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THE ASSESSMENT OF CURRENT REGULATORY GUIDELINES FOR BIOSIMILARS- A GLOBAL SCENARIO

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ABSTRACT

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. 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. 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.

KEYWORDS: Biosimilar, biologic drug products, biosimilarity, marketing approval, harmonization.

1. INTRODUCTION

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[1,2]

- 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.

“Biologics”, considered one of the fastest growing sectors of the pharmaceutical Industry, have introduced many new treatments that have revolutionized the treatment of several diseases. 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 Bio-similars 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 Bio-similar 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.

Bio-similars are “similar but not the same” or in other words Bio-similars are “the twin but not the clone” to the original biologic innovator product. Therefore the field of Bio-similars presents several important challenges, including.

i) Verification of the similarity.
ii) The interchangeability of biosimilars and innovator products.
iii) Regulatory framework.

iv) Commercial opportunities as well as guidelines to assist manufacturers in product development.
v) Intellectual property rights, and
vi) Public safety.

Guidelines have been issued in different countries for the Bio-similars 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. There exists a difference between the regulations of the countries. This approach is to suggest harmonization of the guidelines on the above mentioned biosimilar drugs be sufficiently harmonized to allow one development program to meet requirements for multiple countries, while still allowing regulatory authorities sufficient autonomy to fulfill their national responsibilities.

1.1. PHARMA-EMERGING COUNTRIES

The emerging biosimilars market has grown significantly in the recent past and has the ability to grow in the future due to the expiry of patents for major biological drugs, pressure on governments in emerging economies to reduce healthcare costs, and the savings that can be obtained with biosimilars over branded biologics. The launch of a number of biosimilars that are presently in the late stage of development in the R&D pipeline and government initiatives to develop the biosimilars market in emerging economies, will also drive growth.[3]

Major pharmaceutical companies have created a strong position for themselves in the emerging biosimilars market, with a number of biosimilar products launched and generating revenue. Companies such as Cipla, Ranbaxy and Lupin have shown interest in the opportunities offered by the emerging biosimilars market and have taken initiatives to enter the market through strategic consolidations and biosimilars R&D.[3-4]

a) INDIA

In 1989, the Indian Government published “Rules for the Manufacture/Use/Import/Export and Storage of Hazardous Microorganisms under the provisions of Environment (Protection) Act, 1986 through the Ministry of Environment and Forests. These rules, referred to as ‘Rules 1989’ are implemented the Department of Biotechnology (DBT) of Ministry of Science and Technology, Government of India, who have also issued a guideline in 1999.

"Generating pre-clinical and clinical data for r- DNA based Vaccines, Diagnostics and other biologicals". From time to time, DBT also devises proformas for submission of applications to various competent authorities in India for specific approvals.

Based on these guidelines, the regulatory process is rather complex. An applicant needs to apply first to the regulatory body, Review Committee on Genetic Manipulations (RCGM) for approval of SBPs. RCGM monitors the safety related aspects of genetically engineered organisms to ensure that adequate precautions and containment conditions are complied with as per the Guidelines issued by DBT. DBT also maintains the Indian Genetically Modified Organism (GMO) Research Information System which is a web based database on activities involving the use of GMOs and products thereof in India. The primary purpose of this website is to make available objective and realistic scientific information relating to GMOs and products thereof under research and commercial use to all stakeholders including scientists, regulators, industry and the public in general. Subsequently, the data will be submitted to Drugs Controller General (India) [DCG(I)] to get approval for clinical trials and final commercial licensure. The product once approved is subjected to joint inspection by the Central and State Drug Control Administration and the manufacturing license is issued by the Central Licensing Approval Authority.[3,4]

b) CHINA

China is the most populous and largest developing country in the world. Millions of people with low incomes who need abundant, available and affordable medicines are a huge potential market for similar biotherapeutic products (SBPs). For decades, Chinese drug regulatory agencies have been working hard to establish and improve the approval documents and technical guidelines for biological products consistent with national conditions and scientific principles. China's efforts have been not only to assure the quality and efficacy of licensed products, but also to prompt bio-industry development. In the Chinese market, the available biological products have played an extremely important role in clinical treatment. In recent years, China has actively participated in WHO's conferences focusing on guidance development for SBPs.[4,5]

2. COMPARISON OF GUIDELINES[6-8]

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

1) Quality aspects

a) Choice of Reference Product.

b) Comparability Exercise.

c) Manufacture.

d) Analytical Characterization.

e) Specifications.

f) Stability.

2) Safety aspects

a) Pre Clinical tests.

b) Clinical Trials.

c) Clinical Safety and Pharmacovigilance/Risk Management.

d) Immunogenicity assessment.

3) Efficacy aspects

a) Efficacy.

b) Extrapolation of indication.

4) Regulatory aspects

a) Terminology used.

b) Definition of biosimilar product.

c) Scope of the guidelines.

d) Nomenclature.

e) Labeling.

f) Interchangeability and Substitutability.

g) Market Exclusivity for Innovator Product.

h) Data Exclusivity for Innovator Product.

i) Market Exclusivity for interchangeable biologic.

3. REGULATORY ASPECTS[9,10]

a) TERMINOLOGY

COUNTRIES	TERMINOLOGY
EU, Malaysia, Singapore,	Similar Biological Medicinal Product (SBMP)
USA	Follow on Biologic (FOB)
Canada	Subsequent- entry Biologic (SEB)
Japan	Follow on Protein (FOP)

S. Korea, Saudi Arabia	Biosimilar
India	Similar biologic product
China	Biogeneric
WHO, Brazil, Argentina, Chile, Mexico, Venezuela, Iran, Turkey	Similar Biotherapeutic Product (SBP)

b) DEFINITION OF BIOSIMILAR PRODUCT[11]

EU, Australia, Turkey

A Similar Biological Medicinal Product is said to be "similar" to an approved reference medicinal product, marketed by an independent applicant and is subject to all applicable data protection periods and/or intellectual property rights for the originator product. The requirements for the Marketing Authorization Applications for biosimilars are based on the demonstration of the similar nature of the two biological medicinal products (biosimilar versus reference biologic product) and require comparative quality, non-clinical and clinical studies to demonstrate safety and efficacy. (as per Art. 10(4) of Directive 2001/83/EC).

USA

Biosimilar means that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components," and "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.".

Canada

A biologic drug that enters the market subsequent to a version previously authorized in Canada, and with demonstrated similarity to a reference biologic drug. An SEB relies in part on prior information regarding safety and efficacy that is deemed relevant due to the demonstration of similarity to the reference biologic drug and which influences the amount and type of original data required.

Japan

A biosimilar product is a biotechnological drug product developed by a different company to be comparable to an approved biotechnology-derived product (hereinafterreference product) of a innovator. A biosimilar product can generally be developed on the basis of data that demonstrates the comparability between the biosimilar product and the reference product with respect to quality, safety and efficacy, or other relevant data.

Republic of Korea

Biological products which demonstrated its equivalence to an alrealy approved reference product with regard to quality, safety and efficacy.

Malaysia

A new biological medicinal product developed to be similar in terms of quality, safety and efficacy to an already registered, well established, medicinal product. (Malaysian Biosimilar Document).

Singapore

A similar biological (biosimilar) product is a biological medicinal product referring to an existing registered product, submitted for medicinal product registration by an independent applicant and is subject to all applicable data protection periods and/or intellectual property rights for the original product.

India

A biological product/ drug produced by genetic engineering techniques and claimed to be "similar" in terms of safety, efficacy and quality to a reference biologic, which has been granted a marketing authorization in India by DCGI on the basis of a complete dossier and with a history of safe use in India. The products, where the reference biologic is not authorized in India shall be considered on a case by case basis if such products have been granted marketing approval in countries with well established regulatory systems such as US FDA, EMA etc. and have been in wider use for a minimum of four years.

China

Not defined.

WHO, Iran

A bio therapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference bio therapeutic product.

LATAM Countries (Brazil, Argentina, Chile, Mexico, Venezuela), Saudi Arabia,

Not defined.

Turkey

The name given to drugs showing similarity to a licensed biological reference drug. The

active substances of biosimilar products are drugs similar to the related biological reference drugs. Biosimilar and biological reference drugs are generally used at the same strength to treat the same disease. Biosimilar drugs are only different from biological reference drugs based on trade name, appearance and packaging features.

c) SCOPE OF GUIDELINE[12]

COUNTRY	SCOPE OF GUIDELINE
EU	Medicinal products containing biotechnology derived proteins as active substance, immunologicals such as vaccines, blood-derived products, monoclonal antibodies, etc.
USA	Therapeutic protein products (except LMWH)
Canada	The guidance applies to biologic drugs that contain, as their active substances, well characterized proteins derived through modern biotechnological methods such as use of recombinant DNA and/or cell culture.
Japan	Recombinant proteins and polypeptide products, their derivatives, and products of which they are components, e.g., conjugates. Those proteins and polypeptide products that are produced from recombinant expression systems using microorganisms or cultured cells and highly purified and well-characterized using an appropriate set of analytical procedures. (except LMWH which is considered as generic)
Republic of Korea	Products that contain well characterized therapeutic protein as active substance.
Malaysia	Biologic drugs that contain, as the active substances, well characterised proteins derived through modern biotechnological methods such as recombinant DNA, into microbial or cell culture. (It does not cover complex biologics such as blood-derived products, vaccines, immunologicals and gene and cell therapy products)
Singapore	Describes the basic principles of a similar biological product, as well as the procedures and requirements for registration of a similar biological product.

India	These guidelines apply to similar biologics that contain well characterized proteins as their active substance, derived through modern biotechnological methods such as use of recombinant DNA technology
China	Applicable to Biogeneric drugs
WHO	Applies to well-established and well-characterized biotherapeutic products such as recombinant DNA-derived therapeutic proteins. Vaccines, plasma derived products, and their recombinant analogues are excluded from the scope
Brazil, Mexico, Chile, Venezuela, Argentina	For the approval of biologics, complex medications derived from live proteins or recombinant DNA
Saudi Arabia	Applicable to r-DNA produced therapeutic proteins
Iran	Applies to well-established and well-characterized biotherapeutic products such as recombinant DNA-derived therapeutic proteins. Vaccines, plasma derived products, and their recombinant analogues are excluded from the scope
Turkey	Applicable to recombinant DNA-derived therapeutic proteins.

d) NOMENCLATURE[13]

There is no specific guideline or any mention about the nomenclature of biosimilars in the following countries.

EU, US, Canada, Republic of Korea, Malaysia, Singapore, India, China, LATAM Countries, Saudi Arabia, Iran and Turkey.

Japan

Japanese notification for naming of follow-on biologics has been published at the same time of guideline for follow-on biologics. The notification describes the Nonproprietary & Brand Names of follow on biologics. For Nonproprietary Names, Biosimilar should be suffixed to the Nonproprietary name of the original biologic at the time of the approval. The individual products are determined to be the follow on biologics through a reviewing process for the approval. On the other hand, for brand name, the dosage form, dosage and company name should be attached to the nonproprietary name.

WHO

The WHO has given its proposal on the nomenclature of similar bio therapeutic products in WHO Informal Consultation on International Nonproprietary Names (INN) Policy for Biosimilar Products which is yet to be drafted.

e) LABELING[14]

EU

Not specified.

US

Labeling of a proposed product should include all the information necessary for a health professional to make prescribing decisions, including a clear statement advising that: This product is approved as biosimilar to a reference product for stated indication(s) and route of administration(s). This product (has or has not) been determined to be interchangeable with the reference product.

Canada

The reference biologic drug in its entirety as that of its own product. The PM for an SEB should be developed in a manner consistent with the principles, practices, and processes outlined in the "*Guidance for Industry: Product Monograph* (2004)". The contents of the PM for SEBs will include following information:

- A statement indicating that the product is an SEB2
- Key data on which the decision for market authorization was made
- Tables showing the results of the comparisons between the SEB and reference biologic drug Information on the indications approved for use.
- There should be no claims for bioequivalence between the SEB and reference biologic

drug.

- There should be no claims for clinical equivalence between the SEB and the reference biologic drug.

Japan, Republic of Korea,

Not specified.

Malaysia

The labeling of biosimilars should provide transparent information to healthcare professionals and patients on issues that are relevant to the safe and effective use of the medicinal product. It is expected that the labeling of biosimilar meet the following criteria:

- A clear indication that the medicine is a biosimilar of a specific reference product.
- The invented name, common or scientific name and the manufacturer's name
- Clinical data for the biosimilar describing the clinical similarity (i.e safety and efficacy) to the reference product and in which indication(s)
- Interchangeability and substitution advice. should clearly and prominently state that the biosimilar is not interchangeable or substitutable with the reference product.

WHO, LATAM Countries (Brazil, Mexico, Chile, Venezuela, Argentina), Iran

The SBP should be clearly identifiable by a unique brand name. Where an INN is defined, this should also be stated. WHO policy on INNs should be followed (http://www.who.int/medicines/services/inn/innquidance/en/index.html). Provision of the lot number is essential as this is an important part of production information and is critical for traceability in cases where problems with a product are encountered.

The prescribing information for the SBP should be as similar as possible to that of the RBP except for product-specific aspects, such as different excipient(s). This is particularly important for posology and safety-related information, including contraindications, warnings and adverse events. However, if the SBP has fewer indications than the RBP, the related text in various sections may be omitted unless it is considered important to inform doctors and patients about certain risks; *e.g*. because of potential off-label use. In such cases it should be clearly stated in the prescribing information that the SBP is not indicated for use in the specific indication(s) andthe reasons why. The NRA may choose to mention the SBP nature of the product and the studies that have been performed with the SBP including the specific RBP in theproduct information and/or to include instructions for the prescribing physician on

how to use SBP products.

India, China, Turkey

Not specified.

Saudi Arabia

This issue deals with the information shown on the outside package and the inside leaflet. In both, the chosen brand name of the product must be clearly written, with the scientific name of the product [international non-proprietary name, INN, if there is any designated by WHO] written underneath in parentheses, with the company"s name and logo clearly demonstrated. Storage conditions, names and quantities of the API and other excipients, as well as other vital instructions should be written.

f) INTERCHANGEABILITY AND SUBSTITUTABILITY[14]

Biosimilarity: "Highly similar to the reference product notwithstanding minor differences in clinically inactive components" and exhibit "no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product." The BPCI Act requires that an application for a proposed biosimilar product include information demonstrating that the proposed product is highly similar to the reference product based on analytical, animal, and/or clinical studies, and that the FDA at its discretion can determine what is necessary to designate such a product as biosimilar.

Interchangeability: the sponsor must demonstrate that an interchangeable biologic product "produces the same clinical result as the reference product in any given patient" and the "risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product [biosimilar] and the reference product [originator/brand] is not greater than the risk of using the reference product without such alteration or switch."

Substitutability: The biosimilar product can be substituted for the innovator product where the biosimilar exhibits no clinically meaningful differences between the biological product and reference product in terms of safety, purity and potency of the product. Furthermore, the BPCI states that "the [interchangeable] biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.

In **EU** there are no such provisions like Interchangeability and substitutability.

In **US** the Interchangeability and substitutability are drafted and well defined in the Biologics Price Competition and Innovation Act (BPCIA) and both are applicable to follow on Biologics in the USA.

Canada, WHO, India, China, LATAM Countries (Brazil, Mexico, Chile, Venezuela, Argentina) Iran, Turkey

Not specified.

Japan

Interchangeability is acceptable while substitutability is not suitable.

Malaysia

Biosimilars are not generic products and cannot be identical to their reference products. Further, the formulations may be different and these can have profound effect on their clinical behavior. In addition, biosimilars do not necessarily have the same indications or clinical use as the reference products. Therefore, given current science, they cannot be considered interchangeable with the reference product or products of the same class. Automatic substitution (i.e the practice by which a different product to that specified on the prescription is dispensed to the patient without the prior informed consent of the treating physician) and active substance-based prescription cannot apply to biological, including biosimilars. Such an approach ensures that treating physicians can make informed decisions about treatments is in the interest of patients safety. Interchangeability and substitutability are not acceptable.

Singapore

A product is interchangeable with another if both products are approved for the same indication, and can be used for the said indication. Two products are substitutable with each other if they can both be used in lieu of the other during the same treatment period. For interchangeable products, one or the other can be used (prescribed) but these products cannot be substituted with one another during a treatment period. Interchangeability does not imply substitutability. Unlike generic chemical drugs, whereby the chemical structure is identical to that of the reference chemical product, a biosimilar product does not usually have an identical structure to the reference biological product. Therefore, even though a biosimilar product may be approved to be similar in terms of quality, safety and efficacy to the reference product, immunogenicity may preclude switching between products. A warning statement on

the risks associated with switching of products during treatment and against product substitution, is to be included in the package insert of the biosimilar product.

Saudi Arabia

This remains a controversial issue among different regulators worldwide and all concerned parties. Biosimilars are protein therapies similar to indigenous human mediators, are given in microgram quantities, are not exact copies of an original medicine, and have limited clinical experience at approval. Although interchangeability and substitution are not encouraged and can be detrimental to pharamcovigilance and risk management, there could be situations (financial, availability, intolerability, hospital or country necessities) when they are needed. It is generally viewed that changing or substituting a protein medicine produced by rDNA technology, whether original (innovator) or a biosimilar, is the decision of the physician and the patient when the treating doctor explains to the stakeholder the possibility of such substitution and examine the risks versus benefits. Physicians and pharmacist should discuss the issue before talking to the patient to prevent inappropriate substitution. Pharmacists cannot substitute biosimilars without such consultations with treating physicians. However, SFDA strongly recommends the followings:

(1) Changing from an innovator drug to a biosimilar drug which used that same innovator drug as its RMP for comparability (or vice versa) can be accepted after physician and patient discussion.

(2) Changing from a biosimilar drug to another same biosimilar drug from a different manufacturer can be accepted after physician and patient discussion only if they both used the same RMP for comparability purposes.

g) MARKET EXCLUSIVITY AND DATA EXCLUSIVITY ON INNOVATOR PRODUCT

EU

Ten years of market exclusivity and eight years of data exclusivity.

US

Twelve years from date of licensure for the licensed reference product or branded, original and four years of data exclusivity from date of licensure for the reference product or branded, original.

China

Five years for "new" products not previously marketed in China and Six years of data exclusivity for "new" products not previously marketed in China.

Canada, WHO, India, Malaysia, Singapore, LATAM Countries (Brazil, Mexico, Chile, Venezuela, Argentina), Saudi Arabia, Iran, Turkey

No comparable provision.

h) MARKET EXCLUSIVITY ON INTERCHANGEABLE BIOLOGICS[15]

This provision is applicable to interchangeable biologic in the USA for a period of one year as per BPCI Act. This provision has not been recommended in any other country.

4. DISCUSSION

Biosimilar development is riddled with complexities, ranging from regulatory, to manufacturing to marketing and is one of the most expensive propositions in the pharmaceutical 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 years, which is approximately equivalent to that for a biopharmaceutical product. In addition, development costs are expected to increase in the long-term, considering the current state of the pharmaceutical quandary, having to choose between the development 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 management. 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 biosimilars 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, clinicians 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 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:

(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. 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.

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. In sum, the status of biosimilars and implementation of harmonized guidelines is highly diverse worldwide, and a harmonized approach for biosimilars worldwide is unlikely to occur rapidly. Accordingly, in order to promote the global harmonization, National Regulatory Authorities should take an active role in building capacity for regulatory evaluation of biotherapeutics; the existing guidelines should be revised as the considerable experience has been gained through Scientific Advice, Marketing Authorization Applications and Workshops.

5. CONCLUSION

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. Because of the characteristics of biologic drug products (which differ in important ways from small molecules) and the advances in manufacturing and analysis of biologics, innovation has been used to create adequate systems for their regulation and approval. 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.

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. 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. 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.

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