



EMERGING TRENDS IN REGULATORY DEVELOPMENTS FOR BIOSIMILARS: RECENT ADVANCES IN GLOBAL AND INDIAN REGULATIONS

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ABSTRACT

Biopharmaceutical drugs have outperformed the pharmaceutical market as a whole largely due to two factors: they address areas of clinical need that are unmanageable with conventional therapeutics (including cancers) and they are able to command a premium price. With expiry of patent of many biopharmaceutical drugs, the potential of a sizeable market will attract several generic companies. However the process to develop essentially generic version of biopharmaceuticals (biosimilars) is more complex than that of developing a generic copy of a chemical-based compound. These products are approved through an abbreviated route which relies on limited safety and efficacy data enabling the generic companies to keep the production costs low and pass on the price benefit to the patient and make the product affordable to the masses. There are no common regulatory pathways and many countries have published guidelines and it is still evolving in other countries. WHO (World Health Organization), Europe and recently USA have published guidelines for the development and marketing of biosimilar products. These products undergo extensive head to head comparability testing with the reference biopharmaceutical product to show their similarity to the reference product in terms of quality, efficacy and safety. Regulators and administrators of different countries need to strike a balance in cost-to-benefit versus risks that are perceived for these products, keeping in mind global regulatory issues. India's biotechnology industry has been growing towards new heights in conjunction with the economic evolution. The practical way forward for approval of biosimilars in India would have to be unique to the Indian context as it should balance the scientific aspects and consider needs and limitation of the country.

Keywords: biopharmaceutical drugs, generic products, biosimilars, marketing authorization, regulatory agency, EMA, US FDA, WHO, India.

INTRODUCTION:

Following the patent expiries of the first biotechnology-derived therapeutic proteins, off-patent biopharmaceuticals in general are becoming an increasingly attractive target for pharmaceutical companies. Currently there is considerable interest in the legislative debate around generic biological drugs or "biosimilars" in the Europe and USA due to the large, lucrative market that it offers to the industry. While some countries have issued a few regulatory guidelines as well as product specific requirements, there is no general consensus as to a single, simple mechanism similar to the demonstration of bioequivalence for the approval of generic small molecules. In general, the concept of comparability has been used for evaluation of the currently approved "similar" biological where a step by step assessment on the quality, preclinical and clinical aspects is made. In India, the focus is primarily on the availability and affordability of life-saving drugs.

A copy that has been granted a marketing approval is defined as a 'similar biological product' or 'biosimilar', and its marketing authorization (MA) requires a reduced dossier. Unlike generics, which contain the same active substance(s) as that of a reference medicinal product and have a bioequivalence demonstrated through appropriate bioavailability studies; biosimilars are demonstrated to be similar but not identical to their reference products because of their complex structure. Their chemical characteristics are directly related to the manufacturing process, and cannot be precisely duplicated due to the strong relationship between the manufacturing processes and the characteristics of the final product¹. Moreover, because analytical techniques are not always able to detect or predict all biological and clinical properties of proteins, differences between biopharmaceutical products can remain undetected and, even when detected, subtle differences are difficult to interpret². Thus, to grant a MA for biosimilars, a different

approach is required compared with that used for originators and generics.³

Clinical Development of Biosimilars: General Principles

Prior to proceeding to clinical studies, biosimilars will have been extensively characterized in an iterative process to closely match the reference product (Fig. 1). The comparability exercises follow the same principles as those used for establishing comparability of originator biologics after changes in manufacturing. Manufacturers of biologics frequently make changes to the manufacturing processes of their products both during development and after approval⁴. Ample guidance exists regarding comparability exercises both for biotechnology-derived therapeutic proteins and for development of biosimilars^{4,5}. Often non-inferiority designs have been used in the clinical comparability studies of originator molecules.

In general, the clinical program for biosimilars development will consist of studies to demonstrate a comparative pharmacokinetic (PK) and pharmacodynamic (PD) profile in a sensitive population (usually healthy subjects). Crossover designs are mainly preferred as they are highly sensitive to detect any differences between the reference product and biosimilars⁶. Once PK/PD comparability has been established comparative safety and efficacy studies will follow to confirm therapeutic similarity. The confirmation of a comparable profile in the PK/PD studies will justify the same posology of biosimilars and reference products. No additional dose finding studies are needed.

Comparative efficacy and safety is best demonstrated in head-to-head studies in a study population that is sufficiently sensitive to detect differences between the products, if such differences exist. In the WHO guidelines, equivalence study designs (requiring lower and upper comparability margins) are preferably recommended for the comparison of efficacy and safety of biosimilars with reference products. However, non-inferiority designs may

also be used to demonstrate clinically relevant comparability. It is not to be expected that the biosimilars products will be inferior or superior to the reference products if physicochemical, biological, non-clinical, and PK/PD comparability has been proven.

Finally, conclusion of biosimilarity will be provided by the totality of evidence (e.g., quality, non-clinical, and clinical data).

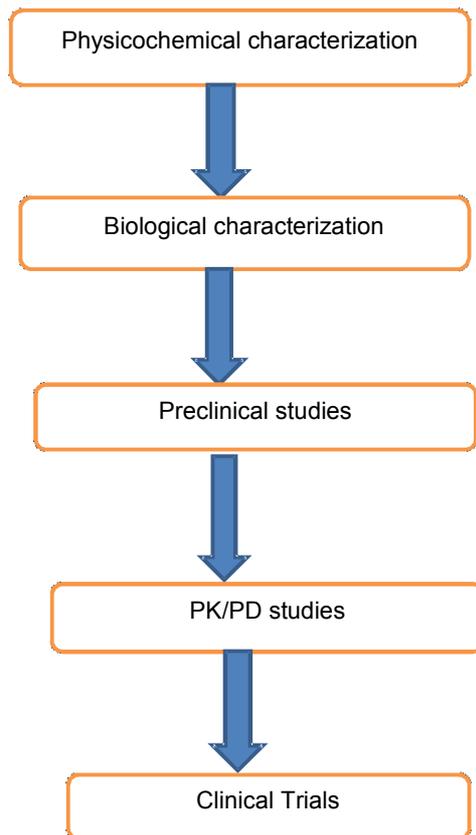


Figure 1: Major steps for clinical developments of biosimilars

EUROPE: REGULATORY SCENARIO

Legal Framework for Marketing Application

In Europe, the legal basis for biosimilars was established by an EU Directive, which lays down the requirements for the MAAs (marketing authorization application) based on the demonstration of the similar nature of two biological medicinal products, with the requirement that the amount of nonclinical and clinical data are determined on a case-by-case basis in accordance with relevant scientific guidelines. Regulation EC No. 726/2004, which was issued by the European Parliament in 2004, lays down Community procedures for the authorisation and supervision of medicinal products that need a centralised procedure, including biotechnological products⁷. At the same time, the regulatory policy for biosimilars is governed mainly by the European Medicines Agency (EMA), through both general guidelines addressing quality, nonclinical and clinical issues, and additional product class-specific guidelines.

In the Europe, technologically advanced medicinal products, such as those developed by means of a biotechnological process (e.g. recombinant DNA technology), can be placed on the market only after a MA has been issued by the Community in accordance with the provisions of Regulation (EC) No. 726/2004 (centralised procedure)². The same regulation also provides an alternative procedure, where clinical data can be omitted in the case of exceptional circumstances. In addition, a

centralised procedure can lead to a conditional MA under the provisions of Regulation (EC) no. 507/2006.⁷

The number and extent of comparability studies required for granting a MA are detailed in guidelines issued by the EMA's Committee for Medicinal Products for Human Use (CHMP). These guidelines cover a range of issues, including manufacturing, demonstration of comparability for quality (module 3), nonclinical (module 4) and clinical study reports (module 5), physicochemical and biological analyses and clinical trial requirements, and additional data (i.e. toxicological, other nonclinical and appropriate clinical data) whose relevance has to be determined on a case-by-case basis, owing to the complexity and diversity of the products. The purpose of the comparability exercise is to demonstrate the similar nature of the biosimilar and the reference product and, consequently, to reduce the amount of data to be submitted in modules 4 and 5 of the CTD.

Additional product class-specific guidelines on preclinical and clinical studies have been developed for several therapeutic proteins, providing guidance on appropriate pharmacodynamic and toxicological studies (in the nonclinical section), and on pharmacodynamic, pharmacokinetic, efficacy and safety studies (in the clinical section). In the case of biosimilars containing recombinant human erythropoietins, the EMA guideline has been recently revised⁹, drawing on experience gained from the products authorised over the past few years.

It is clear that the dossier for a biosimilar is more cumbersome than that of a generic medicinal product. They both comprise full modules 1, 2 and 3, but biosimilars need the comparability exercise for modules 3, 4 and 5, whereas in the case of generics, module 4 is omitted and module 5 is replaced by demonstration of bioequivalence.¹⁰

USA: REGULATORY SCENARIO

The Biologics Price Competition and Innovation Act (BPCIA) of 2009 was a statutory provision in the Affordable Health Care Act of 2010 that provided the rationale for the establishment of an abbreviated regulatory procedure in the United States for licensing biosimilars as a means of providing lower-priced versions of biologics and promoting innovation.¹¹ The Act defines biosimilar products as biologics that have the same mechanism of action, route of administration, dosage formulation, and strength of active ingredient as the reference product and that are highly similar to the reference product. In the context of the Act, highly similar is defined as “no clinically meaningful differences between the biological products and the reference product in terms of tolerability, purity, and potency.”¹²

In the United States, with the patents of many biologics approaching expiration or having reached expiration, biosimilar drugs are projected to bring about a cost savings of 20% to 40%.^{13,14}

The comparability exercise has been introduced by the US Food and Drug Administration (FDA) to allow manufacturers of ‘well-characterised biopharmaceutical products’ (i.e. proteins whose identity, purity, impurities, potency and quantity can be determined and controlled) to implement changes in the manufacturing process. This includes a change in manufacturing site, or modification to cell and seed strains, or fermentation and purification processes, in most cases without conducting additional clinical trials to demonstrate efficacy.⁸

In Feb 2012, US FDA issued three draft guidance documents on biosimilar product development to assist industry in developing such products to market in the United States. The three guidance documents provide the FDA’s views on key scientific and regulatory factors involved in submitting applications for biosimilar products to the agency.

1. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product:

This draft guidance describes a risk-based “totality-of-the-evidence” approach that the FDA intends to use to evaluate the data and information submitted in support of a determination of biosimilarity of the proposed product to the reference product.

2. Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product

This includes the importance of extensive analytical, physico-chemical and biological characterization in demonstrating that the proposed biosimilar product is highly similar to the reference product notwithstanding minor differences in clinically inactive components.

3. Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009

The question and answer format addresses questions that may arise in the early stages of product development, such as how to request meetings with the FDA, addressing differences in formulation from the

reference product, how to request exclusivity, and other topics.

According to this new pathway, biological products will be approved on demonstrating that they are biosimilar to, or interchangeable with, a biological product that is already approved by the US FDA.

These regulatory guidelines will also help Asian biosimilars developers to enter the US market. So far, the biggest challenge for Asian players is the absence of clearly defined regulations in different countries to develop biosimilars. They have limited close interactions with regulatory agencies, which is very critical for a successful biosimilar application. With the clarity coming from the US, the Asian players will now get a chance to develop generic drugs for the vast market of the US, supplying cheaper versions of highly crucial drugs.

INDIA: REGULATORY ADVANCES

In country like India and other developing countries mass affordability is a genuine problem. Because of this pressure, the regulatory process reflects a complex interplay between economics, science, public health and politics. The country also has a robust biopharma sector with over 50 companies actively engaged in development or production of similar biotherapeutic products. The emphasis of the Indian biopharma industry had been directed more toward development of ‘copies’ rather than original molecules because of much lower developmental costs and risks, less spending on research and development, reduced time to market and expertise in reverse engineering drug development process. Over 50 different brands of copy products are approved for more than 20 different biopharmaceutical companies and some of these molecules have completed a decade of market presence with several thousand doses already administered. Even though there have been some concerns and questions that all locally manufactured products are not truly biosimilars, their acceptance by both, the prescribers and the patients has been good.^{15,16}

Presently, more than 15 brands of Erythropoietin (EPO) and 12 brands of granulocyte colony stimulating factor (G-CSF) available in the Indian market and new ones are being added every few months.¹⁶ There have been concerns regarding the quality of available molecules and questions whether these copy products are at all ‘similar’ to the innovator products. Another major concern in India and other developing countries is the maintenance of the cold chain at the stockist level and the viability of the product when it reaches the consumer.

The Indian regulators are attempting to ensure a high quality of the products. The 6th Edition of the Indian Pharmacopoeia (August 2010) includes product-specific monographs for 5 biological drug substances including insulin, interferon, EPO, G-CSF and streptokinase and monographs for other biologic products are under development.¹⁷ The approval requirements comprise physico-chemical and biological characterization, non-clinical toxicity studies and Phase III confirmatory clinical trials.

There are several regulatory bodies and committees are involved in the approval of biotechnology derived products. For example, Review Committee for Genetic Manipulation (RCGM) which monitors all research scale activity and regulate approval for non-clinical studies. Genetic Engineering Advisory Committee (GEAC) involved in Environmental safety for large-scale operations of Live

Modified Organism (LMO) based products. Drug Controller General of India (DCGI) regulates product safety and efficacy as well as clinical trial & marketing approval for biotech drugs. Food & Drugs Control Administration (FDCA) approves plant & ensures cGMP manufacturing facilities. The other unit involved are department of biotechnology (DBT), Indian council for medical research (ICMR), Institutional biosafety committee (IBSC) etc.

Very recently, India reiterated its commitment to providing a conducive policy environment for the development of biotechnology with the release of its guidelines for similar biologics. The policy document broadly speaks about the relevant authorities involved in granting approvals, the clinical trial requirements and also the market authorization of these similar biologics. In July 2012, DBT and CDSCO (central drugs standard control organization) have issued guideline for biosimilar "Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorization in India".¹⁸ As per latest update from CDSCO, the guideline will be implemented by 15 Sept, 2012.

So far, similar biologics were approved by Review Committee on Genetic Manipulation (RCGM) and the CDSCO using an abbreviated version of the pathway applicable to new drugs on a case by case basis. The guidelines clearly mark the roles of each of these organizations including that of the Drug Controller General of India (DCGI) for approving the clinical trials and manufacture and market authorization of the biosimilars.

The current guidelines dictate that a similar biologic can only be developed against an authorized reference biologic that has been approved in India. In case the reference biologic is not authorized in India, it should have been licensed and marketed for at least 4 years with significant safety and efficacy data. This requirement can however be waived off if there is no medicine currently or only palliative therapy is available or in case of a national healthcare emergency. Also in case the reference biologic is not marketed in India, the reference biologic should have been licensed and widely marketed for at least 4 years post approval in innovator jurisdiction in a country with well-established regulatory framework.

The guideline also clearly outlines the data requirements to be provided by the applicants for conducting preclinical studies as well as clinical trials for similar biologics. They also state, in detail the requirements for preclinical evaluation of the similar biologic which include pharmacodynamic studies, toxicological studies and the study of immune responses in animals. The applicant should submit the data generated along with the basic clinical information and preclinical study protocols to RCGM for obtaining permission. This is supposed to be accompanied by an approval by the Institutional Biosafety Committee (IBSC) of the applicant and an Institutional Animal Ethics Committee (IAEC), if available.

Other features of this policy document include the data requirements for market authorization application and post-market data. For cases where commercial manufacturing is performed either at a different scale or with a different process as compared to that used for manufacturing phase III clinical trial batches, the information on comparability of quality needs to be additionally submitted.¹⁹

REGULATORY UPDATES IN OTHER EMERGING COUNTRIES

Reverse engineering of existing drugs have a considerable learning effect for industries in China, India and Brazil, facilitating the adoption of new technologies and easing the transition into innovative activities. Firms have not only gained experience in health product manufacturing and marketing, but have also developed the necessary technical expertise to allow them to venture into more sophisticated areas. In this respect, the absence of a strong domestic pharmaceutical manufacturing sector in South Africa puts it in a different category than the other three countries studied. A key driver of technological upgrading has been an interest in export markets, including the major markets of the U.S. and Europe. While domestic populations constitute the main market presently, for most health biotech enterprises, there is a growing interest in many medium and large firms to export products, particularly in India. In contrast, few companies in China, Brazil, and South Africa have thus far exported finished medicines to highly regulated markets. This trend is likely to change however, as these countries continue to enhance their own manufacturing standards. The Chinese vaccine-manufacturing sector is one of the largest in the world in terms of production volume, where approximately 30 vaccine manufacturers, mostly domestic enterprises, produce over a billion vaccine doses annually.²⁰ As a sign of recent progress, Sinovac Biotech (Beijing) gained manufacturing approval in September 2009 from the Chinese State Food and Drug Administration (SFDA) for its single-dose H₁N₁ vaccine.

The Brazilian health biotech industry is populated by a growing number of technology-based small and medium sized enterprises as well as generics-based pharmaceutical incumbents, some of whom are transitioning to innovative R&D activities. Overall, the sector remains very young with the vast majority of health biotech enterprises coming into existence in the past decade.²¹ However, regardless of size, Brazilian companies tend to shy away from vaccine development and production due to the dominant role played by the country's public sector in this area. Furthermore, in Brazil and China the public sector supplies a considerable portion of basic medicines deemed essential for public health.

The nascent health biotech sector in South Africa relies considerably on the research capabilities of the country's universities and research institutes to identify novel technologies and products for commercial development.²² Smaller countries such as South Africa with more limited biopharmaceutical purchasing power and skill-base to build on appear to be at a disadvantage vis-à-vis China and India.

Regulatory Issues

One of the most common challenges facing innovation-inspired firms in the emerging economies relates to the clarity and effective enforcement of regulations governing health products. Again, while the outcome often manifests in delays in regulatory approval, the underlying causes often vary across nations. For, lack of practical experience on the part of Brazilian and South African regulators was thought to make product approval challenging in these countries. Other challenges in Brazil and South Africa were primarily related to delays in approval of clinical trials, which was perceived to detract from a major competitive advantage possessed by these countries. In this sense, India is missing the opportunity to create a truly centralized regulatory

agency, which can oversee all health products and optimize resultant synergies.

China's regulatory regime has also had significant setbacks in recent years due to corruption scandals involving some high-ranking officials at the country's SFDA. However, the agency has rebounded from these challenges and has recently made progress in a number of areas. For example, in early 2009 the SFDA instituted its Green Channel initiative, which is an expedited approval process, allowing regulators to waive requirements for Chinese trials for innovative new drugs, new combinations, and those targeted at unmet medical needs in the country. Furthermore, it has undertaken a variety of initiatives aimed at addressing product quality issues in the country's vast and complex pharmaceutical sector.²³

DISCUSSION

Variation among and between originator biologics and their biosimilars is an attribute of their molecular complexity and the manufacturing processes that contribute to their heterogeneity. Regulatory processes seek to quantify and understand these effects. Currently, the question of how similar a biosimilar must be to a reference drug to obtain approval cannot be answered by any single standard set of methodologies. Abbreviated approval processes for biologic products present challenges given the scientific and technical complexities associated with their larger and often more complex structures compared with LMW chemically synthesized products. In 2006, the EMA became the first regulatory body to establish a process and to provide guidance for the approval of biosimilars. Since that time, more than 10 biosimilars have been approved under these guidelines.⁷

TABLE 1: BIOSIMILAR PRODUCTS MARKETED IN EUROPE

Medicinal product	INN*	Reference medicinal product
Omnitrope	Somatropin	Genotropin
Valtropin	Somatropin	Humatrope
Retacrit	Epoetin zeta	Eprex/Erypo
Silapo	Epoetin zeta	Eprex/Erypo
Abseamed Recombinant human	Recombinant human erythropoietin alfa	Eprex/Erypo
Binocrit	Recombinant human erythropoietin alfa	Eprex/Erypo
Epoetin alfa Hexal	Recombinant human erythropoietin alfa	Eprex/Erypo
Biograftim	Filgrastim	Neupogen
Filgrastim Ratiopharm	Filgrastim	Neupogen
Ratiograftim	Filgrastim	Neupogen
Tevagraftim	Filgrastim	Neupogen
Nivestim	Filgrastim	Neupogen
Zarzio	Filgrastim	Neupogen
Filgrastim Hexal	Filgrastim	Neupogen

(*INN- International non-proprietary name)

Data from comparability evaluations and clinical trials supporting these applications are reported widely in the literature, allowing for guarded assessment of this regulatory process. Such an assessment has important ramifications for the regulation of biosimilars in the United States, here the recently established approval pathway currently lacks the detailed product-specific guidance enacted by the EMA. Recently, EMA officials developed relationships with the US regulatory bodies to serve as consultants in the development of the US guidelines.²⁴ The EMA guidelines emphasize comparable quality, tolerability, and efficacy, as well as the need for clinical trials and postmarketing risk management. Going forward, it will continue to be important to evaluate the predictive value of each of these exercises in terms of the subsequently available postmarketing efficacy and tolerability data; thus, the predictive value of detectable variations in quality is of key importance. Given the trend toward both the increased complexity of biosimilars and an increased ability to detect biophysical variation, comparative studies are likely to paint differences in quality with an ever-finer brush. Regulatory bodies have taken the position that for a treatment to be designated as biosimilar to the reference drug, evidence of molecular similarity to the reference drug must be provided at the maximum resolution achievable by current state-of-the-art technologies available for physicochemical characterization, in addition to functional assays and clinical trials. Failing to meet this standard, the compound can be approved only via the pathway for novel biologic agents. From the standpoint of public access to high-quality,

affordable biologic medicines, an approval process that results in full applications for clinically equivalent biologics is highly undesirable because it may lead to a proliferation of essentially identical agents, each with minor changes in prescribing criteria. Such a system may generate confusion among health care providers in choosing appropriate treatments, and it may not result in any cost savings. This situation would be especially problematic in cases in which the compounds have no discernible clinically differentiated target populations.

Qualitative comparability requirements between an originator biologic and its biosimilars are similar in scope and technical rigor to the detailed comparability exercises that manufacturers of originator biologics are required to carry out for major in-house changes in manufacturing processes for the certification of new batches and process improvements. Batch consistency reflects the quality of the development process and production procedures. Although variations in the batch-to-batch consistency of biologics are quite common, these variations, if maintained within the acceptable range, are usually not clinically meaningful based on the available data on approved biosimilars and originators that have undergone manufacturing changes.²⁵ Manufacturing-process changes undertaken with most biologics can be extensive over the course of the product life cycle but rarely require systematic clinical trial evaluation of comparability between the pre- and post-change products. Empirical evidence suggests that microheterogeneity in biophysical parameters among originators and biosimilars does not necessarily result in any

significant differences at the clinical level. Biosimilars and originators that have undergone manufacturing changes have been approved in the European Union despite minor differences in comparability versus respective reference products, either in physicochemical or PK characteristics, and evidence of similarity in their clinical efficacy and safety profiles has also been reported.^{26,27,28} For these reasons, the requirements for clinical trials should be evaluated case by case.

CONCLUSION

With more and more innovator product going off patent, urgent attention is required to regulate the increasing number of biosimilars. New biosimilars should be made available as soon as patent protection is over so that the economically compromised patients who cannot afford the high cost of the originator molecule have an option to opt for the cheaper copy versions. Reducing the cost of drugs is now a global priority rather than just being a major issue in developing economies.

Observations from comparative studies of approved biosimilars offer an opportunity to frame the discussion beyond the microheterogeneous level and suggest that careful consideration is needed of the role of active-controlled clinical trials for the assessment of the efficacy and tolerability profiles of biosimilars. Experience from Europe and other regions support the concept that the quality and comparability standards applied for process changes for the originator biologic products may be applied for biosimilar-development programs when the risk/benefit profile of the originator is well characterized. Biopharma industry in many developing countries is ready and capable of manufacturing world-class non-innovator biotherapeutic products. However, it is imperative that the local regulatory authorities ensure that the manufacturer maintains the quality and consistency of the finished product across batches over time.²⁹ This can be a major challenge especially in developing countries.^{30, 31} India, having the benefit of in-house expertise in the area, should utilize the various agencies to come up with working group or taskforce whose goal is to develop product-specific guidelines for approval. These can be developed using available worldwide regulatory knowledge, studying the scientific literature and understanding industry practice with respect to characterization. Thus focus on specific areas and propose an approval path having global acceptance for biosimilars.

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