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GUIDELINES FOR APPROVAL OF BIOSIMILARS IN DIFFERENT COUNTRIES

KOMANDLA ANUGNA REDDY

Assistant Professor, Omega College Of Pharmacy, Ghatkesar, Hyderabad, TS, India.

Email id: anugna1518@gmail.com

ABSTRACT

Biosimilars are biologic medical products that are highly similar to already approved reference products, with no clinically meaningful differences in safety, purity, and potency. Guidelines for their approval vary across countries but generally include comprehensive comparability studies to demonstrate similarity to the reference product. These studies typically encompass analytical, non-clinical, and clinical evaluations. Regulatory agencies such as the European Medicines Agency (EMA), the U.S. Food and Drug Administration (FDA), and other national bodies have established frameworks that often include specific requirements for quality, efficacy, and safety. Additionally, considerations for immunogenicity, manufacturing processes, and pharmacovigilance are crucial aspects of the approval process. These guidelines aim to ensure that biosimilars are as safe and effective as their reference counterparts while fostering market competition and increasing patient access to biologic therapies.

Keywords: FDA, EMA, Biosimilars, US, safety, purity.

I INTRODUCTION

The increasing demand from government agencies, insurers and patients to reduce the steep cost of blockbuster biopharmaceutical products has created considerable opportunities in the global biosimilar market. By the end of this decade, a significant number of blockbuster drugs will go off patent, allowing a large number of biosimilar products to enter the market. Regula- tory developments favouring the biosimilar market in countries such as the US are expected to boost the profits and market share of the companies involved. In the US, the Biologics Price Competition and Innovation Act (BPCIA), included in the Patient Protection and Affordable Care Act (ACA), created an abbreviated licensure pathway for products demonstrated to be interchangeable with a US Food and Drug Administration (FDA)-licensed biological product.1 The EU developed guidelines for the approval of biosimilars in 2005, established an abbreviated registration process for biosimilars in 2006, and has since published a guideline for the approval of similar biological medicinal products containing monoclonal antibodies.2–6 In Asia, regional differences are common. In Japan, guidelines based on the EU processes were published in 2009. In China, there is

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no explicit process for biosimilar approval; all pharmaceuticals go through basically the same drug registration process with the China Food and Drug Administration.8 In India, specific guidelines for approval of biosimilars are largely absent.8 Therefore, there has been a virtually unrestrained flood of biosimilars into the Indian market. A new research report states that, regionally, the US stands first in line to be the most lucrative market for biosimilars, followed by the EU and Japan. Regardless of the region of manufacture, the end result must be the production of a safe and efficacious product by market players. Clearly navi- gable regulatory pathways are essential for this outcome. This article reviews the various re- gional regulatory processes in effect to date and highlights the need for harmonization.

"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 ex- pand treatment options for patients with systemic lupus erythematosus or other systemic autoimmune diseases, life- threatening, rare illnesses and have huge market potential. The first generation of biopharmaceutical products manufactured using recombinant technologies was launched in the 1980s, and they are now on the verge of patent expiration. As a result, research based and generic pharmaceutical companies alike are pursuing the opportunity to develop "generic" substitutes for original biologics, referred to as biosimilars due to the global market demand of 3.6$ billion by 2016 with a Compound Annual Growth Rate (CAGR) of 7.7%. However, the process of introducing a biosimilar to an innovator product is far more complex than the relatively straightforward process of introducing a generic equivalent to an innovator product based on a new chemical entity. Biologics are produced by cells in culture or whole organisms, which are inherently more variable than chemical synthesis meth- ods. Therefore, unlike generic pharmaceuticals, it is impossible to generate the same or identical copy of an innovator product. They are similar, but not identical versions of endogenous human proteins, such as erythropoietin (EPO), insulin, growth hormones and cytokines, granulocyte colony-stimulating factor (G-CSF), heparin, monoclonal antibodies (Mab) that were developed using recombinant DNA (rDNA) technology or hybridoma techniques.

Strategy of Biosimilars in the countries chosen for the study:

EUROPE

The European Union (EU) has pioneered in the development of a regulatory system for bi- osimilar products. The European Medicines Agency (EMA) began formal consideration of scientific issues presented by biosimilar products at

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least as early as January 2001, when an ad hoc working group discussed the comparability of medicinal products containing bio- technology-derived proteins as active substances. In 2003, the European Commission amended the provisions of the EU secondary legislation governing requirements for mar- keting authorization applications for medicinal products and established a new category of applications for similar biological products. In 2005, the EMEA issued a general guideline on similar biological medicinal products, in order to introduce the concept of similar bio- logical medicinal products to outline the basic principles to be applied, and provide appli- cants with a user guide , a showing where to find relevant scientific information. Since then, 13 biosimilar products have been approved by EMA under the pathway. Two of them are somatropins, five are epoetins, and six are filgrastims. One of the rejected biosimilar is Alpheon (interferon alfa-2a). It was devepahloped by BioPartners GmbH, and designed to become a biosimilar of the reference product Roferon-A for the treatment of adult patients with chronic hepatitis C. The EMA refused the marketing authorization for Alpheon due to the difference identified between Alpheon and the reference product, such as impurities, stability, and side effects.

NORTH AMERICA:

USA

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 Cosmet- ic 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.

Following the passage of the BPCI, in order to obtain input on specific issues and challenges associated with the implementation of the BPCI Act from a broad group of stakeholders, the US FDA conducted a two-day public hearing on Approval Pathway for Biosimilar and Interchangeable Biological Products held on November 2-3, 2010 at the FDA in Silver Spring, Maryland. The scientific issues covered in this public hearing included, but not lim- ited to, criteria and design for biosimilarity and interchangeability, comparability between manufacturing processes, patient safety and pharmacovigilance, ecclusivity and use fees.

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In practice there is a strong industrial intrestand desire for the regulatory agencies to develop review standards and an approval process for biosimilar rather than an adhoc case-by-case review of individual biosimilar applications. For this purpose, the FDA has established three committies are the center for drug evaluation research board (CDER)/ center for bio- similar evaluation research (CBER), Biosimilar implementation committee (BIC), the CDER Biosimilar review committee.

The CDER/CBER BRC will focus on the cross center policy issues related to the imple- mentation of the BPCI act.

The CDER BRC and CBER BRC are responsible for considering requests of applicants for advice about proposed development programs for biosimilar products, reviewing Biologic License Applications (BLAs) that are submitted under section 351(k) of the PHS Act, and managing related issues. Thus, the review process steps of CDER BRC and CBER BRC include:

(1) Applicant submits request for advice, (2) internal review team meeting, (3) internal CDER BRC (CBER BRC) meeting, (4) internal post-BRC meeting, and (5) applicant meet- ing with CDER (CBER). Another important issue aroused by the BPCI Act is the inter- changeability 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.

CANADA

Health Canada, the federal regulatory authority that evaluates the safety, efficacy, and qual- ity of drugs available in Canada also recognizes that with the expiration of patents for bio- logic drugs, manufacturers may be interested in pursuing subsequent entry versions of these biologic drugs, which are called Subsequent Entry Biologics (SEB) in Canada.

In 2010, Health Canada issued the "Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs)", whose objective was to provide guidance on how to satisfy the data and regulatory requirements under the Food and Drugs Act and Regulations for the authorization of subsequent entry biologics (SEBs) in Canada .

The concept of an SEB applies to all biologic drug products; however there are additional criteria to determine whether the product will be eligible to be authorized as SEBs:

A suitable reference biologic drug exists that was originally authorized based on a complete data package, and has

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significant safety and efficacy data accumulated;

The product can be well characterized by state-of-the-art analytical methods;

The SEB can be judged similar to the reference biologic drug by meeting an appropriate set of pre-determined criteria.

With regard to the similarity of products, Health Canada requires the manufacturer to eval- uate the following factors:

Relevant data for physicochemical and biological characterization,

Analysis of the samples from the appropriate stages of the manufacturing process,

Stability data and impurities data,

Data obtained from the multiple batches of the SEB and reference to the understand the variability ranges,

Australia

The Therapeutic Goods Administration (TGA) is the regulatory authority in Australia. TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating therapeutic goods including medicines, medical devices, blood and blood products. It administers the Therapeutic Goods Act 1989.

This legislation provides a framework for a risk management approach that allows the Aus- tralian community to have timely access to therapeutic goods which are consistently safe, effective and of high quality.

TGA carries out a range of assessment and monitoring activities to ensure therapeutic goods available in Australia are of an acceptable standard with the aim of ensuring that the Australian community has access, within a reasonable time, to therapeutic advances.

Australia adopted the following guidelines from the EU on similar biological medicinal products in August 2008.

Aim and Objective:

There is large market needs and growing affordability for biosimilars. They offer competi- tive pricing advantage over the reference product in global market. The focus within the biopharmaceutical sector in India is directed more towards development of biosimilars be- cause of much lower developmental costs and risks reduce spending on research and de- velopment, reduced time to market and expertise in reverse engineering drug development process.

In recent scenario there is increasing understanding and applicability to biological drugs i.e. biosimilars. In India apart from Biogenerics a host of molecules especially have Biosimilar copies of compounds especially in endocrinology namely insulin, Exenatide, growth hormone, teriperatide like peptides are made in India.

II AIM AND OBJECTIVE

- The aim of this study is to analyze and compare the current regulatory

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guidelines for Biosimilar s recommended by the following regulatory/international agencies:

- Food and Drug Administration (USA)
- European Medicines Agency (Europe)
- Health Canada (Canada)
- Therapeutic Goods Administration (Australia)
- Ministry y of Health Labour and Welfare (Japan)
- Korean Food and Drug Administration (South Korea)
- Central Drugs Standards Control Organization (India)
- State Food and Drug Administration (China)
- National Pharmaceutical Control Board (Malaysia)
- Health Sciences Authority (Singapore)
- World Health Organization
- National Health Surveillance Agency (Brazil)
- Saudi Food and Drug Authority (Saudi Arabia)
- National Regulatory Authority (I ran) and
- Pharmaceuticals and Pharmacy General Directorate (Turkey)

Objective:

- The study objectives are the following:
- To describe the main regulatory procedures for biosimilars.
- To compare the quality aspects of biosimilar guidelines in different countries
- To compare the safety aspects of biosimilar guidelines in different countries
- To compare the efficacy aspects of biosimilar guidelines in different countries
- To compare the regulatory aspects of biosimilar guidelines in different countries

III SURVEY OF RESEARCH

[1] Monika Misra. 2012 Biosimilars are biological products that are the replicas of their innovator biopharmaceuticals. These are developed after patent expiration of innovator biopharmaceuti- cals and are submitted for separate marketing approval. In view of the structural and manufac- turing complexities of biopharmaceuticals, biosimilars should not be considered as “biological generics”. These are rather unique molecules with limited data at time of approval, so there are concerns about the safety and efficacy of biosimilars. This article will address the differ- ences between biosimilars and chemical generics, issues of concern with the use of biosimilars and need of appropriate regulations for their approval.

[2] R. Suthakaran. 2013 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

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regulations in place and are beginning to evaluate biosimilars for marketing approval. The study objectives are to describe the regulatory procedures, quality, safety, and efficacy and compare the regulatory aspects of biosimilar guidelines in different countries.

[3] Bhairav Bhushan A et al., 2014 Biologics are a major growth driver for global pharmaceutical market. Biosimilars are those biologics which are developed after patent expiration of innovator biopharmaceuticals. They are known as similar biologics, follow-on biologics, follow-on protein products, subsequent-entry biologics, bio-comparables, second-entry or off-patent biotechnology or multisource products in different countries. They require separate marketing approval since they are not generic versions of biologics. They are rather new molecules owing to a number of heterogeneities as compared to the refer- ence innovator biologics. Hence, they require full documentation on quality, safety and efficacy. Several challenges in the form of structural variability, immunogenicity, regulatory, etc. impede the way of growth of biosimilars. Structural variability results due to the complexity of structure of biologics. Immunogenicity is inherent to these products since they are proteins. The lack of a robust regulatory framework poses a risk to patient safety. This article aims to highlight the biosimilars scenario on a global basis and it throws light on the regulatory guidelines of different countries. It also discusses the major challenges involved therewith. It also considers some trends that promise the bright future of biosimilars.

[4] Rashness kumar gaur et al., 2012, The expiry of patents on innovator biologicals allures the interest of many companies to copy-cat their production as biosimilars. Regulatory agencies of various countries devised a mechanism to ensure their quality, safety and efficacy. India is in a process of developing the guidance document for copy-cat biotech products and adopted a term 'Similar Biolog- ics' as substitute for biosimilar. Like EMA, the term covers only recombinant-DNA tech- nology derived biotech products including recombinant vaccines and blood products. The aim of the article is to provide a brief overview of the scientific and regulatory challenges in developing and evaluating similar biologics products.

[5] Sagar J. Kanase et al., 2013 **B**iosimilars are defined as officially approved new version of innovator bio-therapeutic products for which the patent has expired. Biosimilars the ge- neric versions of biopharmaceuticals, continue to enter Indian pharmaceutical market, to treat a variety of diseases. Biosimilars available in India include monoclonal antibodies for treating various malignant and immunological disorders, growth factors like erythropoietin and granulocyte colony stimulating factor (G-CSF), human insulins

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for treating diabetes mellitus etc. In the recent scenario, there is an increasing demand for biological drugs. The development and production of biosimilars are boosted by existing manufacturing technol- ogy.

[6] Krishna Undela 2012 Biosimilars are defined as officially approved new version of in- novator biotherapeutic products for which the patent has expired. Globally, a large number of blockbuster biotherapeutic products are going off patent in the next few years. India has a robust pharmaceutical industry including the biopharmaceutical sector which is actively engaged in the production and marketing of biosimilar products. In the less regulated Indian market, however, there exist many biosimilars, despite the fact that no specific guide- lines exist in India for their approval. In this article attempts are made to find out the cur- rent and future market potential for biosimilar products in India. This article also reveals the loopholes present in the regulations for controlling the biosimilar market.

[7] Jun Wang et al., 2012 Biosimilars (or follow-on biologics) are a new class of medicine which enters the market subsequent to a previously approved version. They have demon- strated similarity to innovator biologic products in terms of quality, safety, and efficacy. The EMA has taken the lead in the regulatory approval framework for biosimilar products, and WHO has published guidelines on the evaluation of biosimilars in order to facilitate the global harmonization. Based on EMA and WHO guidelines, many other countries such as Canada, Japan and Korea have also issued their own guidance for evaluating follow-on biologics. The US FDA was authorized to approve follow-on biologics by the BPCI Act passed by the US Congress on March 23, 2010, and has just issued a draft guidance in early 2012. The basic concepts and main principles of approving biosimilars are similar among various nations, notwithstanding some differences in regard to the scope, the choice of reference product, and the data requirement. This article reviews the regulatory approval pathway of biosimilar products in different regions.

[8] N. Vishal Gupta et al., 2013 Biosimilars is a term 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. The purpose of this article is that an uncertainty over terminology on ‘Biosimilars’ has led to concerns about patient safety due to misleading published reports on its apparent ills. Therefore, a comparison is made among the different regulatory approvals globally with intend of achieving harmony in regulations and escalating entree to safe medicines globally. Every country should have a guideline for evaluation of Biosimilars, which should be a

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very similar approach to that described in the WHO guidelines.

IV METHODOLOGY

A high degree of similarity between the SBP and the RBP is the basis for reducing non- clinical and clinical requirements for licensing. However, some differences are likely to be found, e.g. due to differences in impurities or excipients. Such differences should be assessed for their potential impact on clinical safety and efficacy of the SBP and a justification, e.g. own study results or literature data, for allowing such differences provided. Differences of unknown clinical relevance, particularly regarding safety, may have to be ad- dressed in additional studies pre- or post-marketing. Differences in quality attributes known to have potential impact on clinical activity will influence the judgment of consideration whether to name such product as 'SBP'. For example, if differences are found in glycosylation patterns that alter the biodistribution of the product and thereby change the dosing scheme, then this product can not be considered a SBP. Other differences between the SBP and RBP may be acceptable, and would not trigger the need for extra non-clinical and/or clinical evaluation. For example, a therapeutic protein that has lower levels of protein aggregates would, in most cases, be predicted to have a better safety profile than the RBP and would not need added clinical evaluation. Along the same lines, if heterogeneity in the terminal amino acids of the RBP is known, and sufficiently documented, without affecting the bioactivity, distribution, or immunogenicity of the RBP or similar products in its class, then there may be no need for added clinical safety or efficacy studies based upon this heteroge- neity of the RPB and SBP. Due to the unavailability of drug substance for the RBP, the SBP manufacturer will usually be using commercial drug product for the comparability ex- ercise.

Choice of Reference product:

The chosen reference medicinal product must be a medicinal product authorised in the Community, on the basis of a complete dossier in accordance with the provisions of Article 8 of Directive2001/83/EC, as amended. The chosen reference medicinal product, defined on the basis of its marketing authorisation in the Community, should be used throughout the comparability program for quality, safety and efficacy studies during the development of a similar biological medicinal product in order to allow the generation of coherent data and conclusions.

Data generated from comparability studies with medicinal products authorised outside the Community may only provide supportive information. The active substance of a similar biological medicinal product must be similar, in molecular and biological terms, to the active substance of the reference medicinal product. For example, a medicinal product containing interferon alfa-2a manufactured by

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Company X claiming to be similar to another biological medicinal product should refer to a reference medicinal product containing as its active substance interferon alfa-2a. Therefore, a medicinal product containing interferon alfa-2b could not be considered as the reference medicinal product. The pharmaceutical form, strength and route of administration of the similar biological medicinal product should be the same as that of the reference medicinal product. When the pharmaceutical form, the strength or the route of administration is not the same; additional data in the context of the comparability exercise should be provided. Any differences between the similar biological medicinal product and the reference medicinal product will have to be justified by appropriate studies on a case by-case basis. Consultation with the EMEA is highly reccommended to discuss all those issues.

Comparability Exercise:

The commercial drug product will, by definition, be in the final dosage form containing the drug substance(s) formulated with excipients. It should be verified that these do not interfere with analytical methods and thereby impact the test results. If the drug substance in the RBP needs to be purified from a formulated reference drug product in order to be suitable for characterization, studies must be carried out to demonstrate that product heterogeneity and relevant attributes of the active moiety are not affected by the isolation process. The approach employed to isolate and compare the SBP to the RBP should be justified and demonstrated, with data, to be appropriate for the intended purpose. Where possible, the product should be tested with and without manipulation.

Manufacturing process:

Manufacture of a SBP should be based on a comprehensively designed production process taking all relevant guidelines into account. The manufacturer needs to demonstrate the consistency and robustness of the manufacturing process by implementing Good Manufacturing Practices 5 modern quality control and assurance procedures, in-process controls, and process validation. The manufacturing process should meet the same standards as required by the NRA for originator products. The manufacturing process should be optimized to minimize differences between the SBP and RBP in order to (a) maximize the ability to reduce the clinical testing requirements for the SBP based upon the clinical history of the RBP, and (b) minimize any predictable impact on the clinical safety and efficacy of the product. Some differences between the SBP and RBP are expected and may be acceptable, provided, appropriate justification with regard to lack of impact on clinical performance is given.

It is understood that a manufacturer developing a SBP does not have access to confidential details of the manufacturing process of the RBP such that the process

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will differ from the licensed process for the RBP (unless there is a contractual arrangement with the manufacturer of the RBP). The manufacturing process for a SBP should employ state-of-the-art sci- ence and technology to achieve a high quality SBP that is as similar as possible to the RBP.

This will involve evaluating the RBP extensively prior to developing the manufacturing process for the SBP. The SBP manufacturer should assemble all available knowledge of the RBP concerning the type of host cell, formulation and container closure system used for marketing the RBP. If applicable, the SBP manufacturer should then determine the poten- tial impact of changing any one of these elements on product quality, safety and efficacy based on available evidence from public information, experience with previous use of the RBP. SBP manufacturer is encouraged to apply this knowledge to the design of the manufacturing process. The rationale for accepting these differences needs to be justified based upon sound science and clinical experience, either with the SBP, or the RBP.

A complete description and data package should be provided that delineates the manufacturing process, starting with development of expression vectors and cell banks, cell culture/ fermentation, harvest, purification and modification reactions, filling into bulk or final containers, and storage. The development studies conducted to establish and validate the dos- age form, formulation, and container closure system (including integrity to prevent microbial contamination) and usage instructions should be also documented (see relevant guide- lines such as ICH).

Characterization:

Thorough characterization of both RBP and SBP should be carried out using appropriate, state-of-the-art biochemical, biophysical and biological analytical techniques. For the active ingredient(s) (i.e. the desired product), details should be provided on primary and higher-order structure, post-translational modifications (including, but not limited to, glycoforms), biological activity, purity, impurities, product-related (active) substances (variants), and immunochemical properties, where relevant. When conducting a comparability exercise, head-to-head characterization studies are required to compare the SBP and the RBP. The primary structure of the SBP and the RBP should be identical.

V RESULTS AND DISCUSSION

Biopharmaceuticals are different from small molecule chemical drugs in terms of the com- plexity which makes characterization difficult as well as a regulatory requirement. Generic drugs may not have the same elaborate and stringent approval processes, but face similar mar- keting concerns as biosimilars.

Both generics and biosimilar markets share the same concerns, which are varied between es- tablished markets like

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EU/US and other emerging markets. According to Hordur Thoralissonn (Actavis Inc.), the term “emerging” is used to define the level of development of generics ra- ther than development of the country per se. Extrapolation of such general issues apart from regulatory hurdles could be done from generics to biosimilars quite seamlessly. Peter Wittner (Interpharm Consultancy) suggested that a Darwinian survival of the fittest theory is almost invisibly present in the generics market to provide affordable drugs, which we may, in all probability, extend to biosimilars as well. According to him the European markets are attrac- tive but need extensive and careful preparation before entry. Spain and Italy were good mar- kets according to him, considering the underuse of generics in these countries.

The “pharmerging” countries like the BRIC nations (Brazil, Russia, India, and the People’s Republic of China) according to him can prove to be attractive and huge, but their poor infra- structure, reduced health insurance coverage, and so forth can be intimidating.

Biosimilar development is riddled with complexities, ranging from regulatory, to manufac- turing to marketing, and is one of the most expensive propositions in the Pharma- ceutical industry. The current industry average cost of bringing a biosimilar to market is around $100-$200 million. This is in addition to a development period ranging from eight to ten year s, which is approximately equivalent to that for a biopharmaceutical product. In addition, development costs are expected to increase in the long-term, consider- ing the current state of the pharmaceutical quandary, having to choose between the de- velopment of a new product or a biosimilar. Thus, current trends indicate that the sort of resources that will be required for biosimilar development create high barriers of entry, not just for small to mid-sized companies, but even the larger, and well-established generics players, and biopharmaceutical companies.

Since a number of biosimilar products are either already approved or are under development, these agents will undoubtedly play an increasing role in disease man- agement. While biosimilars provide a number of opportunities, it is important that they be introduced in an appropriate manner. There are potential concerns regarding the use of bio- similar s in patients with cancer that warrant consideration when making a biopharmaceutical product choice. Clinicians require a thorough understanding of the issues associated with biosimilars so that they can make informed decisions. Of primary importance, clini- cians need to be aware that biosimilars are not generic versions of innovator products. Biosimilars will be approved as safe and efficacious agents by the National Regulatory Agency but they will be inherently different from innovator products. Therefore, switching or substitution between innovator products and

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biosimilars should be viewed as a change in clinical management.

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:

The generic approach is not appropriate for biosimilars

Biosimilar products should be similar to the reference in terms of quality, safety, efficacy; A step-wise comparability approach is required that indicates the similarity of the bio- similar to Reference Biologic Product in terms of quality is a prerequisite for the reduction of non-clinical and clinical data submitted

The analytical characterization of the biosimilar product with that of the reference product;

The immunogenicity testing

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:

The scope of the guidelines;

The choice of the reference product;

The amount of data required for product approval;

Interchangeability and Substitutability of biosimilar

Market and data exclusivity for biosimilar

And there seems to be not much data finalized by regulatory authorities regarding nomen- clature 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, bloodderived products, monoclonal antibodies, gene and cell-therapy, etc. However, the scopes of other organization or countries are lim- ited 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 Biothera- peutic Products” based on EU experience to provide globally acceptable principles for licensing similar biotherapeutic products. The EU guidelines for biosimilars were adopted by Australia and Turkey. So this shows that there is some similarity in the nature of

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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 bio-therapeutics. 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 in- experience with regulatory processes.

Harmonization

The global harmonization of regulatory requirements for follow-on biologics/biosimilars/ SEBs is severely lacking. This may be the result of several factors. Although entities such as the International Conference on Harmonisation aid in the establishment of standards, worldwide regulatory authorities and pharmaceutical industries did not convene to discuss the issues concerning biosimilar product development prior to the establishment of local guidance and regulations.

CONCLUSION

Based on the above consensus there is a scope for harmonization of guidelines on biosimi- lars 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 harmo- nization due to increased healthcare costs, R&D expenditure and public expectation to safe and effective biological drugs for the myriad of diseases and illnesses. Consideration of the current drug approval system (the Hatch-Waxman Act) and the avail- able options for a regulatory pathway for generic biologics (Waxman's and Eshoo's Bills) reveals that the bills currently pending before Congress still need revision. Specifically, the bills should include a statutory requirement for a one year clinical trial period to examine the immunogenicity and ensure the safety of follow-on biologics. Also, follow-on biologics should be held to a higher, "substitutable" standard when being compared with the original brand biologics, requiring that the follow-on biologic be sufficiently the "same" as the original, pioneer biologic. Additionally, while the bills before Congress await approval, the FDA should set up guidelines to allow for the approval of follow-on versions of well known biologics such as insulin and human growth hormone whose patents have already passed expiration. Considering the importance of biologics as a growing field of medicine that treats many medical ailments, Congress should ensure an abbreviated approval process for follow-on biologics. An abbreviated process with a mandatory one year clinical testing period that requires follow-on biologic to be the same as its reference biologic would be the best option to address the issues currently facing biologics.

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The generic companies and biosimilar associations have united to counter misconceptions regarding their drugs. They have been applying continuous pressure on the regulatory agencies to favor the manufacture of generic/biosimilar drugs for the benefit of the patient population with low-cost alternatives. Unifying the approval pathway globally will abolish the need for bridging studies, which could make biosimilar development cost effective (since the sponsors will then have a single product development cycle for all geographies) but with the same standards of safety and efficacy.

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