Review Article

Biobetters: Betting on the Future

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Abstract

With the advent of biotechnology, considerable advances have been made in the treatment of various diseases. Original products created with biotechnologyand patented by various companies have entered the market and so have entered products similar to them (but not the same), termed biosimilars. However, instead of copying the original product, some innovators have modified it so as to make the final product even better than the original one. This is a biobetter. Biobetters may in fact be a path to be adopted by the pharma industry in the future. This review article focuses on the various aspects of biobetters.

Keywords: Biobetters, Biosimilars, Biologicals, Biopharmaceuticals

INTRODUCTION

Biotechnology, Biopharmaceuticals and Biosimilars

Biotechnology is the application of scientific and engineering principles to the processing of materials by biological agents.[1] Simply put, it utilizes living organisms to make useful products. Production may be carried out by using intact organisms (yeasts and bacteria) or by using natural substances (e.g. enzymes) from organisms. Overtime, biotechnology has given rise to biopharmaceuticals - also known as a biological medical products/ biotherapeutic products/ biological/ biologics - defined as any pharmaceutical product synthesized or extracted from biological sources. Biopharmaceuticals include vaccines, blood and blood products, allergenic extracts, human cells and tissues, monoclonal antibodies, hormones, gene therapies and cellular therapies.[2]

According to the WHO definition, a biotherapeutic product similar in quality, safety and efficacy to an already licensed reference biotherapeutic product is called a biosimilar.[2] They are intended to be identical to the originator biologic drugs but since they are manufactured using a new process, they have subtly different structures and possibly different actions. In other words, it contains a version of an active substance of an already approved biopharmaceutical (the 'reference medicine' or 'originator

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medicine').[4] Organizations across the world (like FDA, EMA, WHO) have more or less a similar definition- all emphasizing on the similar quality, safety and efficacy aspects.[3,4,5] A number of synonyms exist for the term biosimilar – "Follow-on biologic" (FoBs)/ "Follow-on protein" (in the US), "Subsequent Entry Biologics" (in Canada), "Similar Biological Medicinal Product" (SBMP) (in the EU) – but "Biosimilars" is by far the most commonly used term. Since biosimilars are similar but not same as the original product, the term "Biogenerics" is not appropriate for them.

Understanding biobetters better: What it is and what it isn't

(a) What it is:

The importance of the concept of biosimilars arose when the patent for certain biopharmaceuticals started to expire in the past decade. Approximately $110 billion worth of biopharmaceuticals are expected to be off patent by the year 2020, and almost a third of the pharmaceutical industry pipeline is comprised of biopharmaceuticals. So, the enormous scope that biosimilars offer is very clear. 6 However, considering this atmosphere of opportunity, some innovators thought of improving on biologic drugs as an alternative to taking a more generic route of biosimilars, thereby bringing into existence a novel concept- that of "Biobetters".

A biobetter, sometimes also referred to as a biosuperior, is a biological product related to an already approved biological product but superior in one or more product characteristics to achieve a clinically meaningful performance. The term currently has no legal or regulatory recognition.[7,8]

In simpler terms, they are enhanced or upgraded versions of an original biologic. A biobetter aims for the same target as original biological but has its effect on that target for a longer episode. Their amino acid sequences very closely resemble the original biologic but are slightly modified. Biobetters, thus, can be considered as hybrids which straddle the space between biosimilars and classical new biologic entities (NBEs).[9] Biobetters build on the success of existing approved biologics but are considered less of a commercial risk than developing a brand new class of biologic.

(b) What it's not:

A number of terminologies exist in relation to biologics based on the similarity demonstrated to the originator product. These have been described in Figure 1. Biobetters may thus be considered as agents with characteristics of both - a novel biological and a biosimilar.

Biobetter vs Innovative / Novel Biologic:

A novel biologic uses a new target for its action. It is possible that the newer mechanism may fail to be adequately effective for an indication. A biobetter, on the other hand, has a higher probability of success due to established mechanism and validated target compared to it. Moreover, with a biobetter there is a possibility to demonstrate pharmacologic comparability with the reference biologic and this may help accelerate development program. This is because there is refined preclinical and clinical development path as experienced with original biologic which can help in selection of dose and

biomarkers. Overall the development costs are lower as compared to working on a fresh biological due to lower early stage research requirements. The only drawback of a biobetter vis-à-vis a new biological could be that the price premium over the existing biologic would be limited.[10]

Biobetters vs Biosimilars:

Over the years, the pharmaceutical industry took up the perspective that why make a copy of a drug developed 15-20 years ago, when biopharmaceutical science has advanced so far since?

Though both biosimilars and biobetters are derived from the same biologic molecule, there are clear cut distinctions between these two classes which have been described in the following Table 1:

Table 1 Comparison between Biosimilars and Biobetters

Biosimilars	Biobetters
Highly similar to the innovator molecule.	Upgraded or modified versions of the innovator molecule.
Regulatory processes are clearly defined by the authorities.	There is a lack of specific regulatory framework.
Development process is simpler as they are approvedafter demonstrating similarity between the biosimilar and the reference product.	Biobetters are like new drugs so there are relatively extensivepreclinical and clinicaldevelopment requirements.
Relatively lower cost of development as there isextrapolation of the efficacy and safety data toall approved indications of the originator product.	Higher cost of developmentdue to requirement forclinical trials for eachindication.
Not entitled to have patent protection or data exclusivity.	Biobetters may obtain patent or data exclusivity based on how innovative they are.
Economic return less than biobetters.	High return depending on the added-value, may gain a premiumpriceas it has a clinical advantage over theoriginator product.

Regulatory Perspective – Biosimilars Vs Biobetters

Biosimilar development follows a stringent legal and regulatory pathway across the globe. On the other hand, there are no specific guidelines for biobetters and it comes down to negotiating the package of data required for approval with regulatory agencies on a case-by-case basis.[11] From a regulatory stance, a biobetter is a new chemical entity, and therefore applications follow the established regulatory pathways for a new chemical entity in both the US via the BLA, and the EU i.e. a stand-alone application.

The following Table 2 gives a summary of differences between biosimilar and biobetter development.

Table 2 Comparison between development of Biosimilars and Biobetters

Studies	Biosimilar	Biobetter
Quality Package	✓ + additional comparative data	✓
Non-Clinical	✓ Abbreviated – Focus on comparability.	✓
Clinical	✓	✓
Phase I (PK/ PD)	Large Trial – Focus on comparability.	
Phase II	×	✓
Phase III	One pivotal trial – possibility to extrapolate to other approved indications of originator product	✓ Trials for each Indication (Non- Inferiority Trials)
Phase IV (Safety)	✓	✓

Why is it "better"?

A biobetter may provide one or more of the following several advantages over the reference biologic such as greater efficacy, greater purity, longer product half-life, less frequent dosing, lower likelihood of aggregation, fewer adverse events, streamlined manufacturing, longer shelf-life and greater stability and easier administration/ packaging improvements,

Examples of Value Addition Offered by Biobetters

A number of examples of biobetters and the improvement offered over the reference biologic are provided in Table 3.

Table 3 Examples of biobetters and the improvement offered by them

Reference Biologic	Biobetter	Improved Characteristic Compared to the Original
Erythropoietin-alpha	ARANESP® (Amgen) FDA approval in 2001.	Reduced dosing frequency to once every fortnight.
	MIRCERA® (Roche) FDA approval in 2007.	Reduced dosing frequency to once monthly.
Filgrastim	NEULASTA® (Amgen) FDA approval in 2002.	Once in a 21-day chemotherapycycle versus once daily.
Follicle Stimulating Hormone	ELONVA® (Merck) [Corifollitropin - alpha]Sustained follicle stimulant EC approval in 2010.	Single subcutaneous injectioninstead of first seven injections of daily FSH preparation.
Trastuzumab	KADCYLA® (Genentech) [Trastuzumab emtansine or T-DM1: Anantibody–drug conjugate, combining theHER2 inhibition of trastuzumab and the microtubule inhibition of DM1] FDA approval in 2013.	Combination with improved efficacy over current standard of care, Trastuzumab emtansine is indicated as a single agent for thetreatment of HER2-positive, unresectable, locallyadvanced or metastatic breast cancer who previously receivedtrastuzumab and a taxane, separately or in combination.
Rituximab	GAZVYA® (Roche) [Obinutuzumab] FDA approval in 2013.	Improved pharmacokinetics.
Recombinant Anti-hemophilicFactor	ELOCTATE™ (Biogen Idec) [B-domain deleted recombinant Factor VIII,Fc fusion protein (BDD-rFVIIIFc)] FDA approval in 2014.	Reduced dosing frequency.

Modification Strategies

The modifications for improvement in one or more of the characteristics of the original biological molecule are brought about by the use of following techniques.[8]

Glycosylation

This is the process wherein a sugar moiety, usually an oligosaccharide, is enzymatically linked to a protein. It occurs naturally in cells as a part of post-translational modification of proteins. It has been observed that the addition of glycan appendages adds additional "sites" to the original molecule and this imparts stability by inhibiting aggregation, degradation or denaturation and can also lead to increased half-life for therapeutic proteins.12 For example, ARANESP® (Darbepoetin-alfa) developed by Amgen has been produced using this technology, thereby improving its half-life. This has translated clinically into a reduced dosing frequency of administering Erythropoietin to once every fortnight.[13]

PEGylation

PEG (Polyethylene Glycol) is a hydrophilic polyether. PEGylation involves covalently bonding PEG moiety to a protein. The hydrophilic nature of PEG polymers results in an increase in the molecular size of a protein, reducing its renal filtration as the pore size in the nephrons is too small to allow big molecule to pass. The result is an increased half-life. In addition, the large size due to PEGylation also 'masks' or protects it from proteolytic degradation. PEGylation technology has been utilized for modification of several products including PEGINTRON® (PEGylated interferon), PEGASYS® (PEGylated interferon), NEULASTA® (PEGylated granulocyte colony-stimulating factor),and MIRCERA® (Methoxypolyethylene glycol- epoetin beta).[8]

Fusion Modification

In this technique, a recombinant protein is fused to a partner protein having a long half-life which improves its pharmacokinetics. Examples of naturally occurring partner proteins being used for fusion are albumin and Fc fragment of immunoglobulin. ELOCTATE™ where, recombinant Factor VIII is fused with Fc fusion protein (BDD-rFVIIIFc), increasing its half-life by 1.5 to 2 fold.[14]

Humanization

Monoclonal antibodies (mAbs) from non-human sources have a high propensity to cause immune mediated adverse events. Therefore, chimeric mAbs have been engineered by replacing the non-human Fc regions with the human ones. Going a step forward, humanized mAbs have also been created by converting large parts of the Fab regions into human counterparts. More recently, the advance in transgenic mouse technology and development of phage display technique has made fully human mAbs possible; although the immunogenicity still exists to some extent.[15] For example, GAZYVA®(Obinutuzumab), a biobetter to Rituximab, is a fully humanized monoclonal antibody that binds to an epitope on CD20 that partially overlaps with the epitope recognized by Rituximab. 16 Another example is Golimumab, which is a human monoclonal antibody used as

an immunosuppressive drug and marketed under the brand name SIMPONI® (Janssen Biotech and Merck).[17]

Altering Amino Acid Sequences

In this process, there is attachment or alteration of a peptide sequence (Carboxyl Terminal Peptide - CTP) to the existing proteins, stabilizing them and extending their lifespan without additional toxicity or loss of desired biological activity.[18]

Sustained release

Biobetters are sometimes developed to reduce the dosing frequency by creating a new formulation which is sustained release. For example, Dong-A ST Pharma is developing a sustained release, subcutaneous formulation of Exenatide, known as DA 3091, for treatment of type 2 Diabetes Mellitus.[19]

New routes of administration

A biobetter may be developed for easier administration through oral, dermatological, topical, subcutaneous injections, or inhaled formulations. A good example of this is FLUMIST®(AstraZeneca)- Influenza intranasal vaccine for easier administration compared to the difficult injectable routes. 20 Also, AFREZZA® (Mannkind) - the only inhaled insulin working to help control adult diabetics' blood sugar during mealtime is approved.[21]

New manufacturing process

This includes changes like use of a new cell platform (introduction of newer cell culture method to replace egg based manufacturing system results in increased efficacy of vaccine)[22], switching from live-attenuated or inactivated vaccines to recombinant products, using increasing number of serotypes and so on.[8]

Drawbacks of Biobetters

Now that we have a slightly better idea about the advantages of biobetters, it is quite needless to say that they have certain formidable risks that are considered challenging for their development:

– Approval of a biobetter also requires a traditional Biologic License Application (BLA) with a full complement of pre-clinical and clinical data. As a result, research and development costs are still high relative to drugs and some biosimilars. There are longer and more expensive clinical trials which must follow new-drug approval pathway. Large clinical trials are likely needed to prove clinical superiority and they must be significantly better to gain acceptance over established reference product or biosimilars.[23]

– Biobetters may have new and unexpected side effects that are different from that of the originator biologic.[24]

– Sophisticated patent analyses or litigation costs still may be required.

– As a new chemical entity a biobetter may be potentially given data exclusivity for 12 years in the US and 8 years in the EU. However, the 12-year exclusivity is not guaranteed for every case and there is no exclusivity vis-à-vis other biobetters filed as original BLA products.[7]

– Marketing requirements may be high, especially to convert patients from referenced product to Biobetter.[8]

Companies Developing Biobetters

Novo Nordisk, Merck & Co, Roche Group, Biogen Idec, Amgen, Sanofi-Aventis, Eli Lilly and GlaxoSmithKline have all expressed interest in the development of biobetter drugs. Several of them are acquiring smaller, innovative bio-pharmaceutical companies that have promising pipelines.

For example, British pharma AstraZeneca purchased the biotech company MedImmune which intends to focus on biobetter research and development.[25] Also, Compass Biotechnologies Inc., announced in late December 2011 that it is focusing on development of improved biosimilar proteins such as EPO and GCSF. Compass also has an agreement to source recombinant protein biosimilars manufactured in "Chinese Hamster Ovary" cells from PanGen Biotech of Seoul, South Korea, and an agreement with Arecor Ltd. of Cambridge, England, to develop a biobetter, heat-stable formulation of the commercial hepatitis B vaccine.[26,27]

Market participants may look forward to collaborations with these companies in order to develop the improved versions of biologics. Organizations well known for innovation and experience with generics might be best positioned to achieve success with biobetters.

CONCLUSION

Biopharmaceutical industry is in a state of tremendous evolution. Biotechnology is a valuable tool that gave rise to biologics with novel mechanisms. With time the need to introduce generic versions of these molecules was felt and biosimilars were born, but biobetters – with their superiority over the original product in spite of maintaining certain similarities with it - are here now, and as the biosimilar competition is emerging, biobetters may become better approach for the future. Biobetter development requires a large investment and a certain appetite for risk which may reflect in the overall cost of the drug. Keeping in mind the clinical and financial gains they promise, they have potential to change the treatment patterns and industrial approaches for a number of diseases.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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