Review article:

Biosimilars : Simnilarities and Differences

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Abstract:

In the 1980s novel biological medicines produced by recombinant DNA technology appeared on the horizon. The biopharmaceutical industry has expanded dramatically over the last 30 years since the first successes of recombinant DNA technology. Biopharmaceutical drugs have become an essential part of modern pharmacotherapy. Biopharmaceuticals are well established in biomedicine and have opened new therapy options particularly in disease areas where previously no, or only insufficient, therapies were available. These comprise proteins derived from recombinant DNA technology and hybridoma technique. Examples include biological proteins (cytokines, hormones, and clotting factors), monoclonal antibodies, vaccines, cell and tissue based therapies. The rising pressure of cost-containment in all major markets is driving the uptake of generics and also creates a demand for biosimilars. However, the cost and duration of development for biosimilars are much greater than for small-molecule generics, and presents a significant barrier to entry and a resistor of biosimilars market growth.

Keywords : Biopharmaceuticals , DNA Technology

Introduction

In the 1980s novel biological medicines produced by recombinant DNA technology appeared on the horizon. The biopharmaceutical industry has expanded dramatically over the last 30 years since the first successes of recombinant DNA technology. Biopharmaceutical drugs have become an essential part of modern pharmaco-therapy. Biopharmaceuticals are well established in biomedicine and have opened new therapy options particularly in disease areas where previously no, or only insufficient, therapies were available. These comprise proteins derived from recombinant DNA technology and hybridoma technique. Examples include biological proteins (cytokines, hormones, and clotting factors), monoclonal antibodies, vaccines, cell and tissue based therapies.[1-4]

The expiry of patent protection of many biopharmaceuticals has initiated the development of a category of alternative versions of innovator biopharmaceuticals known as biosimilars. Because of the structural and manufacturing complexities, these biological products are considered as similar, but not generic equivalents of innovator biopharmaceuticals.[5]

Meanwhile it has been recognized by all stakeholders – politicians,regulators, innovative and generics pharmaceutical industry, payers, physicians, pharmacists, and patients – that there are fundamental differences between conventional small-molecule based drugs and biopharma-ceuticals. This has led to the adoption of distinct legal and regulatory frameworks for follow-on products to biopharmaceuticals (‘‘biosimilars”) in various parts of the world.At present, India is one of the leading contributors in the world biosimilar market. India has demonstrated the greatest acceptance of biosimilars, which is reflected from over 50 biopharmaceutical brands getting marketing approval.[6]

Definition

Several terms are used in various countries for ‘‘intended copy” products to biopharmaceuticals e.g., biosimilars (European Union), follow-on biological (American context), follow-on protein products, subsequent-entry biologicals, similar biological medicinal products.

Biosimilars are defined as biological medicinal products which are

- 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
- authorised for marketing through a procedure based on the proof of similarity to the reference product, using certain pre-existing scientific and regulatory knowledge

It should be emphasized that this definition excludes biopharmaceutical products developed and licensed as ‘‘stand-alone” products based on a full data package according to national regulations, but without comparative studies versus a reference product.

Due to the inability to characterize complex biological products sufficiently, the ‘‘biosimilar” approach is focussed on highly purified products, usually drugs containing recombinant proteins as the active pharmaceutical ingredient. It is presently not applied to blood or plasma-derived products, immunologicals, and emerging new therapies such as gene and cell therapies. However, regulators seem to be ready to accept other classes of compounds, e.g. polysaccharides such as low-molecular weight heparins.[7]

How are biosimilars different from chemical generics?

Generic drugs are characterized by their chemical and therapeutic equivalence to the branded, original, low molecular weight chemical drugs whose patents have expired. These are essentially identical to the original product and sold under a common name. These are approved through simplified registration procedure as abbreviated new drug application (ANDA), with demonstration of bioequivalence. However, it is not possible to employ the same standards for the evaluation or appraisal of biosimilars, as there are various differences between chemical generics and biosimilars.[8]

Size - unlike chemical drugs , biopharmaceuticals are high molecular weight compounds. For example, the molecular weight of aspirin is 180 Da whereas interferon-β is 19,000 Da.[9]

Structure - To possess biological activity, proteins have to adopt the correct three-dimensionally folded secondary, tertiary, and quaternary structures. The typical biologic drug is 100 to 1000 times larger than small molecule chemical drugs and possesses fragile three-dimensional structure as compared to well-characterized one-dimensional structure of chemical drug.

Structure–function relationship : Whereas in small molecules, it is often known that every atom of the molecule will play a role in defining the clinical profile of the compound, the structure–function relationship is usually unknown, or at best partially known, for proteins.

Stability – Proteins are inherently unstable molecules, and may structurally be damaged by heat, prolonged storage, denaturants, organic solvents, oxygen, pH changes, and by other factors, leading to reduction or complete loss of biological activity.

Microheterogeneity - Different manufacturing processes use different cell lines, protein sources, and extraction and purification techniques, which

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result in heterogeneity of biopharmaceuticals. Versatile cell lines used to produce the proteins may have an impact on the gross structure of the protein, and may affect glycosylation and other post-translational modifications. Such alterations may significantly impact receptor binding, stability, pharmacokinetics and safety.[10]

Immunogenicity

Immunogenic potential of therapeutic proteins is another unique safety issue which is not observed with chemical generics.[11,12]

Legal and regulatory status

It has been long recognized by the regulatory authorities that differences in the manufacturing process of biopharmaceuticals necessarily will lead to differences in the product attributes which cannot be fully assessed by analytical characterization. As a consequence, therapeutic proteins derived from independent manufacturing processes can never be identical, but at best be ‘‘similar”, i.e. possessing the same clinical safety and efficacy profile in spite of not being ‘‘the same” molecule.[13]

A legal and regulatory process allowing for an abbreviated approval of biosimilar products has to ensure an appropriate balance between the aim to facilitate market entry and competition for offpatent medicines, the endeavour to foster scientific and medical innovation and reward it appropriately, and particularly the need to avoid any unnecessary risks for patient safety. Whereas it is desirable to avoid unnecessary or even unethical animal or human trials, it has to be kept in mind that biosimilars, although offering economical benefits, by definition do not bring about any medical progress since the reference products are available and have proven safety and efficacy over many years. Thus, the biosimilars approval process should make sure that the same high standards and stringent requirements for quality, safety, and efficacy are ensured as for innovative medicines.

The EMA (European Medicines Agency) was the first regulatory authority to tackle this problem when in 2004 it developed the concept of similar biological medicinal products, popularly shortened to biosimilars, and in 2005 developed a regulatory framework and guidelines for dealing with them. This involves a comparability exercise which relies on a head to head demonstration of “similarity” of the new product’s characteristics (physicochemical and biological activity) to a chosen licensed reference biological product (RBP) which in turn, providing similarity is shown, can lead to a reduced non-clinical and clinical data package.[14,15]

At the International Conference of Drug Regulatory Authorities (ICDRA), Seoul, 2006, WHO was requested to develop a global regulatory consensus and guidance on this evolving topic and the following years have seen a number of WHO consultations on nomenclature (INNs) and on regulatory evaluation of “biosimilars”, involving regulators and manufacturers. An important point of agreement globally was that biosimilars do not meet criteria for true generics and should not be regulated under generic (small molecule) drugs regulations.[16]

French legislation and Spanish ministry of health and consumer affairs have also issued the law that prevents one biological medicine being substituted for another. US-FDA and several other regulatory agencies are still working on formulation of guidelines for marketing approval of biosimilars. In India, the specific guidelines for approval of biosimilars are lacking. Thus, there is unrestrained flooding of biosimilars in Indian market.The WHO Guidelines on the Evaluation of Similar Biotherapeutic Products, published in 2010, rely on a head to head demonstration of

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"similarity" of new product characteristics (physicochemical/ biological activity) to a chosen licensed reference product to justify a reduced non-clinical and clinical data package.[17]

Issues of concern with use of biosimilars

Although regulatory frameworks for biosimilars have been adopted, or are upcoming, in many parts of the world, there are some open issues left which are presently under intense discussion.

Reference product

According to the EMEA guidelines, the reference product has to be authorised in the EU based on a full dossier, and the same reference product has to be used throughout the comparative studies for quality, safety and efficacy. However, innovator products authorised in different countries may differ concerning, e.g. production site, formulation, and strength, so if the same demand would be made for all countries, a biosimilars manufacturer may be faced with the need to do comparative studies separately for each country versus the locally authorised reference product (provided a suitable nationally licensed reference product is available). Therefore, the option of national regulatory authorities to accept a reference product not licensed within their jurisdiction is under discussion but would call for information sharing between the regulatory authorities, and/or additional data to be provided by the biosimilars manufacturers.[18]

Labelling

The summary of product characteristics (SmPC) as well as the package insert (collectively called ''the labelling") should provide transparent information to healthcare professionals and patients on issues relevant to the safe and effective use of a medical product. Therefore, the labelling should differentiate clinical safety and efficacy data which have been obtained with the biosimilar product itself from those which just have been taken over from the reference product, particularly in extrapolated indications where no studies have been done with the biosimilar at all.[19]

Pharmacovigilance

for all new medicines, marketing authorisation holders of biosimilars should make sure that they have an appropriate system of pharmacovigilance in place to assure responsibility for their products on the market and to ensure that appropriate action can be taken if necessary. For biosimilars, this requirement is even more important because the pre-authorisation safety database will be relatively small due to the abridged clinical development program. Pharmacovigilance is of special importance in case of rare serious adverse events (such as the PRCA cases on epoetin treatment) which might not be evident at approval due to the limited data package available at this time.

Naming

In order to support post-approval monitoring, the specific medicinal product given to the patient must be clearly identified. International non-proprietary names (INNs) are assigned to drug substances by the WHO INN Programme. WHO does not intend to introduce a specific process for naming biosimilars , and the INN as a cataloging system for drug substances can neither be relied upon as an appropriate means to ensure identification and traceability of biological, including biosimilar products nor as the sole indicator of product interchangeability. Therefore, it will be necessary that biosimilar products are marketed using brand names.[21]

Interchangeability and Substitution

Whereas conventional generic medicines are usually considered or classified as interchangeable, this is not necessarily the case for biosimilars: here interchangeability should be demonstrated by scientific data proving that two products can be safely substituted for one another and do not create

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adverse health outcomes, e.g. generating a pathologic immune response after repeated switching. In the absence of such data patients and physicians should be aware that protein products with similar molecular composition may indeed not be interchangeable.[14]

The strategic perspective

The rising pressure of cost-containment in all major markets is driving the uptake of generics and also creates a demand for biosimilars. However, the cost and duration of development for biosimilars are much greater than for small-molecule generics, and presents a significant barrier to entry and a resistor of biosimilars market growth.[22]

The ‘‘philosophy” of the European biosimilars guidelines is based on the request that the applicant has to provide comparative data convincingly showing similarity vs. the reference product concerning quality, safety, and efficacy.[23]It has even been considered that competition in future indeed might not primarily be between innovators and price-cutting copiers, but rather with second-generation biopharmaceuticals based on improved formulation or delivery systems, or derivatized biologics with improved performance. Thus the ultimate benefit of the emergence of biosimilars, in the end, may be in stimulating innovative research resulting in new options to treat serious diseases. It will be essential that the regulations introduced in various parts of the world do not hinder, but promote pharmaceutical innovation to the benefit of patients, healthcare systems, and industry.[24]

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