**RESEARCH ARTICLE**

# Biobetters: Are They Truly Better?

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**Abstract:**

Biologics have seen an explosion in application for a myriad of diseases. Recently the term "biobetter" has entered the lexicon of the pharmaceutical industry. This marketing term refers to a drug that is supposedly a "better" version of a reference biologic. By this definition, these biologics must invariably have some improved pharmacologic and/or pharmacokinetic parameters, such as a better safety/efficacy profile. In actuality, this is not necessarily the case. Additionally, to-date there is neither a legal nor regulatory pathway in place for the development of said, biobetters. This lack of any classification has led to its inconsistent and often inaccurate use within scientific literature. To rectify this, a framework for the potential correct use of the term biobetter within scientific literature (not regulatory) has been provided. Additionally, an exhaustive reclassification of any drug that have been previously termed "biobetter" has been conducted. We believe this classification system, specifically: true-biobetter, potential-biobetter, or non-biobetter will prevent further misuse of the term in the scientific community without modifying the clinical application of such biological entities in practice and in research.

**Keywords:** True-Biobetter; Potential-Biobetter; Non-Biobetter

## 1. Introduction

The global market share of biologics has seen tremendous growth as of late. In the United States alone the revenue has increased from an estimated $85 billion in 2014 to $144 billion in 2018.[1] Following these successes coupled with updated and new Food and Drug Administration (FDA) regulations, a new class of biologics was developed referred to as biosimilars. These are highly similar in terms of their pharmacokinetic profile with no clinical meaningful difference compared to the reference product. Biosimilars are sometimes inaccurately referred to as the "generic drugs" of the biologic world. The FDA and European Medicines Agency (EMA) have laid out clear regulatory pathways for the approval of biosimilars in both the US and Europe, respectively. These pathways are much less complicated, time consuming, and costly compared to traditional biologics. This has led to the production of cost-effective biologics which are more accessible to patients.

As the patents of the original biological products come to an end, pharmaceutical companies are also striving to develop new biologics that improve the efficacy and safety profile over the original. These new drugs have occasionally been marketed as "biobetters" or "biosuperiors." The term biobetter was first mentioned at a biologics conference in 2007 by G.V. Prasad, the CEO of Dr. Reddy Laboratories, in Mumbai, India.[2] However, there is no legal definition of biobetter published by the FDA or EMA. Moreover, a defined regulatory pathway does not exist for the approval of biobetters. Currently, they are simply treated as a new biological entity and thus follow the regulatory pathway for any new biologic. Therefore, the term biobetter is more of a marketing term used by pharmaceutical companies, however it has slowly crept into scientific literature and has led to its misinterpretation and improper use. For example, there were several press releases in 2011 about the biotechnology company Glycotope GmbH starting a Phase 1 clinical trial of an investigational drug TrasGEX which is a "biobetter" of Transtuzumab/ Herceptin (TM).[3] However, this drug has yet to be approved by any regulatory authorities, thus it cannot be truly better.

As this term will most likely remain within the scientific lexicon, it is vital that it be consistently applied. Herein, we are attempting to provide clarification on a definition outlining specific parameters that a biologic should follow to be classified within literature as a biobetter. Specific examples of "biobetters" that are currently in development as well as on the market will be highlighted. We will also address the current discrepancy in the literature regarding the term biobetters and thus ultimately classify these biological entities into the three distinct categories of: true-biobetters, potential-biobetters, and non-biobetters.

## 2. Biologics

Biological products are made by living organisms, including animals, plants, and microorganisms. They are important in the treatment of various serious and rare medical conditions. In contrast to small molecules which are usually chemically synthesized and have a known structure, biologics are often large and complex protein-based drugs. In comparison to small molecules (aspirin: 180 Daltons), biologics are more complex and have a higher molecular mass (IgG1: 150,000 Daltons).[4] The purity and composition of a small molecule drug can be verified easily and are consistent regardless of the manufacturing site. However, this is not the case with biologics. These products are derived from various living expression systems and produced via intricate manufacturing processes. There are differences seen even within different batches of the same product. Hence, for a biologic it is often stated "that the process defines the product."[5] Biologics are known to be very sensitive to temperature and

require complex stabilization systems. They can also elicit an immunogenic response in the human body due to their primary structure (amino acid sequence) derived from other living systems.

In the late 1800s, Europe was among the first to begin the development of the precursors of today's biologics. The introduction of biologics in the United States occurred with the passing of Biologics Control Act (BCA) in 1902. One of the first biologics were vaccines against infectious diseases such as polio, Pertussis, German measles, and influenza. The BCA act provided governmental oversight over the processes used to make biologics, as well as regulations regarding safety concerns for the use of these products. At the time, Hygienic Laboratory (later known as National Institute of Health) mandated licensing, supervised manufacturing, and oversaw labeling of biologics, in addition to conducting inspections.

Under the Federal Food, Drug and Cosmetic Act (FD&C Act) passed in 1938, biologics were publicly established as drugs. From the time that the NIH came into existence in 1948 until 1972, it was this agency's responsibility for regulating biologics, after which time it was transferred to the Food and Drug Administration (FDA). Currently, the FDA's Center for Biologics Evaluation and Research (CBER) monitors biological products such as vaccines, blood components, hepatitis tests, gene therapy products, etc.[6]

Similar to small molecule drugs, the biologic approval starts with an Investigational New Drug (IND) Process. This is followed by a Biologics License Application (BLA) which requests permission from the FDA for the introduction and distribution of a biologic product into interstate commerce.[7]

## 3. Biosimilars

Beyond biologics, commonly known as 'reference medicine', manufacturing companies have begun to introduce biosimilars into the market. Biosimilars are approved only once the period of market protection expires for the reference medicine. As defined by the FDA and EMA, a biosimilar is a biological product that is approved based on it having demonstrated to be highly similar to an already approved biological product (a reference product) and having no clinically meaningful differences between said reference product in terms of safety, purity, and potency. Since these are manufactured through biological processes there will invariably be subtle differences between the two products. However, the FDA and EMA require these differences to not affect the therapeutic efficacy and safety. This is also true for different batches of any reference product as well.[8,9]

The EU approved its first biosimilar in 2006. Within Europe, all biologically manufactured medicines must pass through the 'centralized procedure' of the EMA to be approved. The EMA's Committee for Medicinal Products for Human Use (CHMP), the Pharmacovigilance Risk Assessment Committee (PRAC), the Biologics Working Party (BWP), and the Biosimilar Medicinal Products Working Party (BMWP) review any application related to biosimilars. This review is then sent to the European Commission which can grant the marketing rights to the company.[10]

Stemming from the Affordable Care Act, the Biologics Price Competition and Innovation Act (BPCIA) of 2009 created a licensure pathway for the manufacturing and distribution of biosimilars within the US. The act stated that in order to submit a biosimilar application it is necessary to present evidence from analytical, animal, and clinical studies showing that there are no clinically meaningful differences from the reference product. The products must also utilize the same mechanism of action, have the same delivery route and

dosage form, and be used under the same conditions.[11]

**4. Biobetters**

As discussed earlier, biobetter is a marketing term loosely defined as a better version of an existing biologic. These improvements comprise of altering the duration of therapy, allowing for fewer doses, increasing half-life and binding affinity in order to improve efficacy, and/or minimizing adverse events caused by multiple dosing. Neither the FDA nor the EMA have a classification of biobetters and thus these are referred to as new drugs and follow the aforementioned new-drug approval pathways and not the streamlined biosimilar route.

Within literature there has been a prevailing increase in classifying certain biologics as biobetters. These inconsistencies include categorizing biologics as a biobetter that are yet to be approved by the respective government authorities, drugs that exhibit safety concerns, and/or those that have completely different target/class/indication when compared to a reference drug. To address this issue, we have created three concrete parameters. Only if a biologic drug meets all three of these parameters can it be termed as a true biobetter. These parameters are: 1) the target/class/indication is the same as a reference drug, 2) has improved pharmacologic, pharmacokinetics, safety, and/or efficacy over the reference drug, and 3) a biologic that has been approved by the respective government authorities as a new drug. Using these three simple parameters it is therefore possible to categorize a biologic as either a *true-biobetter*, a *potential-biobetter*, or a *non-biobetter*. Only if a biologic meets all three parameters can it be termed a true-biobetter. Likewise, if a biologic has met the only first two parameters and has yet to be approved, it can be categorized as a potential-biobetter. Finally, a biologic that fails to meet the first and/or second parameter will be relegated as a non-biobetter (**Table 1**).

**Table 1.** Categories for biobetters and requirements.

| | |
|---|---|
| **True-Biobetter** | - Target/class/indication is the same as a reference drug<br>- Improved pharmacologic, pharmacokinetics, safety, and/or efficacy over reference drug<br>- Approved by the respective government authorities as a new drug |
| **Potential-Biobetter** | - Has yet to be approved by the government authorities but has met the first two parameters |
| **Non-Biobetter** | - Failed to meet two of the three necessary parameters or has already been approved by the FDA as a reference drug or biosimilar |

Using these new definitions, we compiled an exhaustive list of biologics that have been termed as a "biobetter" somewhere in the literature. We have subsequent re-categorized each of these into their new classifications based on the parameters discussed above. Utilizing this new characterizations it is hoped that this will assist to address the "biobetter" misnomer.

**Table 2.** Biologics termed as biobetters in literature and their correct classification based on the aforementioned criteria.

| Biologics of interest | True-Biobetter | Potential-Biobetter | Non-biobetter | Ref. |
|---|---|---|---|---|
| Adalimumab [AbbVie] | X (infliximab) | | | 12 |
| ado-trastuzumab emtansine [Genentech] | X (trastuzumab) | | | 5 |
| Albiglutide [GlaxoSmithKline] | X (liraglutide) | | | 13 |
| Balugrastim [Teva Pharmaceuticals] | | | X[a] (filgrastim) | 13 |
| Belatacept [Bristol Myers Squibb] | X (abatacept) | | | 13 |
| brentuximab vedotin [Seagen] | | | X[b] | 14 |
| CHO-C225 | | X (cetuximab) | | 12 |
| CMAB008 [Mabpharm Limited] | | X (TNF-α) | | 15 |
| Corifollitropin alfa [Merck] | X[c] (FSH) | | | 14 |
| CPGT329 A | | X (carboxypeptidase G2) | | 16 |
| CPG2G123S | | X (carboxypeptidase G2) | | 16 |
| CPG1I100 T | | X (carboxypeptidase G2) | | 16 |
| CSL654 | X (rhFactor IX) | | | 13 |
| CSL689 [CSL Behring] | | | X[a] (rhFactor VIIa) | 13,17 |
| Darbepoetin alfa [Amgen] | X (epoetin alfa) | | | 18 |
| Denileukin diftitox [Eisai Co.] | X (aldesleukin) | | | 13 |
| Dulaglutide [Eli Lilly] | X (liraglutide) | | | 13 |
| efraloctocog alfa [Biogen] | X (recombinant antihemophilic factor) | | | 13 |
| eftrenonacog alfa [Biogen] | X (coagulation factor IX) | | | 13 |
| Factor IX-CTP [Medexus Pharma] | | X[e] (rhFactor IX) | | 13 |
| Glymera | | X[e] | | 13 |

| | | | | |
|---|---|---|---|---|
| [PhaseBio Pharmaceuticals] | | (liraglutide) | | |
| GX-G3 [Genexine, Inc.] | | X (G-CSF) | | 19 |
| hGH-CTP [OPKO Biologics] | | X[e] (somatropin; hGH) | | 13 |
| HSA-CPG2 | | X (glucarpidase) | | 20 |
| IFN-α2b-HSA [Novartis] | | | X[a] (IFN- α2b) | 13 |
| IL-2/anti-GD2 antibody 14.18 [Children's Oncology Group/NCI] | | X[e] (aldesleukin) | | 13 |
| Methoxy PEG epoetin beta [Roche] | X (epoetin alfa) | | | 18 |
| Mogamulizumab [Kyowa Hakko Kirin Pharma, Inc.] | X (KM2160) | | | 13 |
| moss made aGAL [Greenovation] | | X (alpha galactosidase) | | 21 |
| Moss made asialo EPO | | | X[d] (erythropoietin) | 21 |
| MM-111 [Merrimack Pharmaceuticals] | | | X[a] (trastuzumab) | 13,22 |
| Motavizumab [Medimmune] | | | X[a] (palivizumab) | 12,23 |
| Obinutuzumab [Glycart Biotech] | X (rituximab) | | | 5,12 |
| Ocrelizumab [Roche] | | | X[b] | 12 |
| PEG-crisantaspase [Sigma-Tau Pharmaceuticals] | X (crisantaspase) | | | 24 |
| PEG-CPG2 | | X (glucarpidase) | | 20 |
| PEG-filgrastim [Amgen] | X (filgrastim) | | | 13 |
| PEG-IFN- alpha 2a [Hoffman-La Roche] | X (IFN-alpha2a) | | | 13 |
| PEG-IFN- alpha 2b [Merck] | X (IFN-alpha2b) | | | 13 |
| PEG-IFN- beta 1a [Biogen] | X (IFN-beta1a) | | | 13 |
| PE0139 [PhaseBio] | | X[e] (insulin) | | 13 |
| Q160S and E195N variants [Genentech] | | X (bevacizumab) | | 25 |
| rFVIIa-CTP | | X[e] | | 13 |

| | | | | |
|---|---|---|---|---|
| | | (rhFactor VIIa) | | |
| R27T | | X[e] (rhIFN-β 1a) | | 26 |
| Somavaratan [Versartis] | | | X[a] (somatropin) | 13,27 |
| TrasGEX [Glycotope] | | X (trastuzumab) | | 28,29 |
| Tomuzotuximab [Glycotope] | | X (cetuximab) | | 30 |
| TV-1106 [Teva Pharmaceuticals] | | | X[a] (somatropin) | 13,31 |
| VRS- 859 [Versartis] | | X[e] (exenatide) | | 13 |

(Name of reference drug), a – Terminated or failed clinical trials, b – FDA approved biologic with no reference to compare with, c - Approved in EU not in US, d - Drugs with different target than the reference drug, e– correctly classified as a potential-biobetter in the literature.

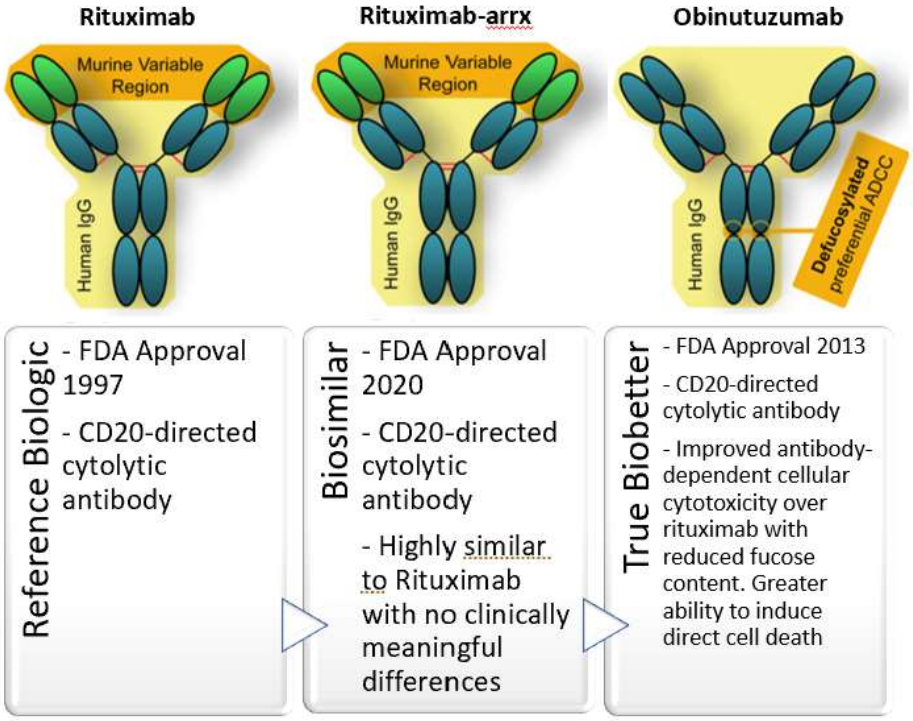
### *4.1. Instances of true-biobetters in the literature*

Darbepoetin alfa (Aranesp) was developed by Amgen and was termed a biobetter within the article, "Physiology and Pharmacology of Erythropoietin."[32] Based on our aforementioned criteria, darbepoetin alfa can be classified as a true-biobetter since it meets all three parameters listed above. 1) Both it and the reference drug epoetin alfa (Epogen/Procrit) are used for the treatment of anemia associated with the chronic kidney disease (CKD) and stimulate erythropoiesis by acting on the erythropoietin receptor. 2) Compared to epoetin alfa, darbepoetin alfa is hyperglycosylated with a terminal half-life of three - four times (25 hours) greater than that of epoetin alfa (6-9 hours) with IV administration, thus allowing it to be administered less frequently.[32] 3) It was approved by the FDA in 2001.[33] Methoxy PEG-epoetin beta (Mircera) is another example of a true-biobetter drug of epoetin alfa with longer half-life of 130-140 hours, having the same target and mechanism of action, and being FDA approved in 2007.[34]

Obinutuzumab (Gazyva) was developed by Genentech, Inc. and approved by the FDA in 2017. Again, this drug can be classified as a true-biobetter. Rituximab (Rituxan) is the reference drug which is used in the treatment of Non-Hodgkin Lymphoma. Both of these are cytolytic antibodies and target CD-20 antigen receptor expressed on B-lymphocytes. Obinutuzumab has improved antibody-dependent cellular cytotoxicity (ADCC) over rituximab with reduced fucose content.[35] [35]. It also has a greater ability to induce direct cell death and binds with a higher affinity to FcγRIII. Riabni (Rituximab-arrx) is a biosimilar of Rituximab. It was developed by Amgen and approved in 2020.[36]

**Figure 1**: Rituximab biosimilar and true biobetter:




*4.2. Instances of potential-biobetters in the literature*

GX-G3 is an investigational drug developed by Genexine and is herein classified as a potential-biobetter. This drug is indicated for the treatment of severe neutropenia following myelosuppressive chemotherapy and is currently in Phase 2 clinical trials.[37] The reference drugs of GX-G3 are filgrastim (Neupogen) and Peg-filgrastim (Neulasta) both of which also target the granulocyte colony stimulating factor (G-CSF). In preclinical studies done on healthy rats it was reported that the half-life of GX-G3 was twice that of Neulasta and four times greater than Neupogen.[19] If approved it would meet the final criteria and thus be a true-biobetter.

TrasGEX, by Glycotope is an investigational drug currently completing Phase 1 clinical trials. The drug is considered a better version of trastuzumab (Herceptin) and targets the HER-2 receptor to treat breast cancer.[38] After the company announced the beginning of their Phase 1 clinical trial declaring it a biobetter version of trastuzumab, several companies including Creative Biolabs also classified this drug as a biobetter on their website.[28] Since the drug has yet to be FDA approved it does not fall under the true-biobetter category. The Phase 1 clinical trial results have however shown higher efficacy and hence at this juncture can only be classified as a potential-biobetter.[29]

*4.3. Instances of non-biobetters in the literature*

Brentuximab vedotin (Adcetris) is an antibody drug conjugate (ADC) directed against the CD30 antigen.[39] It was developed by Seattle Genetics/Takeda, FDA approved in 2011,[40] and can also be used for the treatment of classical Hodgkin's lymphoma in combination with adriamycin, vinblastine, and dacarbazine after seeing significantly improved survival rates in ECHELON-1 and 2 clinical trials.[41-43] Similar to TrasGEX above, Creative Biolabs classified this drug as a biobetter.[14] However, this drug falls under the

category of non-biobetters since there is no reference drug to compare it with. Thus, when reported as a biobetter the question arises "better than what"?

Motavizumab was a humanized monoclonal antibody investigated for use in pediatric population to treat respiratory syncytial virus (RSV) infections. It was reported to have better *in vitro* binding affinity than its reference drug, palivizumab and referred to as a biobetter by Creative BioLabs.[44] However, in a Phase 3 randomized controlled trial, "Motavizumab Versus Palivizumab for the Prophylaxis of Serious Respiratory Syncytial Virus Disease in Children" it was found that it led to increased cutaneous hypersensitive adverse reactions compared to palivizumab.[23] Ultimately, the FDA did not approve motavizumab for the treatment of RSV infections. Accordingly, since a biologic must be first approved by the FDA and have improved pharmacology, pharmacokinetic, safety and/or efficacy profile, this fails two of the three parameters and thus is a non-biobetter.

Moss-made asialo erythropoietin is an investigational drug for the treatment after stroke. This drug lacks sialic acid residues and has a very short half-life with no hematopoietic activity when compared to erythropoietin. The article, "Moss-made pharmaceuticals: from bench to bedside" classifies the moss-made version as a biobetter when compared to its reference drug, erythropoietin.[21] Several *in vivo* studies demonstrated that moss made asialo erythropoietin did not have any of the thromboembolic risk that was reported with erythropoietin and therefore could be beneficial in the treatment of stroke. Erythropoietin has been associated with use in illegal doping activities, whereas asialo erythropoietin cannot be abused for this purpose as it does not promote the maturation of red blood cells.[45,46] However, the asialo erythropoietin targets a different receptor, tissue-protective receptor (TPR) versus erythropoietin receptor (EPO).[47] Since the targets are different, it does not meet the first parameter and thus it is classified as a non-biobetter.

## 5. Conclusion

Biobetter is a marketing term originally used by the pharmaceutical industry and has slowly crept into the scientific literature. Since there is no legal or regulatory pathway defined by the FDA or EMA for the development of biobetters they are considered as a new biologic entity and thus follow the same regulatory pathway as any novel biologic. By first acknowledging that this term will most likely not go away we identified biologics of interest that were misclassified in the literature as biobetters and re-classified them into three categories: true-biobetters, potential-biobetters, and non-biobetters. For example, a biologic that has improved efficacy and/or safety profile and has the same target as the reference drug but has not yet been approved by regulatory authorities would be considered potential-biobetter. A biologic that does not have an improved efficacy data over the reference drug or has been previously approved by FDA as a biosimilar would be considered a non-biobetter. Likewise, a biologic that has been approved by FDA, has improved efficacy and safety data, and has the same target as the reference drug falls under true-biobetter category. This new classification system will hopefully assist the scientific community as a means to clean up the literature until such time, it any, that a regulatory agency modifies their definition(s).

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