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BIOSIMILARS OR "FOLLOW ON BIOLOGICS" - A REVOLUTIONARY CHANGE IN BIOTECHNOLOGY

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ABSTRACT

Biosimilars or "Follow-on-Biologic" defined as biologic medicinal products comparable in quality safety and efficacy to reference products, follow the independent regulatory pathway in the EU for marketing authorizations after the patent expirations of the reference products. Also these are similar to, but not the same as, innovator biologics which are vastly more complex than traditional pharmaceuticals and are produced through biological processes that generally involve recombinant DNA technologies. These are manufactured in a living system such as a microorganism, or plant or animal cells and mostly are very large, complex molecules or mixtures of molecules and hence they are typically injected and interact within the body in the bloodstream or on the surfaces of cells, rather than within the cells. Few examples of approved biosimilar drugs are Enbrel, Rituxan, Humira, Avastin, Gleevac. Biosimilars are only similar in composition to a reference product, but may not be identical or even interchangeable whereas, generic drugs are required to be identical in safety, efficacy, dose, and administration to the brand name counterpart. These drugs are the protein products and include recombinant DNA technology, monoclonal antibodies, and gene therapy revolutionizing treatment of diseases and complex conditions. Biosimilar drugs make up 10 to 15% of the pharmaceutical market in the United States, and this sector is growing faster than any other class of drugs, but it should also provide cost savings and greater accessibility to biopharmaceuticals.

KEYWORDS: Biological, biopharmaceutical, biosimilar, generic, biogeneric.

INTRODUCTION

Biosimilars are medicines that are similar to, but not the same as, innovator biologics. Biologics are vastly more complex than traditional pharmaceuticals and are produced through biological processes that generally involve recombinant DNA technologies. Biosimilars or "Follow-on Biologic" defined as biologic medicinal products comparable in quality safety and efficacy to reference products, follow the independent regulatory pathway in the EU for marketing authorizations after the patent expirations of the reference products. [1] Since the advent of biotechnology era heralded by the launch of recombinant human Insulin, biologicals, as revolutionary medications, have continuingly made several achievements. These compounds, e.g. erythropoietin (EPO), insulin, growth hormones, granulocyte colony-stimulating

factor (G-CSF), monoclonal antibodies (mAbs), have successfully transformed the ways in treating many severe diseases, such as anaemia, diabetes, cancer, hepatitis and multiple sclerosis.[2] Patents for many biologicals have either expired or are about to expire. Thus, the playing fields of biopharmaceutical market have opened to "generic-like" versions of these products, which are called biosimilar in the European Union (EU) and follow-on biologicals in the United States (US). As a pioneer, the European Medicines Agency (EMA) has established regulatory pathways specific for biosimilars since 2004, while the counterpart legislation in the US is still under preparation and contentious discussion.[3] These biologicals with high molecular weight are complex molecules with secondary and tertiary structures

subject to post-translational modifications such

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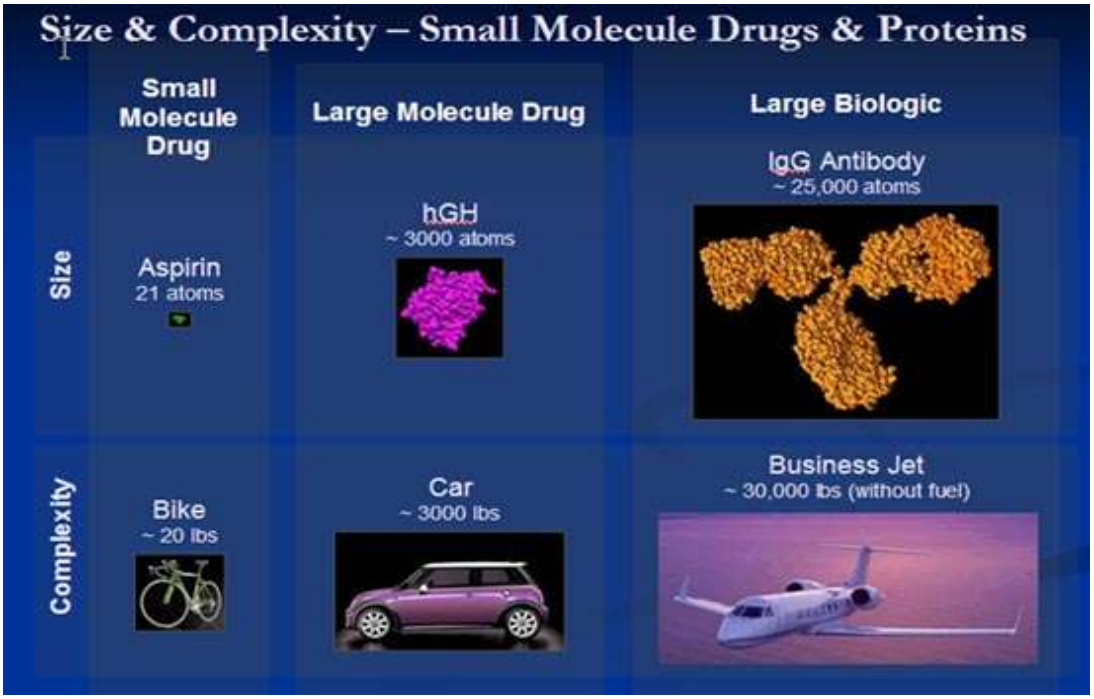

Figure-1 showing size and complexity of small molecule and proteins

as glycosylation as shown in figure [1]. Secondly, biologicals are usually recombinant proteins produced in living cells with controlled and tailored gene expression systems by recombinant DNA technology. The active substances of drugs its self and its final product tend to be heterogeneous and often incorporate variants, which might vary by as much as 1000 Daltons.[4] A well-crafted pathway for the approval of biosimilars will lower costs through increased competition, expand access to lifesaving medicines, protect patient safety and promote further biomedical innovation. In this review article we attempt to outline recent advances of biosimilars in the field of biotechnology and list of approved drugs by EU and also what are the major challenges which is going to be faced regarding the cost effectiveness.

Biosimilars vs Drugs

Biosimilars are medicines whose active drug substance is made by a living organism or derived from a living organism by means of recombinant DNA and/or controlled gene expression methods. These products are polypeptides, (glyco-) proteins, and/or nucleic acids and their molecular characteristics are much more complex than traditional chemical drugs.[5]Biosimilars are not like generic pharmaceuticals which can be analyzed in a laboratory to confirm that they are exact copies of chemical drugs. Biosimilars are vastly more complex than traditional pharmaceuticals, and producing an exact duplicate of an existing biologic is not possible with today's science. The major difference between generic drugs and biosimilars is shown in <<Table-1>>. For this reason, the term "biogeneric" is misleading. Many small molecule drugs can be taken orally, and tend to work in the body within cells. Since biosimilars are significantly larger in size, they are typically injected and interact within the body in the bloodstream or on the surfaces of cells, rather than within the cells. In contrast, small molecule drugs are typically composed of only 20 to 100 atoms. The main difference between low molecular weight (chemical) drugs and biological drugs are summarised in <<Table -2>>.[6] Small biologics, such as hormones, are typically composed of 200 to 3000 atoms, while large biologics, such as antibodies, are typically composed of 5000 to 50,000 atoms. [7]

Need for Biosimilars.

Medicinal products developed through biotechnology constitute an essential part of medicines available to patients today. They represent approximately 6% of the pharmaceuticals

Table -1 showing difference between the small molecule generics and biosimilars.

	Small molecule generics	Biosimilars
Product characteristics	• Small molecules • Often very stable • Mostly without a device	• Large, complex molecules • Stability requires stable handling • Device is often a key differentiator
Production	• Produced by chemical synthesis	• Produced in living organisms • Highly sensitive to manufacturing changes • Often comparatively high costs
Development	• Very limited clinical trials (often only phase I(PK/PD) studies	• Significant R&D(i.e. cell lines) • Extensive clinical trials, including phase I and phase III studies
Regulation	• Abbreviated registration procedures in Europe / US • Usually enjoy substitutability status	• Regulatory pathway now defined by EMEA • "Comparatively" status • No pathway yet in US under BLA
Marketing	• No or limited detailing to physicians • Key role of wholesalers and payors • Market substitution in pharmacies • High price discounts	• Detailing to (specialist) physicians required • Pharmacist may not substitute • Price discounts smaller; price sensitivity is product specific

currently marketed and account for more than 9% of total pharmaceutical expenditure.[8] More importantly, 'a third of products in the development pipeline are biotechnology products. Oncology is the largest area.' Some major biotechnology-derived medicines are, or will soon, no longer be protected by patents.[9] As for all other medicines when their 20-year patent expires, they will become open to development and manufacture by other companies. This introduces competition on the market which ensures patient access to safe and effective — and more affordable —biotechnology-derived medicines. Without competition the prices of the originator biotechnology-derived medicines would remain artificially high. Similarly, this competition will serve to stimulate research into new originator medicines. This fact is borne out by the situation in the USA where more than 50% of medicines used are generic medicines and where, at the same time, more new originator medicines are developed than anywhere else in the world. [11]Another important reason for introducing biosimilar medicines is, of course, that the scientific basis for biosimilar development and technology exists to obtain approval and bring this new of medicines to the market. As a result, a legal framework has been established in Europe govern their development and approval. (10) A list of top 25 biosimilar drugs is as follows-[12]

Top 25 Biosimilar Drugs

1. Enbrel (Amgen)

2. Rituxan (Genentech)
3. Humira (Abbott)
4. Avastin (Genentech)
5. Herceptin (Genentech)
6. Remicade (Johnson & Johnson)
7. Gleevec (Novartis)
8. Neulasta (Amgen)
9. Lantus (sanofi-aventis)
10. Aranesp (Amgen)
11. Prevnar (Wyeth)
12. Taxotere (sanofi-aventis)
13. Procrit/Eprex (Ortho Biotech)
14. Epogen (Amgen)
15. Copaxone (Teva)
16. Avonex (Biogen Idec)
17. Truvada (Gilead Sciences)
18. Lucentis (Genentech)
19. Humalog (Eli Lilly)
20. Rebif (Merck Serono)
21. Atripla (Gilead Sciences)
22. Erbitux (ImClone)
23. Cialis (Eli Lilly)
24. Betaseron (Bayer Schering)

It was found that Amgen's Enbrel topped the list with worldwide sales of US$5.9 billion (Euros 4.01 billion), followed by Genentech Rituxan (US$5.08 billion/Euros 3.45 billion), Abbott's Humira (US$4.5 billion/Euros 3.06 billion) and Genentech's Avastin (US$4.5 billion/Euros 3.06 billion). Genentech and Amgen both have four drugs in the top 25, with total sales of Genentech drugs reaching US$15.7 billion (Euros 10.66 billion) in 2008 and Amgen's totalling US$14.9 billion (Euros 10.12 billion). These blockbuster biotech drugs may very likely be the next biosimilars targets.[13]

Approval of Biosimilars

Patient safety because of the differences between biologics, challenging issues exist relating to the development, approval and marketing of biosimilar products are the three main concerns. Keeping safety in mind;

- Each clinical indication for a biosimilar should be established by indication-specific clinical trials to ensure the safety and efficacy of the biosimilar;
- Biosimilars should only be substituted for an innovator biologic if comparative clinical trials demonstrate that substitution is appropriate; and
- Biosimilars should be uniquely identified and should be traceable to ensure patient safety.

Need for Clinical Trials and Indication Specific Approval Due to the complexity of biologics as well as the distinctions introduced by differing manufacturing processes, Genentech believes that

TABLE-2 SHOWING OVERVIEW OF THE MAIN DIFFERENCES BETWEEN CHEMICAL AND BIOLOGICAL DRUGS.

CHEMICAL	BIOLOGICAL
Produced by chemical synthesis	Produced by living cell cultures
Low molecular weight	High molecular weight
Well defined structures	Complex heterogenous structures
Mostly process-independent	Strongly process- dependent
Completely characterised	Impossible to fully characterise the molecular composition and heterogeneity
Stable	Unstable, sensitive to external conditions
Mostly non-immunogenic	Immunogenic

Biosimilars Targets?

each biosimilar must be shown to be safe and

effective on the basis of its own adequate and well-controlled clinical studies. Biosimilar products should only be approved initially for the indication that is directly supported by the non-clinical and clinical safety and efficacy data package submitted by the sponsor. [10] When an innovator product has been approved for more than one indication, any biosimilar product should likewise be studied in each indication to support approval. Further, different manufacturing processes mean that each biosimilar is likely to be inherently different from the corresponding innovator biologic. As such, pharmacists should not be allowed to freely substitute the follow-on biologic for the innovator's product. Rather, we believe that substitution may only be possible if the sponsor performs adequate comparative clinical trials to establish that its marketing risk management plans must be an essential element of any approval of a biosimilar product. Although we believe that follow on products must contain their own adequate and well-controlled trials, we recognize that because they would be approved based in part on the prior approval of the innovator product, sponsors might be allowed to submit less data than that of the innovator to support approval of their products. As such, biosimilar manufacturers would have less experience with their products upon approval.

A biosimilar product would be approved based on an analytical determination that the product is similar to the innovator product. Due to the importance of trade secret protections, the biosimilar sponsor would not have access to the cell line or the critical manufacturing processes that are

Table-3 showing different brand of erythropoietin products and their company with clinical development for each type of biologicals.

Brand (generic name)	Company	Biosimilar clinical development for each type of biological
Erythropoietin alpha		**Reference products: eprex/erypo (epoetin alpha)**
Abseamed (recombinant human erythropoietin alpha)	Medicine arzneimittel putter	Five pharmacokinetics/ pharmacodynamics studies in healthy volunteers(four comparative; compartor; epoeitin alpha and epoeitin beta single and multiple dose)
Binocrit (recombinant human erythropoietin alpha)	Sandoz	One comparative pivotal therapeutic equivalence phase three study(comparative erypo) in IV use in patients with renal anaemia.
Erythropoietin zeta		**Reference products: eprex/erypo (epoetin alpha)**
Retacrit (epoetin zeta)	Hospira Enterprises	Two pharmacokinetics studies in healthy volunteers(single dose, comparative) Two phase 3 studies (one correction phase study, one maintenance phase study) both for intravenous administration
Silapo (epoetin zeta)	STADA arzneimittel	One supportive uncontrolled safety trial in cancer patients with chemotherapy-induced anaemia

product acts the same as (rather than similar to) the innovator product in the body and the treating physician agrees to prescribe the biosimilar. Post-Marketing Risk Management Plans Required Post-

essential to production of the innovator product. No Reliance on Trade Secret or Confidential Commercial Information Finally, we believe that regulatory agencies should not refer to or rely on innovator

trade secrets and confidential commercial information to approve a biosimilar product. [14]

Approval of Biosimilar Epoetins: How similar are they?

A consensus has emerged that approval of biosimilars requires both biological and clinical evidence. The 'comparability exercise' requires consideration of a wide range of aspects, including analytical and physico-chemical characterisation by several methods, comparative biological assays, comparative immunogenicity assessment, among others. The use of different host cells for the biosimilar product and the comparator in principle is possible, as shown in <<Table-3>>[15, 16]

Why is Patient Safety a Concern in the case of Biosimilars?

Safety is a priority for the development of all medicines, but biosimilars raise safety considerations above and beyond those of chemical drugs. This is because biosimilars are more structurally complex medicines than chemical drugs, and even slight changes in their manufacture can cause undetected changes in the biological composition of the product. These changes can in turn affect the safety and effectiveness of the product in patients. [17]

Products that lost patent protection some years ago, such as human insulin, still don't have a biosimilar in Western Europe or the US. However, biosimilars approvals have gathered momentum in Europe of late. The so-called first wave that began losing patent protection in the past decade is now a crowded arena. For instance, India itself has at least 13 companies that hawk EPO (erythropoietin), which is the precursor to darbepoeitin. (The latter is a long-acting version of EPO and injected less often.) At least three of them are priming for a Europe entry. EPOs from Sandoz and Teva, the world number one and two in biosimilars, are already there; so are some others.

Where Does India Stand?

While Biocon and Dr Reddy's are the two most advanced Indian players in the biosimilars field, others such as Ranbaxy Laboratories and Cipla have also made investments in biosimilars. Dr Reddy's has two biosimilars in India and a few other markets, while India's biggest drugmaker by sales, Ranbaxy, had acquired Hyderabad-based biotechnology firm Zenotech Laboratories to strengthen its biosimilar pipeline. Biocon, which has multiple biosimilar drugs on the market, last year struck a deal with Mylan to develop and sell biosimilars for the global market. It also has a long-term research deal with Bristol-Myers Squibb.

Indian Copies of Biosimilars and Need for Pharmacovigilance for Biosimilar Accidents

If we have a look at the Indian scenario, there are established guidelines for approving generic version of small molecule chemical drugs, however there are no specific guidelines for biosimilars, even though requirements for granting approval forbiosimilars are more intricate. In most of the cases manufacturers of these biosimilars, conduct clinical trials with small number of subjects to take advantage of lacunae in the existing system. The OPPI (Organization of Pharmaceutical Producers of India) has compiled a white paper on this subject of "Biosimilars". [18] We need to study as clinicians whether these biosimilar will have a clinical impact on our practice trends. This calls for aggressive pharmacovigilance.[19, 20] There have been several withdrawals of batches of Biosimilar or their copies in India due to accidents in the past decade. Recently a consumer court in Maharashtra awarded victim of a Biosimilar Insulin accident compensation and penalized the manufacturer as well. This calls for a stringent law for process of Biosimilar approval in India. Also aspects of cold chain and quality issues related to Biopeptides safety need closer vigilance. Lack of efficacy appears to be the commonest accident followed

by allergic or immunological reaction of such copy peptides.

Future of Biosimilar

Currently, biosimilar drugs make up 10 to 15% of the pharmaceutical market in the United States, and this sector is growing faster than any other class of drugs. Biosimilar drugs include recombinant DNA technology, monocolonal antibodies, and gene therapy, and these drugs are revolutionizing treatment of diseases and complex conditions that previously had an unmet clinical need. The field of biosimilar is relatively new, and these drugs were like something out of science fiction novels only a few decades ago. Today, they are a reality, but they have come at a cost.

Now, with the original patents ready to expire within 5 years on many biosimilar products, a new category of drugs is emerging that may help control

biosimilar drug costs. “Biosimilars” or “follow-on biologics” are therapeutic biological products that are similar to generic versions of

brand name drugs. [21] Biosimilars are not manufactured until the original patent expires on the innovative biological product, and are considered new non-innovative products. Biosimilars build on the research of the original product, but are not entirely therapeutically equivalent. Biosimilars are only similar in composition to a reference product, but may not be identical or even interchangeable. Generic drugs, on the other hand, are required to be identical in safety, efficacy, dose, and administration to the brand name counterpart.

CONCLUSION

Undoubtedly, the level of biosimilars adoption will have as much to do with the outcome of a public relations battle as with practical matters such as biosimilars' price and performance compared with those of biologics. Competition from biosimilars manufacturers will prompt innovator companies to modify their strategies to sustain revenue growth. Attaining biotech expertise through partnering and acquisitions will be one technique for success, but some branded companies will solidify their own presence in the biologics space. Regardless of the approach, product-positioning strategies will be imperative in a market where building reputation and trust among physicians, patients, and payers will be key to acceptance in the short term. With the soaring pharmaceutical expenditure, especially in the sector of therapeutic mAbs, the advent of forthcoming biosimilar mAbs in the EU and US is merely the matter of time. Healthcare payers worldwide are urgently looking for solutions to bridge the gaps brought by innovative biologicals with daunting price tags. On the other hand, pharmaceutical companies, while confronting predicaments of drying-out pipelines of new drugs and perceiving the upcoming patent expirations of many mAb blockbusters, are keen for the emerging market of biosimilars to replenish their portfolios. These are the driving forces to make the scenarios of biosimilar mAbs inevitably to happen in the near future, however, at the same time, leaving numerous debatable issues and challenges for regulators.[22, 23]

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