Biologics, biosimilars, intended copies and the era of competitive medicine

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\textbf{Abstract}

Biologics have helped treatment of diseases including cancers, rheumatoid arthritis, etc. in entirely new ways. Because they are expensive, there is a demand for generic versions (biosimilars). Biologicals and biosimilars consist of large complex molecular entities difficult to characterize. An innovator and a biosimilar will never be entirely identical because their manufacturing processes are different; hence both need to be evaluated for potential adverse effects and clinical impact, and thus require a separate regulatory approval process. Biosimilar manufacturing has to follow a similar process as biologics, but may not produce exactly identical result. Hence, there can be variations owing to differences in cell line, transfection and the process in fermentation or purification. Also since biosimilars approval is on limited preclinical and clinical data, it is essential to have a comprehensive post-marketing surveillance to detect safety risks, immunogenic, or adverse reactions. Currently, several products labelled as ‘biosimilars’ are approved in some developing countries, which, at the time of approval, did not have a formal regulatory processes in line with EMA and US-FDA. These products should be considered ‘intended copies’ rather than biosimilars. Physicians should know the difference among biologic, biosimilar, bio-better and an ‘intended copy’ to make an informed prescribing decision or substitution.

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1. Development of biosimilars

1.1. Definition of biosimilars

Biotechnology has revolutionized the way diseases are treated. Recombinant DNA technology has allowed the development of bio-pharmaceuticals, which can mimic the complex body proteins. These unique agents have helped the treatment of diseases in entirely new ways. Biotechnology-derived drugs are called biologics which today have become an essential part of modern pharmacotherapy.

The ability to produce biologics has resulted in an improved understanding of mechanisms of diseases and resulted in the development of a plethora of innovative drugs and vaccines that have improved outcomes in the areas of un-met clinical needs, including cancers, rheumatoid arthritis, Crohn’s disease, multiple sclerosis, macular degeneration, retinal vein occlusions, psoriatic skin diseases and Gaucher disease.

Today several biologics have entered into the global market of pharmaceuticals. These include biosynthetic monoclonal antibodies, insulin, peptide hormones and analogues, hematopoietic and non-hematopoietic growth factors, interferons, interleukins, erythropoietins, fusion proteins, recombinantly produced antigens (vaccines) and other innovative products that account for a substantial portion of human medicines. It is an astonishing fact that one third of new medical entities launched are biologics.

Globally the sale of biologics was approximately $142 billion in 2011. Global Industries Analysts have forecasted that the market for biologics would be $158 billion by 2015. Approximately, 30% of the pharmaceutical and biotech industries pipeline is composed of biologics, and it is anticipated that by 2016 ten of 20 top selling drugs will be biologics. Presently biologics, including Humira (Adalimumab), Enbrel (Etanercept), Remicade (Infliximab), Avastin (Bevacizumab), Lantus (Insulin Glargine), Rituxan (Rituximab), Herceptin (Trastuzumab), Prolia (Denosumab) and Lucentis (Ranibizumab), are among the top selling pharmaceuticals worldwide.

Though biologics are highly effective, life-altering therapies, yet they are expensive and often prescribed long-term for chronic medical conditions. This imposes a burden either on national health care systems or on the patients' pocket.

Hence, there is a natural demand for generic cheaper versions of these drugs. The patents of many first generation biologics developed in 1980s and 1990s have started to expire and there is a growing market demand for generic versions of these innovators called bio-similars. The terminology 'bio-similar' is used in accordance with the fact that second generation biologics cannot be exactly the same as innovators owing to structural and manufacturing complexities of biopharmaceuticals, making them similar but not exactly same as in the case of less complex small molecule drugs.

In principle, biosimilars are the biologic medicines' equivalent of chemical generics and have a similar active component. However, biologicals and biosimilars are manufactured from living cells or organisms and consist of relatively large and often highly complex molecular entities that may be difficult to fully characterize. Even among different batches of the same biologic, there would be variability, because the manufacturing process is complex, besides the inherent variability of the biologic system. As the way these molecules are manufactured is different, an innovator and a biosimilar will never be entirely identical. Differences would need to be evaluated for potential adverse effects and impact on the clinical performance of the biosimilar. These reasons mandate a separate regulatory and license approval for biosimilars.

Different countries have established legal and regulatory pathways for bringing in biosimilars to the market. The regulatory body for the European Union (EMEA) and US (US-FDA) have developed guidelines for the approval of manufacture and sale of biosimilars. A variety of terms, such as 'biosimilar products', 'follow-on protein products' and 'subsequent-entry biologics' have been coined by different jurisdictions to describe these products.

The European Union was the first region in the world to have set up a legal framework and a regulatory pathway for biosimilars.

The EMEA defined biosimilars as 'A biological medicine that is developed to be similar to an existing biological medicine. When approved for use, any differences between it and its reference medicine will have been shown not to affect safety or effectiveness'. The US-FDA defined biosimilars as 'A biological product that is highly similar to a US licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which 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'. The Australian Therapeutic Goods Administration as well as the Canadian health authorities biosimilar guidance document is based on European guidelines.

World Health Organization defined biosimilars as 'A biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product'. Biosimilars have to depend on the efficacy and safety data of innovators for their licensing.

1.2. Rationale for development

The biosimilar market is expanding rapidly and the main incentives for driving the development of biosimilars are quite the same as those for developing small molecular weight chemical 'generic' drugs. Key factors driving market growth include availability of new innovative technology, to promote market competition, patent expiries of key biological drugs, produce efficient and safe medicines at affordable prices, cost containment measures from governments, meet the worldwide demand and the increasing ageing population globally.

1.3. The 'Patent Cliff'

Since early 1980s biologics have revolutionized the treatment of many diseases. But as the patents and data protection measures expired or are nearing expiration, considerable interest has turned to making biosimilars. This expiration of a 20 year exclusivity period for a lot of biologics, has given rise to the "patent cliff" (clustering of patent expirations of numerous biologics occurring between 2011 and 2019 (Table 1). This
A patent cliff refers to an abrupt drop in sales of a group of blockbuster products after reaching the end of their patent life by the availability of its biosimilar versions in the market. In the next half of the decade, a new generation of complex biosimilars will be developed, as leading biologics will lose their patents by 2020. The biologic medicines market is expected to grow to $190–200 billion by 2015, with biosimilars a small but growing proportion at $2–2.5 billion. The expiration of these patents will compel competing manufacturers to develop biosimilars that can achieve an annual rate of 20% going forward.

2. Health care costs savings

The cost of biotechnology products are a major drain on public funded health programmes, placing an additional burden on healthcare systems and forcing cost-cutting measures in other areas of healthcare delivery. The humanistic burden due to the restricted access to these medicines and the budget constraints in many parts of the world raise significant interest and demand of similar, efficacious safe biosimilars. And this has generated a need to make copies of biologics (biosimilars), accessible and affordable resulting in significant savings to the health care system.

2.1. The manufacturing challenge

Manufacturing of biopharmaceuticals is a highly complex process. While small molecules are produced by chemical synthesis for less than US $5/g, biopharmaceuticals can be produced with genetic engineering and recombinant DNA technology at a cost of US $100–1000/g. Manufacturing of biopharmaceuticals involves several stages, and each stage is an area of intensive research, which includes investigation from the choice of the expression vector, host cell line, purification protocols, quality control assessments, through to the final product formulation (Figs. 1–3). Even minute changes in the process could have profound effects on the biological activity and safety profile of the final product.

The manufacturing process begins with the construction of the master cell bank (Figs. 1–3). The construction of the master cell bank involves the genetic engineering of a host mammalian cell, where the gene of interest producing the protein of interest is inserted into the DNA of the host expression systems. A large number of host systems developed over the years enabled the production of recombinant proteins. Almost all of the 200 or so approved biopharmaceuticals have been produced in one of the following host expression systems: bacteria, yeast, insect cells, transgenic animals as well as mammalian and human cell lines. More than 50% of marketed biopharmaceuticals are produced using mammalian cells, mainly due to the ability of mammalian cells to synthesize proteins that are similar to those naturally occurring in humans with respect to molecular structures and biochemical properties. The recombinant genetic engineering techniques are used for cloning of the appropriate genetic sequence into an expression vector, followed by the generation of a host cell expression system for creating a master cell bank and scaling it up for large-scale protein production. In batch fermentation the cells derived from master cell bank are progressively grown in larger and larger volumes over a period of 3–4 weeks to provide a seed culture for larger fermentation tanks. And this gradual step-up allows rapid growth of a larger volume of cells. A stainless steel tank typically holds 10,000–20,000 L of culture medium where cells are grown to an optimal density over 12–14 days. The desired protein is isolated and purified from the cell culture medium, using a multi-step downstreaming purification process that maintains the protein’s structural and functional integrity. And finally, it is brought into a formulation and device suitable for patient use. The whole
The process has to be run under strictly controlled, validated conditions in closed systems to assure consistency and avoid any contamination, and in accordance with GMP requirements. For the manufacture of biosimilars, the product has to independently go through a similar process which may not produce exact identical result, if there is no access to originators protocol. Hence, there can be variations owing to differences in cell line, transfection and the process in fermentation or purification. The microheterogeneity will depend on the manufacturing technique. Although not all of these variations will have an impact on the clinical safety and efficacy profile, there could be batch-to-batch variations even in the same biosimilar from the same manufacturer as well as in different biosimilars from different manufacturers for the same biologic, although all heterogeneities should be

Fig. 2 – Biopharmaceutical process chain.
acceptable within the limits defined by the specifications by regulatory authorities as seen in Fig. 1.

2.2. Concerns about biosimilars

Concerns about the production of biosimilars are due to the fact that variation can happen at every stage in the production which could have significant clinical implications. The case of Eprex (Epoetin alfa) serves as a compelling example. It was found that minor manufacturing changes induced antibody-mediated pure red cell aplasia (an immune reaction in which the patient’s antibodies neutralize not only the drug, but also the body’s natural erythropoietin) in chronic dialysis patients.31

Various countries have imposed proper guidelines for the production and manufacture of biosimilars and, which need to be followed to get market authorization. Manufacturers are now expected to provide validated batch-release tests that prove not only the compositional uniformity of biologics, but also their biological functional consistency.31

Undetectable changes to complex three-dimensional proteins can result in significant clinical implications. The major concerns about biosimilars are microheterogeneity, immunogenicity, quality concerns and safety together with efficacy.

(a) Microheterogeneity – Using recombinant technology, it is possible to duplicate the specific amino acid sequence of a protein, but the DNA encoding the amino acid sequence does not control post-translational modifications such as glycosylation. So despite having the same primary structure, biosimilars can differ in sugar moieties attached and other post-translational modifications (acetylation, phosphorylation, methylation, sumoylation) which may not be a clinically significant difference.5

(b) Immunogenicity – For all biologics, immunogenicity is important and is therefore not a unique issue for biosimilars. At present, there are no published reports for any marketed biosimilar associated with any unexpected adverse events as compared with the relevant reference product. There are strict guidelines by BPCIA (Biologics Price Competition and Innovation Act), US-FDA and EMA about the immunogenicity of biosimilars.1,29

(c) Safety and efficacy – Biosimilars have to demonstrate a comparable safety and efficacy with reference biologic. A comparison on various parameters with reference biologic is required to evaluate the relevant quality attributes of the pre- and post-change products in order to demonstrate that no modifications occurred that would affect the drug efficacy and safety.32

Fig. 3 – Manufacture process for a biological.2
It may not be possible to demonstrate the efficacy for every indication for a biosimilar, and for that, guidelines by various countries state that the sponsor must demonstrate that its product is comparable to the reference product. Additionally it is equally essential that, if biosimilarity is demonstrated, then it is not required to prove the safety and efficacy. The US-FDA gives additional opportunity to designate products as interchangeable. For this, the sponsor of the biosimilars must affirm the expectation of identical clinical results for the two products in any given patient, and show that efficacy and safety are not compromised by the switch.3

(d) Quality issues – The manufacturing process for biosimilars must comply with the stringent guidelines set by EMEA and US-FDA. Biosimilars, therefore, have to demonstrate that the production process is capable of consistently producing a high quality product.

3. Regulatory, legal framework and guidelines

3.1. Europe

The European Union (EU) was the first to introduce the term ‘biosimilar’ in 2003 and the US-FDA followed suit. The EU’s EMA revised its previous 2006 guidelines on 10th of July 2013 on the basis of the experience gained since the release of the initial guidelines. The guideline addresses the general principles for the non-clinical and clinical development and assessment of the marketing authorization applications of biosimilars containing recombinant proteins as active substance(s).33

The approach suggested by the guidelines would be tailored for each product separately dealt on a case-by-case basis on the need and the extent of in vitro, in vivo, clinical (Pharmacokinetic/Pharmacodynamic studies) and safety-efficacy data. The Committee for Medicinal Products for Human Use (CHMP) issues specific guidelines concerning the scientific data to be provided to substantiate the claim of similarity (or biosimilarity) used as the basis for a Marketing Authorization Application (MAA) for any biologic. It also has made a RMP (Risk Management Plan) choice of reference product and requirements for establishing biosimilarity.37

The guidelines also separately mention the need for extrapolation of efficacy and safety with respect to change of indication. In case, the reference medicinal product has more than one therapeutic indication, as well as the efficacy and safety of the biosimilar have to be justified or, if necessary, demonstrated separately for each of the claimed indications, although it may not be applicable in all cases or indication and each case would be dealt separately. The guidelines also stress on a strict pharmacovigilance since data from pre-authorization clinical studies are usually insufficient to identify rare adverse effects; hence, clinical safety of biosimilars must be monitored closely on an ongoing basis during the post-approval phase including continued benefit-risk assessment.34

3.2. United States

In US in 2010, the Patient Protection and Affordable Care Act (Affordable Care Act) was passed to create an abbreviated licensure pathway for biological products that are demonstrated to be “biosimilar” to or “interchangeable” with an FDA-licensed biologics. These new provisions may be referred to as the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). BPCI Act creates an abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with a US-FDA licensed reference product.

3.2.1. Scientific considerations in demonstrating biosimilarity

US-FDA considers multiple factors as part of the biosimilarity assessment that includes product’s complexity, formulation, stability and usefulness of biochemical and functional characterizations. US-FDA also determines the amount of testing on animal/human and clinical studies necessary to demonstrate bio-similarity after a thorough review of data from structural and functional analyses.

3.2.2. Quality consideration in demonstrating biosimilarity

US-FDA needs the characterization of the therapeutic protein in different parameters and adequate demonstration of biosimilarity.35

The World Health Organization (WHO) issued guidelines in 2009, Guidelines on Evaluation of Similar Biotherapeutic Products and many countries have taken inputs in forming their own regulatory guidelines.34 Countries like Japan, China, Argentina and Saudi Arabia have also made guidelines on biosimilars.36

3.3. The importance of post-marketing surveillance

Although a biosimilar is not a new drug, their risks are similar to the reference product. Also since the biosimilars are approved for marketing based on limited preclinical and clinical data, it is essential to have a comprehensive post-marketing surveillance to detect inherent safety risks, immunogenic or adverse reactions. The pre-approval regulatory requirements and post-marketing surveillance for biosimilars are more rigorous than for generic medicines, thus adding a further layer to the cost of producing a biosimilar. Once approved, biosimilars must be monitored on an ongoing basis through a rigorous post-marketing risk-management plan set in place prior to marketing. The key post-marketing issues for biosimilars that are taken into account by most of the regulatory authorities around the globe include a ‘Risk Management Plan’ which would include the following considerations:

(a) Pharmacovigilance monitoring – A comprehensive pharmacovigilance plan should be prepared by manufacturer to further evaluate the clinical safety in all the approved indications in the post-marketing phase.32

(b) Adverse drug reaction monitoring – The adverse drugs reactions monitoring data should include the adverse event type, and data about drug such as proprietary name, international nonproprietary name (INN) and dosage given. If an adverse event emerges after switching from innovator biopharmaceutical to its biosimilar without
documentation of product change, the event will not be able to be related to a specific product or it will be ascribed to a wrong product during pharmacovigilance assessment. The prescribers and pharmacists should be aware of it and avoid this inappropriate substitution.

(c) Post-marketing studies – The onset and incidence of immunogenicity are unpredictable; therefore, extended post-marketing surveillance (pharmacovigilance) to monitor potential immunogenicity is very important. Biosimilar guidelines from the EMEA state the need for a pharmacovigilance plan to address immunogenicity and potential rare adverse events.\textsuperscript{25,35,37}

(d) Naming – In order to support post-approval monitoring, optimize adverse events recording and product tractability, the specific medicinal product given to the patient must be clearly identifiable. A distinct international nonproprietary names (INNs) system is to facilitate “clear identification, safe prescription and effective medicine dispensing”. A unique INN name and trade name must be given to each biosimilar product.\textsuperscript{22}

(e) Labelling – The labelling of a biosimilar product must differentiate clinical safety and efficacy data which have been obtained with the biosimilar product from its reference innovator drug, particularly in extrapolated indications where no studies have been done with the biosimilar at all. This distinction is presently not evident from the labelling of many of the presently marketed biosimilars.\textsuperscript{32,38}

4. Bio-betters and intended copies

4.1. Bio-betters

A biosimilar, which is claimed to be better than the innovator biologic, has been produced by state-of-the-art technology, and has enhanced therapeutic effect as the reference biologic, then – if substantiated with appropriate data, they would contradict ‘bio-similarity’ they may be given the term called bio-betters' instead of bio-similars.\textsuperscript{5} Advancement in science and technology, innovation of new machines could aid in the development of better biosimilars.

4.2. Intended copies

Currently, several products labelled as “biosimilars” are approved for the treatment of varied disorders in some Latin American countries, and even developing countries like India, which at the time of approval, did not have a formal regulatory processes in line with EMA and US-FDA.\textsuperscript{39} These products should be rather considered “intended copies” than biosimilars.\textsuperscript{25} It is important to distinguish between biological “intended copies” and biosimilars. To be labelled as a biosimilar, an agent must undergo the required comparability qualification in accordance with scientific principles endorsed by authorities.\textsuperscript{40} Similarity between a biosimilar and its reference biotherapeutic product is evaluated in three main areas, the quality, safety and efficacy. As the patents of a number of biologics expire, many companies would try to capitalize and make the follow-on biosimilar and market their products. Several products that may be labelled as biosimilars which may not have met the stringent regulatory process and undergone satisfactory head-to-head comparisons with their reference product to ensure comparability as defined by EMA and US-FDA and have still got approval from local markets for treatment are called intended copies. These purported copies of biologics put patient safety at risk.\textsuperscript{25}

Physicians should not feel obliged to prescribe any biosimilar drug just because of cost reasons, the ideal medical ethic of ‘do no harm’ must be followed. It is important to understand the process of approval of the biosimilar and to spot the difference between a safe biosimilar and an intended copy.\textsuperscript{32}

It is important for physicians to know the difference among biologic, biosimilar, bio-better and an ‘intended copy’ to make an informed decision before prescribing them for therapy or substitution for a reference product.

Indication that a claimed biosimilar may be an intended copy:

- Intended copies do not follow a pathway consistent with WHO/EMA/FDA guidelines (despite approval in some countries).
- Intended copies do not have a protocol in clinicaltrials.gov, or protocol in clinicaltrials.gov or it is not followed or not verified.
- Intended copies do not have comparative clinical trials published in scientific literature or clinical trials with inadequate number of patients to determine equivalence/non-inferiority.
- Intended copies do not have announcements in global biosimilar news websites.
- There would be surprises: e.g. sudden approval in a given country without stringent regulations (or even despite regulations).
- There is lack of transparency in the regulation and approval process.

4.3. Will they work?

It will be interesting to know in which direction the biopharmaceutical industry will move in the times to come – whether it will become the dumping ground for cheaper intended copies or a more robust and regulated pharmaceutical industry with efficacious and safe manufacturer and developer of biologics and biosimilars.

Conflicts of interest

Dr. Canna Ghia is an employee of Pfizer India Limited. Dr. Gautam Rambhad is an employee of Pfizer India Limited. Dr. Asia Mubashir and Mr. Disheet Shah have nothing to declare.

Dr. Sundeep Upadhyaya has been on the advisory boards of Pfizer and Johnson and Johnson. He has received educational grants from these two organizations in the past. Further he has received speaker honorariums from Eli Lilly and Johnson and Johnson.
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