studies indicate that the products marketed in Europe vary from those developed and marketed by companies in semi-regulated markets. The clinical significances of these differences are not clear, though.

WORLD HEALTH ORGANIZATION

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 Biotherapeutic Products (SBPs)" was developed and adopted by the 60th meeting of the WHO Expert Committee on Biological Standardization in 2009. The intention of the guidelines is to provide globally acceptable principles for licensing biotherapeutic products that are claimed to be similar to the reference products that have been licensed based on a full licensing dossier. The scope of the guidelines includes well-established and well-characterized biotherapeutic products that have been marketed for a suitable period of time with a proven quality, efficacy and safety, such as recombinant DNA-derived therapeutic proteins[4].

BIOSIMILARS

Biosimilars are defined as biologic products that are highly similar to reference products, not withstanding minor differences in clinically inactive components, with no clinically meaningful differences between the biological product and the reference product in terms of safety profile, purity, and potency. Several terms are used in various countries for ''intended copy" products to biopharmaceuticals (e.g., biosimilars, follow-on biologicals, follow-on protein products, subsequent-entry biologicals, similar biological medicinal products). Biosimilars are defined as biological medicinal products which are[5]:

- similar in terms of quality, safety and efficacy to an already licensed, well-established reference medicinal product,
- marketed by an independent applicant following expiry of patent and regulatory data/market exclusivity periods of the reference product, and
- authorized for marketing through a procedure based on the proof of similarity to the reference product, using certain pre-existing scientific and regulatory knowledge.

BIOSIMILARS- AN EMERGING MARKET

Twelve compounds of biological products with global sales of more than US$67 billion will be exposed to biosimilar competition by 2012, with Enbrel (Etanercept) whose US patent has been extended until 2028, scoring global sales of US$7.3 billion by December 2011; comes in second after Humira (Adalimumab) with global sales of US$7.9 billion. The expiration of patents and other intellectual property rights for originator biologicals over the next decade opens up opportunities for biosimilars to enter the market and increase industry competition. Price reduction strategies should increased adoption among physicians and patients alike, spurring increases in the biosimilars market share. The biosimilars market earned revenue of approximately US$172 million in 2010, according to Frost and Sullivan. However, despite estimates that the market will reach approximately US$3,987 million by 2017, the biosimilars industry is not for the faint hearted. Considerable investment is required to manufacture and get a biosimilar to market, and with such complex molecules failure can occur at any stage of the development. Despite this, with a compound annual growth rate of 56.7% expected from 2010 to 2017 many companies – both originator and generics alike – are finding the sector hard to resist[6].

COMPARISON OF GUIDELINES [7,8]

A comparative assessment of guidelines of different countries was done for the following parameters:

Quality aspects: Choice of Reference Product, Comparability Exercise, Manufacture, Analytical Charecterization, Specifications and Stability.

Safety aspects - Pre Clinical tests, Clinical Trials, Clinical Safety and Pharmacovigilance/Risk Management and Immunogenicity assessment

Efficacy aspects – Efficacy and Extrapolation of indication

Regulatory aspects - Terminology used, Definition of biosimilar product, Scope of the guidelines, Nomenclature, Labeling, Interchangeability and Substitutability, Market Exclusivity for Innovator Product, Data Exclusivity for Innovator Product and Market Exclusivity for interchangeable biologic.

DISCUSSION

According to the regulatory requirements of different regions described in the previous section, there seems to be no significant difference in the general concept and basic principles in these guidelines. There are five well recognized principles with regard to the assessment of biosimilar products:

(1) the generic approach is not appropriate for biosimilars
(2) biosimilar products should be similar to the reference in terms of quality, safety, efficacy;
(3) a step-wise comparability approach is required that indicates the similarity of the biosimilar to Reference Biologic Product in terms of quality is a prerequisite for the reduction of non-clinical and clinical data submitted
(4) the analytical characterization of the biosimilar product with that of the reference product;
(5) the immunogenicity testing
(6) the importance of pharmacovigilance is stressed.

A sure prediction is that regulations governing biosimilars will continue to evolve and will become more detailed and specific as more experience is gained with these products and harmonization can be possible. However, differences have been noted in

(1) the scope of the guidelines;
(2) the choice of the reference product;
(3) the amount of data required for product approval;
(4) Interchangeability and Substitutability of biosimilar
(5) Market and data exclusivity for biosimilar

And there seems to be not much data finalized by regulatory authorities regarding nomenclature and labeling of biosimilars. The concept of a "similar biological medicinal product" in the EU is applicable to a broad spectrum of products ranging from biotechnology-derived therapeutic proteins to vaccines, blood-derived products, monoclonal antibodies, gene and cell-therapy, etc. However, the scopes of other organization or countries are limited to recombinant protein drug products. Concerning the choice of the reference product, EU and Japan require that the reference product should be previously licensed in their own jurisdiction, while other countries do not have this requirement.

The biosimilar guidance of Canada, Singapore, Malaysia, Republic of Korea, Saudi Arabia, Iran, Japan, Brazil and Mexico were prepared mainly based on WHO biosimilar guidelines, while the WHO has published its guideline" Guideline on Evaluation of Similar Biotherapeutic Products" based on EU experience to provide globally acceptable principles for licensing similar biotherapeutic products[9,10]. The EU guidelines for biosimilars were adopted by Australia and Turkey. So this shows that there is some similarity in the nature of guidelines and a possibility for harmonization. However, there are also many challenges, which need to be addressed for global harmonization of the regulatory framework for licensure of biotherapeutics. For example, the manufacturing of SBPs in the Arab region is not well-controlled due to the lack of expertise in the assessment of biotechnology products and inexperience with regulatory processes.

CONCLUSION

Based on the above consensus there is a scope for harmonization of guidelines on biosimilars in the above mentioned areas by which registration of biosimilars in different countries can be done in a most efficient and cost effective manner. The name of the game is harmonization due to increased healthcare costs, R&D expenditure and public expectation to safe and effective biological drugs for the myriad of diseases and illnesses.

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