BIOBETTERS: THE BETTER BIOLOGICS AND THEIR REGULATORY OVERVIEW

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REVIEW ARTICLE

Verma Sandeep*, Jain Parveen, Chauhan P

Eli Lilly and Company (India) Pvt. Ltd., India

*Corresponding Author's E-mail: sandeepver88@gmail.com

ABSTRACT

The continuous innovation of the biopharmaceutical industry has led to development of a new category of biopharmaceuticals i.e. Biobetters or Biosuperiors. Biobetters may have better efficacy, a longer half-life, lower dosing frequency, a reduced risk of immunogenicity, reduced toxicity and side effects along with lower early-stage research risk and development costs. Biobetters rather than biosimilars may capture significant share of market and are the next wave for companies to ride on. Although it sounds intuitive, biobetters will have to face various ordeals like identification of the apparent unmet need, quantification of the potential market opportunity, expensive investment in clinical trials, challenging regulatory approval, pressures of price erosion and patent litigations. Thus, development of biobetters truly requires the right balance between providing life-changing medical management for patients and maintaining an innovative pipeline for continued business success. This review will focus on technical and regulatory prospects of biobetters.

Keywords: Biobetters, Biosimilars, Regulatory, Biosuperior, Generic.

INTRODUCTION

Biobetters:

The term biobetter also known as biosuperior which refers to a recombinant protein drug that is in the same class as an existing biopharmaceutical but is not identical; it is improved over the original. Biobetters are better in one or more product characteristics. Product individuality often targeted by biobetter applicants includes longer product half-life in the body, lower likelihood of aggregation, greater efficacy and purity or fewer adverse events. Biobetters are constructed on the achievements of existing, approved biologics but are considered to have less commercial risk than developing a brand new category of biologic. (2, 3)

Biobetters or Biosuperiors are upgraded versions of original biological products that provide enhanced safety, efficacy, or dosing regimen. A Biobetter aims for the same target as the original biological, but has its effect on that target for a longer episode, characteristically at lower doses and with fewer side effects. (4)

Comparison of biosimilars and biobetters:

Both biosimilars and biobetters are derivative variants of the original biologic molecule. Biosimilars are close copies of marketed originator biotherapeutics. The name 'biosimilar' clearly indicates that there can be some differences to the originator product, as divergent to small molecule generics where structural identity is requisite. In certain cases, the biosimilar is so similar to the originator as to be deemed 'interchangeable' with the originator product. In the US and Europe, biosimilars must have the same safety, purity, and efficacy profile as the originator compound. (5-7) On the other hand, by definition a biobetter is superior/better to the originator molecule, by for example, having greater potency/efficacy or lesser side effects/immunogenicity. Biobetters are also considered to have a different 'active compound' when compared to the originator product.

Biobetters may have a benefit over biosimilars as they encompass an improvement over the originator and any biosimilar competitors, and should be patentable. However, it can be challenging, because the active ingredient is so similar to an innovator product, it may not be possible to patent all biobetters. Patents can be granted only to products that show to be a

significant advance over technology already known to the public. Many biobetters may not be able get patented. (8) (Table.1)

Table1: Overview: Comparison Biosimilars and Biobetters

Biosimilar	Biobetter
Biosimilars have limitations with respect to structure i.e. they must be similar active compound as that of reference products.	Biobetters do not have structural limitations, it may include molecular/chemical modifications, and would therefore considered to have a different 'active compound' when compared to the originator product.
Biosimilars should have somewhat similar safety and efficacy profiles	Biobetters should have which has improved safety and/or efficacy profiles.
Biosimilars are very similar to innovator products.	Biobetters are modified versions of innovator products.
Biosimilars are supposed to be approved after demonstrating similarity between biosimilar and reference product i.e. through comparability data	Biobetters are like new drugs and supposed to travel through full new drug application or hybrid product application with all necessary clinical/non clinical trials data.
Biosimilars are not entitled to have patent protection or data exclusivity.	Biobetters may obtain patent or data exclusivity based on how innovative they are.

Despite the fact that patent protection may not be granted, regulatory pathways in the EU and US could still encourage the development of biobetters rather than biosimilars. These biobetters would use the typical biological approval route, rather than the abbreviated pathway adopted for biosimilars or generic drugs. This would mean that biobetters, as 'new drugs' may get benefit from market exclusivity rights, even if they are not different enough to gain patent protection.

Advantage of Biobetters over Biosimilars:

1. While biosimilars are supposed to have equal efficacy as that of the originator drug at a reduced price, biobetters will be improved version of originator with some molecular or chemical modification and possibly a reduced side-effect profile. Biobetters are bound to have a higher success rate than originator biologics due to a validated target for the biologic, but an improved biologic is far from certain and may require significant experimentation.

2. Biobetters can also be developed by understanding the protein folding mechanism and its effect on the drug, whereas biosimilars are replica of the originator.

3. Biobetters are based on well-known target theorythus have lower early-stage R&D costs.

4. Biobetters do not have specific regulatory route as there is for biosimilars. A biobetter follows in the footsteps of a drug that has already been shown to be a therapeutic and commercial success; the risk of failure is probably to be fewer than that with most new drugs.

5. A biobetter does not have to wait until a patent expires on the originator product before the product can be launched in the market.

6. Greater potential to avoid infringing patents or at least lower litigation costs since it is not claiming similarity to the originator product.

7. Biobetters have an advantage over biosimilars as they constitute an improvement over the originator and any biosimilar competitors, and should therefore be patentable.

8. A biobetter can command a price premium, as it has a clinical advantage over the originator product. Biobetters should be less cost sensitive when compared to a biosimilar

because they are in essence a new compound. (2, 9)

9. As a new chemical entity a biobetter will be given data exclusivity for 12 years in the US and 10 years in the EU.

Development cost of biobetters:

The development costs are the same as developing a new biological product, but the probability of regulatory approval is quite higher. This means the business risk in developing a biobetter is significantly less and the potential for return on investment for a manufacturer is greatly high. (2, 10)

Whilst the additional quality comparability requirement for biosimilar development can be of significant cost, the abbreviated non-clinical and clinical package, combined with the possibility of extrapolation of therapeutic similarity from one indication to another is a major advantage for biosimilars compared to that of biobetters, as this represents a significant cost and time saving. (9)

Biobetters offers better savings:

A biobetter will command a premium price for its improved characteristics, but the reduced dosing frequencyof such products can result in significant cost savings for example, based on the treatment used in a pivotal trial for Neulasta—an Amgen biobetter version of their own Neupogen—a single treatment cycle costs $3400 for Neulasta and $6000 for Neupogen, despite the unit prices being $3400 and approximately $300 (body weight dependent), respectively. The biobetter in this case represents a 40% reduction in overall costs for the healthcare provider. (11)

A biobetter drug is developed against an already established biological target that has been validated in human clinical trials and is intended to have attributes that are better than the first-generation product, rather than being a similar copy. The overall pipeline portfolio risk with a biobetter is higher than with a biosimilar, but less than the innovator one because the aim is to demonstrate an improvement over the existing treatment based on already validated targets. At the same time, biobetters can help to generate a more substantial return on investment for a developer. Although biosuperiors represent a higher risk in investment versus biosimilars, they have the potential to capitulate greater business benefits e.g. market share and profitability.

Thus the development of biobetters truly strikes the right balance between providing life-changing medical treatments for patients and maintaining an innovative pipeline for continued business achievements. Given the benefits of biosuperiors, from both a business and a clinical point of view, there is potential to significantly transform the treatment paradigm for many disease areas. (12)

Biobetter Approaches:

While most first-generation biologicals are immediate-release and delivered subcutaneously or via infusion, Biobetters are developed by adopting a better approach like using a new drug delivery system or new formulation techniques or through modifying it by protein or glyco-engineering techniques to make them more efficacious which will require a lower dosing frequency and, most critically, reduce the risk of immunogenicity (Table 2). (13)

Table 2: Biobetter Drug Development Techniques

Techniques	Description	Example
New Formulation- altered New drug delivery methods	Development of new controlled/sustained release, oral, dermatological, topical, sub-cutaneous injections, or inhaled formulations	Flumist (Astrazeneca)- Influenza intranasal vaccine
Using engineering to produce superior drug product	PEGylation technique, Fusion or Conjugation with fused protein, addition of adjuvants, Alteration	Neulasta (Amagen)- Pegylated G-CSF- Biobetter for Neupogen

	in carboxyl terminal peptide (CTP) chain	
New improved recombinant technology or New manufacturing methods	1. Switching from live, attenuated or inactivated vaccines to recombinant products 2. Development of new insects and plant based manufacturing system or humanization 3. Increasing number of serotypes	1. Ixiaro (Novartis/ Intercell) 2. Optaflu(Novartis) 3. Synflorix(Glaxosmithkine)

New Drug Delivery Methods:

Most frequent used method to design biobetters is new drug delivery methods. The best suited example for such products is Astra Zeneca's nasal influenza vaccine. These products produced using these new technologies will be attractive to healthcare providers for treatments amongst elderly, children and especially in developing countries.

Protein Engineering Techniques:

Various new recombinant technologies (engineering) have been developed to produce biobetters. (Table 3) These may include Switching from live, attenuated or inactivated vaccines to recombinant products. For example introduction of newer cell culture method to replace egg based manufacturing system will result in increased efficacy of vaccine. (4)

Table 3: New recombinant techniques to produce biobetters

Techniques	Methodology	Examples
Chemical Modifications/Alterations	PEGylation: Attachment of poly ethylene glycol (PEG) to increase half- life of biologic Addition of glycan appendages may imparts stability and increased half-life for therapeutic proteins	Mircera- Methoxy polyethylene glycol- epoetin beta, Roche Aranesp (darbepoetinalfa), Amgen
Humanization	Use of human cell lines to express proteins with human glycosylation patterns may decrease immunogenicity of mAbs	Simponi (Golimumab), J & J/ Merck Comp.
Fusion Techniques	Addition of albumin or other protein to extend serum half life	
Altered amino acid techniques	Addition of c- Terminal peptide to enhance half life, target function and efficacy or Alteration in carboxyl terminal peptide (CTP) chain	

PEGylation:

PEGylation is a process of covalent bonding of a polyethylene glycol moiety (a neutral and hydrophilic polyether) to a peptide. (3)which in turn results in increase in the in-vivo circulation half-life. It has been observed that the hydrophilic PEG polymers increase the molecular size of a protein as well as masking its surface, thereby increasing its half-life by reducing renal filtration and protecting it from proteolytic degradation. Several products currently on the market employ PEGylation technology including Adagen (Pegylated bovine adenosine deaminase), Oncaspar (PEGylated asparaginase), PEGIntron (Pegylated interferon), PEGASYS (Pegylated interferon), Neulasta (PEGylated granulocyte colony-stimulating factor) and Somavert (PEGylated human growth

hormone). Given its long track record of improving the properties of protein products, PEGylation is a natural strategy for creating additional biobetter products. (14)

Fusion Technique:

Another technique for development of biobetters is fusion of the recombinant factor protein molecule to a partner protein having a long half-life.

Examples of naturally occurring partner proteins being fused to the FVIII or FIX molecule are:

1. Albumin, which allows small molecules through the bloodstream, and
2. Fc, a protein fragment that enables binding and recycling of immunoglobulin G (IgG).

Evidence from clinical trials:

In a clinical study named A-LONG study on patients with severe hemophilia A showed a 1.7-fold increase in half-life during phase 1/2a clinical trials. B-LONG studies on patients with severe hemophilia B showed a nearly threefold increase in half-life during phase 1/2 trials.

Adjunctive therapies, or drugs that are added to the primary factor product, are also being tested in clinical trials. Some use molecules that bind to tissue factor pathway inhibitor (TFPI), preventing it from hindering the action of FXa and thrombin, necessary for clot initiation and formation. Baxter's BAX513 uses fucoidan, a seaweed extract being tested on healthy volunteers without hemophilia. (15)

Post-translational modifications - Glycosylation:

Glycosylation is a naturally-occurring post-translational phenomenon whereby oligosaccharides are enzymatically linked to the surface of proteins. Scientist discovered that the addition of glycan appendages often impart stability by inhibiting aggregation, degradation or denaturation by adding sites prone to glycosylation, and thereby this can also lead to increased half-life for therapeutic proteins. Many biologic products have already employed this technique. (16)For example, Amgen designed Aranesp (darbepoetinalfa) which has been produced using this technology with a longer in-vivo half-life. (17)

These are various examples of 'me better' antibodies with controlled and optimized glycosylation which have been produced using glyco-engineered yeast strains. (18) For example, a copy of the rituximab amino acid sequence but with a fucosylated glycoforms resulting in a 100-fold increase in ADCC and/or with increased plasma half-life. (19)

Humanization:

To reduce adverse immune response raised by mAbs, murine mAbs were engineered into chimeric mAbs (suffix: -ximab, e.g. infliximab) by replacing the non-human Fc regions with the human counterparts. Then, chimeric mAbs stepped forward into humanized mAbs (suffix: -zumab, e.g. trastuzumab) by manoeuvering large parts of the Fab regions into human counterparts. More recently, the advance in transgenic mouse technology and development phage display technique has made fully human mAbs possible (suffix: -umab, e.g. adalimumab); however, while being reduced; the immunogenicity of human mAbs still exists to some extent. Thus, several strategies have been adopted to further tackle the immunogenicity of mAbs, such as humanization of glycosylation pattern. (20)

Amino acid Alteration:

Use of altered amino acid sequence is another approach for biobetters. PROLOR, a biopharmaceutical company, is utilizing patented technology to develop longer-acting, improved versions of already approved therapeutic proteins that currently generate billions of dollars in annual global sales. This technique involve attachment or alteration of the tripeptide sequence, also known as Carboxyl Terminal Peptide (CTP) to a wide array of existing therapeutic proteins, stabilizing the therapeutic protein in the bloodstream and extending its life span without additional toxicity or loss of desired biological activity.

The PROLOR technology platform has proven capacity to provide a significant reduction in the number of injections required to achieve the same or superior therapeutic effect from the same dosage; extended patent protection as

proprietary new formulations of existing therapies; faster commercialization with greater chance of success and lower costs than those typically associated with a new therapeutic protein; and manufacturing using industry standard biotechnology based protein production processes. (21)

Regulatory prospects of biobetters:

There are no specific guidelines for biobetters. Currently biobetters are being regulated as innovator products in all major countries. Regulators understand that these are new molecular entities and will be subject to the standards applied to all new drugs. But USFDA can exempt requirement of some data based on prior knowledge to reduce the scale/duration of Phase 2 trials. Concept of biosimilars lies with biobetters as well. It can be expected that the more "different" the biobetter is from the originator, the higher would be the requirements to prove its safety and efficacy, and hence the regulatory hurdles and the price tag to develop biobetters will also correspondingly increase. (22)

There are a number of significant differences between a biobetter and a biosimilar biologic development program (see Table 4) as by definition a biosimilar is claiming similarity to originator product rather than 'being better'.

Table 4: Summary of Differences between a Biobetter and Biosimilar Development

*CTD Module	Biobetter	Biosimilar
Quality Package	√	√ + additional comparative data
Non-Clinical	√	√ Abbreviated – Focus on comparability
Clinical Phase I (PK/PD)	√	√ Large trial – Focus on comparability to originator product
Phase II	√	X
Phase III	√ Each indication	One pivotal trial – possibility to extrapolate to other approved indications of originator product
Phase IV/Safety	√	√

*CTD- Common Technical Documents

Intellectual property protection for biobetter:

Biobetters are considered as new biologics and the development process involves extensive clinical/ non clinical study. They may become entitled to enjoy patent protection and marketing exclusivity. Biobetters may involve any process which will be a new invention hence become patentable. Patent grants to biobetter vary from country to country based on patent rules(23)

Pharmaceutical companies can opt for strategies of simply improving their own products and coming up with "biobetters" to extend their existing intellectual property rights and get "more mileage out of their chartbuster drugs." There is a problem with this approach though, as "the improvements they make are often incremental in nature. The patent office mayoppose this strategy, so the need of hour is to explore other strategies to get biobetters patented. (3)

CONCLUSION

Research into revolutionary biologic therapies has dramaticallychanged the treatment models for various diseases, especially with the expansion of new bio-therapeutics i.e. "Biosimilars" and "Biobetters". These productsaccompanylowermost risk to a pipeline portfolio as both biosimilars and biobetters are plagiaristic variants of the original biologic. By definition a biobetter is superior to the inventor

molecule by having greater potency or less side effects/immunogenicity. Biobetters are also considered to have a different 'active ingredients' when compared to the originator product. A biosuperior is projected to have characteristics that are better than the first-generation product, rather than being a carbon copy. This uses cutting-edge technologies such as protein engineering, and novel drug formulation and new delivery approaches to facilitate its superiority over a first-generation product, possibly improving its potency or safety profile or improving administration route or reducing dosing regimen. In particular, a few technologies offer great promise for biosuperior antibodies, including affinity maturation, effective function improvement, half-life extension through Fc engineering, bi-specific, and antibody-drug conjugate technology. Ideally, a biosuperior has the potential to be a best-in-class product because it is yielding benefits beyond the innovator product.

One of the major issues in commercialization may be the venture in clinical trials and in obtaining regulatory approvals. Development of a biobetter consequently calls for a large investment and a certain appetite for risk which may reflect in the overall cost of the drug. Amount of safety/efficacy data, Intellectual protection and Regulatory challenges are perhaps just some areas to watch out for biobetters. Biosuperiors have huge potential to provide tremendous clinical superiority to patient and medical communities over biosimilars. Given the benefits of biosuperiors, from both a business and a clinical standpoint, there is potential to significantly change the treatment paradigm and company product development strategy for many disease areas.

ACKNOWLEDGEMENT

I take this opportunity to express my deep sense of gratitude to IJDRA Journal for publishing my Article.

CONFLICTS OF INTEREST

The content and views in article is author independent opinion and in no way related to Eli Lilly and company views and policies.

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