



## Current Perspectives on Biosimilars and Impact of Biosimilars in Supportive Care in Breast Cancer

**R.Mohanty\*, Jassaswi Ray**

Department of Pharmaceutical Sciences, College of Pharmaceutical Sciences, Baliguali, Puri, Odisha, India.

\*Corresponding author's E-mail: [mohantyrashree62@gmail.com](mailto:mohantyrashree62@gmail.com)

Received: 19-04-2022; Revised: 15-07-2022; Accepted: 23-07-2022; Published on: 15-08-2022.

### ABSTRACT

Biopharmaceuticals are medicines whose active drug substance is made by living cells. Copies of these drugs, called Biosimilars are not identical to their reference drug and therefore specific regulatory requirements for registration apply. Whereas pharmaceutical quality evaluation requires a full dossier and a detailed comparative analysis to the reference drug, non-clinical and clinical requirements are much less extensive compared to the requirements for an innovator. Limited clinical experience and their complex nature exclude biosimilars from being considered interchangeable with the reference drug. The utilization of trastuzumab biosimilar medications is of particular interest in HER2-positive breast cancer as these drugs have the potential for cost savings and increased utilization/access to HER2 targeted therapy in both early stage and metastatic HER2-positive breast cancers. Five trastuzumab biosimilars: MYL-1401O (Ogivri), CT-P6 (Herzuma), SB3 (Ontruzant), PF-05280014 (Trazimera), and ABP980 (Kanjinti), have now been approved by the US Food and Drug Administration (FDA) for use in HER2-positive breast cancers. This review provides an overview of these agents with special consideration of the development and approval process, including available clinical data results for these trastuzumab biosimilars.

**Keywords:** Biosimilars, Biopharmaceuticals, Follow-on-Biologics, Monoclonal antibodies, Granulocyte colony stimulating factor (G-CSF), HER2-positive breast cancer, interchangeability, Trastuzumab.

### QUICK RESPONSE CODE →

DOI:  
10.47583/ijpsrr.2022.v75i02.001



DOI link: <http://dx.doi.org/10.47583/ijpsrr.2022.v75i02.001>

### INTRODUCTION

Biosimilars are the “generic” version of biopharmaceuticals, to treat a variety of diseases. Sometimes biosimilars called “Similar biological medicinal product”. Biosimilars ( or follow – on biologics ) are terms used to describe officially approved new version of innovator bio-therapeutic products for which the patent and exclusively expired. Biosimilars derived from the advances in cloning of human genetic material and recombinant DNA technology for development of *in vitro* biological production systems have allowed the discovery of new biological substance for the ultimate development of a drug.<sup>1</sup>

Hybridoma technology ( monoclonal antibody ) combined with recombinant DNA technology has smoothed the way for tailor- made and targeted medicines. Recombinant therapeutic proteins are of a complex nature. These proteins are produced in living cells such as bacteria, yeast, plant, viruses, and animal or human cell lines.

Biosimilars available in India include monoclonal antibodies for treating various malignant and

immunological disorders, growth factors like erythropoietin and granulocyte colony stimulating factor (G-CSF), human insulins for treating diabetes mellitus etc.<sup>1</sup>

The European Medicine Agency (EMA) has developed product class specific guidelines for erythropoietin's, insulin's, growth hormones. Alfa interferon, granulocyte-colony stimulating factors and low molecular weight heparins (LMWH), with three more (beta interferon's, follicle stimulation hormone, monoclonal antibodies ) currently being drafted.<sup>2</sup>

### Definition

Biosimilars are defined as similar biological medicinal product, follow-on biologic, or biogeneric. This is a copy drug that is similar to a biological drug that has already been authorized ( the biological reference medicine ). Its active substance is shown by appropriate testing to have similar physicochemical, preclinical and clinical properties to an originator therapeutic protein.

### Advantages of Biosimilars

Due to competitive pricing biosimilars are available at affordable prices on global market.

1. They are available at cheaper prices than original or reference biological product; hence, there is enhanced demand in the world market for biosimilars.
2. They have less market risk than reference product because of no investment in phase I-II of clinical trials (CT).



- Development and production of biosimilars are boosted by existing manufacturing technology.

### Disadvantages of Biosimilars

- Development and production process of biosimilar is multilayered due to high mol.wt than small molecular wt. when chemically synthesized the drug.
- It can show similar therapeutic effect but not identical to innovator product.
- Development process is lengthy because derived from living cells.
- Down stream process of a biosimilar is costly and time consuming.

Automatic substitution of biosimilar product with another one is not allowed.

### Difference Between Chemical and Biological Drugs <sup>2</sup>

**Table 1:** 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 structure	Complex, heterogeneous structure
Mostly process-independent	Strongly process-dependent
Completely characterized	Impossible to fully characterize the molecular composition and heterogeneity
Stable	Unstable, sensitive to external conditions.
Mostly non-immunogenic	Immunogenic

### Biosimilars Compared to Reference Products <sup>3</sup>

**Table 2:** Overview of Requirements for Approval of Biosimilars Compared to the Reference Product

Quality	Non clinical	Clinical
<b>Drug Substance</b> <ul style="list-style-type: none"> <li>Manufacture</li> <li>Characterisation</li> <li>Control of drug substance</li> <li>Reference standards or materials</li> <li>Container closure system</li> <li>Stability</li> <li>Comparability data (analytical comparison with reference product)</li> </ul> <b>Drug product</b> <ul style="list-style-type: none"> <li>Description and composition</li> <li>Pharmaceutical development               <ul style="list-style-type: none"> <li>Manufacture</li> <li>Control of excipients</li> </ul> </li> <li>Control of drug product</li> <li>Reference standards and materials</li> <li>Container closure system</li> <li>Stability</li> <li>Comparability data (analytical comparison with reference product)</li> </ul>	<b>Pharmacology</b> <ul style="list-style-type: none"> <li>Primary</li> <li>Secondary</li> <li>Safety</li> <li>Interactions</li> <li>Comparability data (primary pharmacodynamics )</li> </ul> <b>Pharmacokinetics</b> <ul style="list-style-type: none"> <li>ADME</li> <li>Interactions</li> </ul> <b>Toxicology</b> <ul style="list-style-type: none"> <li>Single dose</li> <li>Repeat-dose</li> <li>Mutagenicity</li> <li>Carcinogenicity</li> <li>Reproduction</li> <li>Local tolerance</li> <li>Comparability data (repeat-dose)</li> </ul>	<b>Pharmacology</b> <b>Pharmacokinetics</b> <ul style="list-style-type: none"> <li>Single dose</li> <li>Repeat dose</li> <li>Special populations</li> <li>Comparability data (single-dose PK)</li> </ul> <b>Pharmacodynamics</b> <ul style="list-style-type: none"> <li>Appropriate markers</li> <li>Comparability data (PD)</li> </ul> <b>Efficacy and safety</b> <ul style="list-style-type: none"> <li>Dose finding</li> <li>Schedule finding</li> <li>Pivotal               <ul style="list-style-type: none"> <li>Indication x</li> <li>Indication y</li> <li>Indication z</li> </ul> </li> </ul> <b>Comparability data (indication x)</b> <b>Post-marketing</b> <ul style="list-style-type: none"> <li>Safety</li> <li>Other indications</li> <li>Immunogenicity</li> </ul>

### Development Stages of Biosimilars

There are four stages in the development of a biosimilar: 1) product development and comparative analysis; 2) process development, scale up and validation; 3) clinical trials; 4) Regulatory (EMA and FDA) review and approval.<sup>4</sup>

### Development of product and relative analysis

This stage contains the manufacturing of target protein from defined cell culture and evaluating its stability profile. The newly developed product must be highly similar to innovators product.



### Development and optimization of process and validation

This stage can involve complete development and optimization of the process to improve the final yield of the biosimilar product. The scale – up process should follow good manufacturing practice. The production process should be validated for reproducibility of yield.

### Clinical studies

This is an important stage for biosimilars product. Clinical studies will be necessary for nearly all biosimilars product so as to validate bioequivalence to reference or innovator product.

### Regulatory process

In Europe, the committee of medicinal products for human use (CHMP), and the European Medicines Agency (EMA) formed a regulatory system for biosimilars, and the first regulatory guidance was delivered in October 2005.

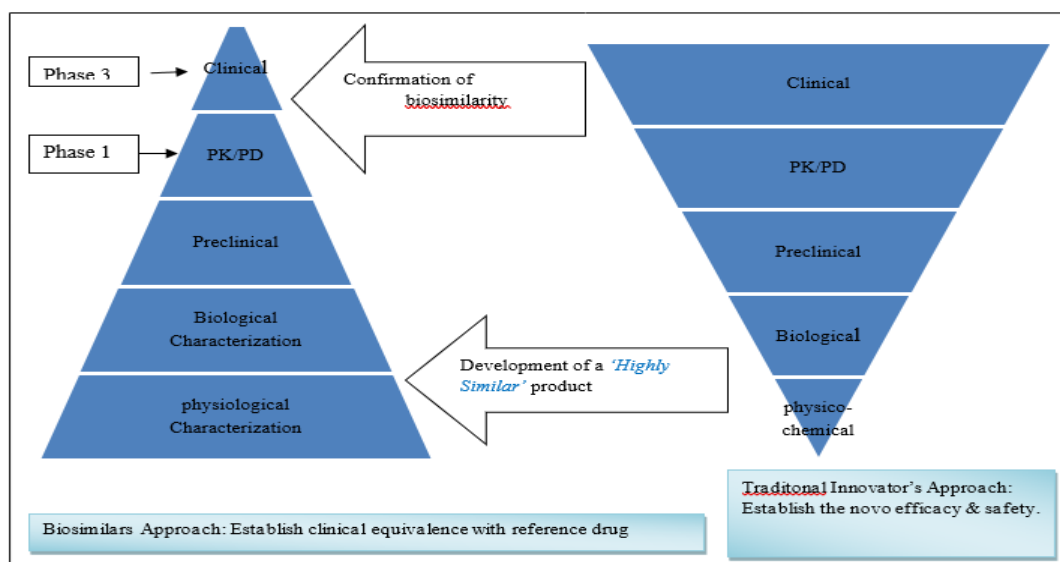
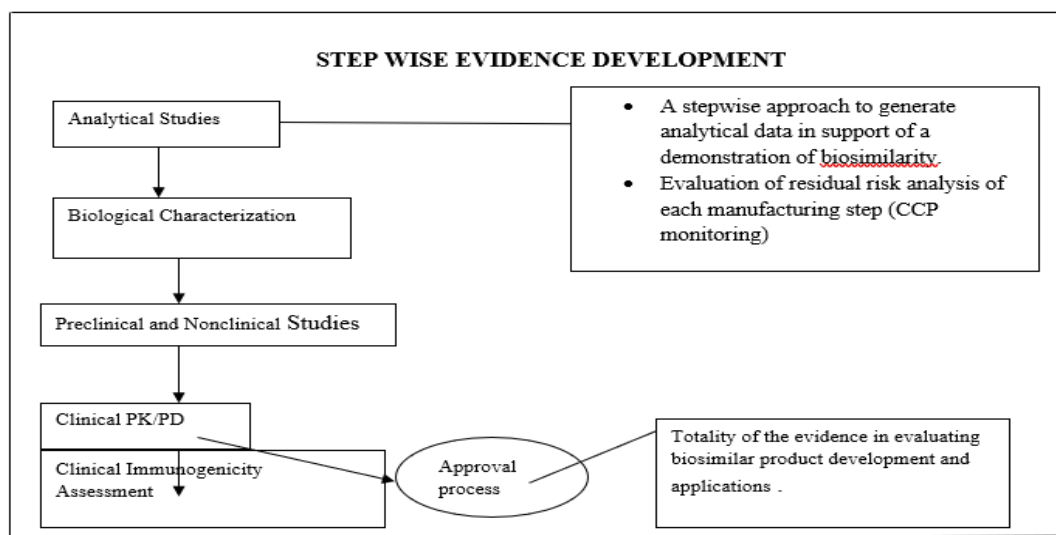


Figure 1: (Biosimilars Approach : Establish Clinical Equivalence With Reference Drug)

### Evidence Development



### Biosimilars Current Status in the World<sup>5</sup>

In 2010, global pharma market reached \$ 830 B. Biologics drugs market exceeded \$116 B (14%). Biosimilars drug sales \$380 M& large number of biological drug patent are expiring in recent times. Biosimilars are follow – on versions of highly complex biopharmaceuticals that are no

longer patent protected. Sandoz was the first company to bring one to the market – human growth hormone Omnitrope in 2006. India has the potential to become a global player in similar biologics or biosimilars. According to ASSOCHAM-Sathguru report released in 2016, biosimilar presents a US\$ 240 billion global

opportunity to Indian biopharmaceutical industry and the domestic market is expected to grow US\$40 billion by 2030.<sup>5</sup>

**Table 3:** Name of the Country and Biosimilar Guidelines Approval

S. no.	Name of the country	Biosimilar guidelines approval
01	CANADA	First Biosimilar Omnitrope 2009
02	AUSTRALIA	Following EU, Omnitrope 2005
03	JAPAN	First Biosimilar Omnitrope 2009
04	EU	World Leader
05	FDA	Not Yet
06	INDIA	Guidelines in place
07	BRAZIL	Final guideline, 2005
08	VENEZUELA	Final guideline, 2000
09	TURKEY	Final guideline, 2008
10	MALAYSIA	Final guideline, 2008

#### India - biosimilar regulatory requirement guideline<sup>8-11</sup>

Regulatory requirements for marketing authorization of similar biologic in India were released in 2012 and require extensive quality/analytical comparative data in addition to abridged clinical/non-clinical studies are required for biosimilar approval.

Data requirement Analytical and quality characterization data Comparability according to critical quality attributes of product including physicochemical properties, biological activity, immunological properties, functional assays, purity (process and product-related impurities, etc.), contamination, strength, and content.

#### Non-clinical studies

- *In vitro* studies: e. g. cell-based bioassay (e. g., cell proliferation assays or receptor binding assays)
- *In vivo* studies: PD activity, immunogenicity, at least one repeat dose toxicity study, local tolerance (may be part of repeat dose toxicity study); safety pharmacology, reproductive toxicity, mutagenicity, and carcinogenicity studies are not required unless warranted by repeat dose toxicity studies.

#### Clinical studies

- *Phase I: Comparative PK (Pharmacokinetics) and PD (pharmacodynamics) studies; PK/PD relationship may be evaluated. PD evaluation can also be done as part of Phase III study (usually 1 or 2 Clinical Trails (CTs) depending on indications)*
- *Phase III: Comparative efficacy and safety/immunogenicity study are essential (usually 1 or 2 CTs, depending on a number of indications and safety profile).*
- *Equivalence design study is preferred.*
- *Non-inferiority design needs to be justified.*

- *Safety and efficacy CT can be waived off if comparable quality, non-clinical and clinical PK-PD data with post-marketing risk management plan is provided (cannot be waived if there is no reliable and validated PD marker).*

- *Post-marketing: Safety and immunogenicity data must be submitted*

Extrapolation to other indication May be possible if the same Mechanism of Action (MOA)/receptors for indications (with similar safety, efficacy, preclinical and quality data) Reference product requirements

- Reference biologic should be licensed in India and should be innovator product.
- If reference biologic is not marketed in India, then it should be licensed and widely marketed for four years post approval in innovator jurisdiction in a country with the well-established regulatory framework.
- In case no medicine or only palliative therapy is available or in the case of national healthcare emergency, this period of 4 y may be reduced or waived.

Interchangeability Not mentioned in the guideline.

#### Europe – Biosimilar Regulatory Requirement Guideline<sup>12-15</sup> Guidelines

- EU Guideline on similar biological medicinal products
- EU Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1)
- EU Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues

Similar Biological Medicinal product is a biological medicinal product that is similar to the active substance of an already authorized biological medicinal product (reference medicinal product) in European Economic Area (EEA). The similarity to reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise must be established. Comparative analytical data along with the clinical and non-clinical data is required to establish the similarity. Data requirement Analytical, quality characterization data Comprehensive analyses of biosimilar and reference product. Any differences detected in quality attributes will have to be appropriately justified concerning their potential impact on safety and efficacy. Non-clinical data

- Phase 1: Comparative PK/PD studies .
- Usually, 1 or 2 CTs depending on indications .
- Phase 3: Confirmatory Safety and Efficacy Studies .
- Usually 1 or 2 CTs, depending on a number of indications and safety profile.



- In general, an equivalence design should be used.
- The non-inferiority design may be acceptable if justified on the basis of a strong scientific rationale.
- Post-marketing: Safety and immunogenicity data.

#### Extrapolation to other indication

- Extrapolation to other indications needs to be scientifically justified .
- Additional data required .
- If the drug acts on multiple active sites/receptors in different indications .
- Immunogenicity and safety are different .
- If studied indication is not sensitive in detecting differences in all aspects of efficacy and safety.
  - The infliximab biosimilar (Remsima) was approved by EMA (European Medicines Agency) for all indications for reference biologic on the basis of submitted clinical data for rheumatoid arthritis and ankylosing spondylitis.

#### Reference product requirement

- Must be authorized in European Economic Area (EEA)
- In the case of non-EEA authorized comparator, bridging data comparing all three products including analytical studies with clinical and non-clinical data should be submitted (proposed biosimilar, EEA-authorized reference product and not EEA-authorized comparator).

#### Interchangeability

- Interchangeability assessment is left to member states.
- In EU countries, treatment decisions to treat patients is left to the physicians and patients to avoid “automatic substitution.”
- France Law (2014) states that a biosimilar may be dispensed only as an initial treatment to a new, or “naive” patient, and only if physician states that prescribed biologic is “non-substitutable.”
- In the case of substitution, records are maintained by the pharmacists.

#### European biosimilar marketing authorization summary

Out of 29 Marketing Authorization Applications (MAA) filed, 21 were approved, one was rejected, and seven were withdrawn by the applicant. Out of 21 approved biosimilars, two were voluntarily withdrawn by the applicant .

#### Brazil-Biosimilar regulatory Summary <sup>16, 17</sup>

##### Guidelines

- ANVISA (National Health Surveillance Agency) Guideline on Biosimilar (Board Resolution-RDC No. 55 OF 16 DECEMBER 2010)

Biosimilar regulatory guideline for Brazil was released in 2010 and is based on WHO and EU biosimilar guidelines. Follow-on biological product which is comparable to reference biological with respect to quality, non-clinical and clinical parameters in terms of quality, efficacy, and safety. Data requirement Analytical, quality characterization data Biological and physicochemical characterization related to quality attributes, purity, and impurity profile, with discussion of potential impact on quality, safety, and efficacy. Non-clinical studies data

- *In vitro studies*
- *In vivo studies*: Pharmacodynamics studies and studies of cumulative toxicity (repeat dose) including parameters characterizing kinetics of toxicity .

##### Clinical studies data

- Phase I: PK and PD studies; can be a combined study (usually 1 or 2 CTs depending on indications)
- Phase III: comparative clinical safety and efficacy pivotal studies (usually 1 or 2 CTs, depending on number of indications and safety profile) .
- Post-marketing: Safety and immunogenicity data.

##### Extrapolation to other indication

- MOA and receptors involved for different indications are same.
- Safety and Immunogenicity are sufficiently characterized.

##### Reference product requirements

- Reference product should be registered with ANVISA Brazil.
- Non-Brazil reference product needs to be registered by another regulatory authority which has similar criteria as ANVISA with full unrestricted access to registration information to ANVISA.

Interchangeability Not mentioned in the guidelines.

##### Current Status of Biosimilars In India

Biosimilar or similar biologic used has increased in the recent year following the approval of the first biosimilar in early 2000. India is one of the leading manufacturers of similar biologics. India has developed a new guideline in 2012 for the pre- and post-marketing approval of similar biologics.

India has a thriving biosimilar ecosystem in comparison to other countries and because of that Indian pharmaceutical companies have risen as the global market leaders in



biosimilars. India approved its first biosimilar much before the United States and Europe. The first biosimilar was approved and marketed in India in 2000 for hepatitis B, although no specific guideline was available at that time for the development and marketing of biosimilar in India. Since then several biosimilars were developed and marketed in India by various biopharmaceutical companies. Recently, an Indian biopharmaceutical company got the USFDA's nod for marketing its novel biologic. Herceptin (active drug is trastuzumab) was the first biologic to be approved by FDA, which is used in certain breast and stomach cancer. This was also the first similar biologics manufactured by an Indian company, which received approval to market in the United States.

Presently, there are more than 100 Indian biopharmaceutical companies, which are engaged in manufacturing and marketing of biosimilar. Biosimilar is called as "similar biologics" by Indian regulatory agencies. No specific guideline was available for "similar biologics," despite the fact that India was one of the first countries in the world to use it, and approval process of similar biologics is more cumbersome and require more data than other generic drugs. To address the issues and challenges associated with the development of similar biologics, Central Drugs Standard Control Organization (CDSCO) in collaboration with the Department of Biotechnology (DBT) has developed "Guidelines on Similar Biologics; Regulatory Requirements for Marketing Authorization in India" in 2012 and has revised it in 2016. These guidelines address the regulation of manufacturing process as well as quality, safety, and efficacy of similar biologics. It also addresses the pre- and post-marketing regulatory requirements for similar biologics. DBT through Review Committee on Genetic Manipulation is responsible for overseeing the development and preclinical evaluation of biologics. The similar biologics in India are regulated as per Drug and Cosmetic Act (1940), Drug and Cosmetic Rules, 1945, and Rules for Manufacture, Use, Import, Export, and Storage of Hazardous Microorganisms/Genetically Engineered Organisms or Cells, 1989 (rules, 1989) notified under Environmental (Protection) Act, 1986. CDSCO has brought some important changes in its earlier guideline, such as earlier it was essential for the reference biologic for which biosimilar is to be developed has to be approved and marketed in India but it has now changed to either India or any other international council for harmonisation countries (i.e., European Union, Japan, United States, Canada, and Switzerland). It also tries to align with other international agencies such as EMA and the World Health Organization. According to Indian guideline, biologics are developed by the sequential approach to show the similarity of the molecular and quality characteristic of a biosimilar with reference products. Another difference between the 2012 guidance and the document issued in 2016 is the emphasis on the post-marketing studies, which CDSCO says are intended "to further reduce the residual risk of the similar biologic," CDSCO has made it essential for the biopharmaceutical company to conduct a Phase IV

study with a minimum of 200 patients within 2 years of getting approval for marketing.<sup>6</sup>

The regulator also added a new section on non-comparative safety and efficacy studies, noting that if a product is found to be similar "in pre-clinical, *in vitro* characterization having established PK (pharmacokinetic) methods and a PD (pharmacodynamic) marker that is surrogate of efficacy, the residual risk is significantly reduced in the Phase I study if equivalence is demonstrated for both PK and PD. Phase III clinical trials of such a Similar Biologics product may be waived...[and] where considered necessary, an appropriate single arm study in at least 100 evaluable subjects may be carried out in the most sensitive indication to address any residual uncertainty."

CDSCO also added new information on when a confirmatory clinical safety and efficacy study can be waived, noting: "In case the safety and efficacy study is waived all the indications approved for reference product may be granted based on comparable quality, non-clinical as well as convincing PK/PD data. Wherever the Phase III trial is waived, the immunogenicity should have been gathered in the PK/PD study and will also need to be generated during post-approval Phase IV study."

Indian companies are taking multiple steps to involve them in manufacturing and marketing to tap this huge potential. Biosimilars approved and used in India mainly consist of the vaccines, monoclonal antibodies, insulin, and recombinant proteins. India has achieved the distinction of being the second largest supplier of vaccines in the world. Various biosimilars have been approved by India for use in different diseases.<sup>6</sup>

**Table 4:** Various Biosimilars Approved By India For Use In Different Disease

Product Name	Active Drug	Indications
Glartus	Insulin glargine	Diabetes mellitus
Grafeel	Filgrastim	Neutropenia
Epofer	Epoetin alfa	Anaemia
Adfar	Adalimumab	RA, Crohn's disease
Erbix	Cetuximab	Colorectal carcinoma
Krabeya	Bevacizumab	Colorectal cancer
Herceptin	Trastuzumab	Breast cancer
Intacept	Etanercept	RA

In September 2017, the FDA approved bevacizumab-awwb (Mvasi) as the first biosimilar to treat cancer. Bevacizumab-awwb treats certain colorectal, lung, brain, kidney, and cervical cancers. Its reference drug is called bevacizumab (Avastin). Bevacizumab-bvzr (Zirabev) is another FDA-approved biosimilar to bevacizumab.



### Impact of Biosimilars in Supportive Care in Breast Cancer

The Current Impact of Biosimilars in Supportive Cancer Care. The current impact of biosimilars in supportive cancer care Supportive cancer therapy is the use of medicines to counteract unwanted effects of cancer treatment. Therapies for supportive care were the first approved biosimilars, represented by filgrastim and epoetin alfa, in the EU in 2007. Since then, many development programmes for biosimilars have been initiated, such as for rituxumab, trastuzumab and bevacizumab. Filgrastim and epoetin are two biologic medicines that offer significant benefits in cancer care that are now patent-expired. Biosimilar versions of both have been approved in Europe by the EMA since 2007. Using the generic model, these should both improve access to better supportive cancer care and save on costs and permit the established budget to be reallocated into novel areas of treatment. A number of biosimilars to filgrastim have been approved for all indications of the reference product. The approvals were based on data that included direct comparisons to the reference product using analytic methods to indicate similarities in molecular structure, in vitro properties, PK and PD properties, and mechanism of action. In addition, efficacy and safety studies were conducted in patients with care.<sup>20</sup>

### The Impact of Biosimilars in Future Cancer Care

The impact of biosimilars in future cancer care the most important health policy objective is the improved health status of the population. In developed healthcare systems, the most common medical treatment is pharmaceutical therapy. Success of public health policies in improving the health status of the total population highly depends on the success of policies to control the cost of drugs and improve patient access. The WHO makes it clear that sourcing and using the lowest cost medicines is a requirement of good prescribing .The WHO, in their 2010 World Health Report, More Health for the Money, wrote: 'All countries can do something, many of them a great deal, to improve the efficiency of their health systems, thereby releasing resources that could be used to cover more people, more services and/

### Biosimilars for Breast Cancer of HER2 – Targeted Antibodies

While there are currently no FDA-approved biosimilars of drugs that treat breast cancer, many biologic antibodies are under investigation. Trastuzumab, a monoclonal antibody that targets human epidermal growth factor receptor 2 (HER2), was shown to hinder the breast cancer cell proliferation that overexpresses HER2. In 2001, it was shown to improve the overall pharmacological response and its duration along with survival rate in combination with chemotherapy compared with chemotherapy alone. This led to the approval of trastuzumab in treating HER2-positive metastatic breast cancer in 2006. Since then, trastuzumab approval has expanded to cover additional settings, treatment regimens, and cancer types. In 2008,

about more than 420,000 women with HER2-positive breast cancer had received trastuzumab treatment which is considered as standard. The US patent for trastuzumab is set to expire in June 2019; it expired in July 2014 in Europe. The success of trastuzumab, in combination with its expired patent, has prompted the investment into competing biosimilars.<sup>21-24</sup>

Although 19 biosimilars for trastuzumab are currently being investigated, MYL-14010 has shown the most success toward the patients with HER2-positive metastatic breast cancer . As progression-free survival or overall survival may be insufficient to demonstrate biosimilarity between reference products and their biosimilars, bodies such as the EMA have recommended using an activity-measuring clinical endpoint such as partial complete response or oxygen reduction reaction (ORR) as the primary endpoint . The primary outcome measure of this study was a comparison of the best ORR at week 24 between the combination of biosimilar trastuzumab (MYL-14010) with taxane and reference trastuzumab with taxane. The study showed that patients receiving reference trastuzumab plus a taxane had an ORR of 64.0% at 24 weeks and patients receiving biosimilar trastuzumab plus a taxane had an ORR of 69.6%, a rate within pre-defined equivalence boundaries. Progression-free survival at 48 weeks was 44.7% and 44.3% for reference and biosimilar trastuzumab, respectively; overall survival was 85.1% and 89.1%, respectively; adverse events affected 94.7% and 98.6% of patients, respectively . PF-05280014, another biosimilar of trastuzumab, was reported as having demonstrated equivalence in its primary endpoint in November of the past year; data from this study have not yet been presented. Finally, biosimilar trastuzumab has been investigated only as a single agent, while trastuzumab plus pertuzumab is considered the standard of care. The development and testing of biosimilar drugs may continue to change the ways doctors to treat their patients. Increased understanding of the approval and testing process, as well as potential benefits and risks of the use of biosimilars, are essential for practicing oncologists. Biologic pharmaceutical options remain costly, and incorporation of biosimilars may lead to health-care savings of 30% or more, with market entry costs, pricing reactions, and many other factors establishing the ultimate level of cost reduction that may be seen.

Biosimilar medications are engineered medications that provide similar pharmacokinetic and pharmacodynamic properties to the original biological medication. Specifically, a biosimilar is defined as a biological medication that is highly similar to a reference product, with only minor differences in clinically inactive components, and has no clinically meaningful differences between the two medications with regard to safety, purity, and potency. These medications typically undergo an abbreviated approval process that is based on the overall evidence supporting the proposed medication as a biosimilar product (Figure 3). Analytical assessment of the structural and functional characteristics of the potential



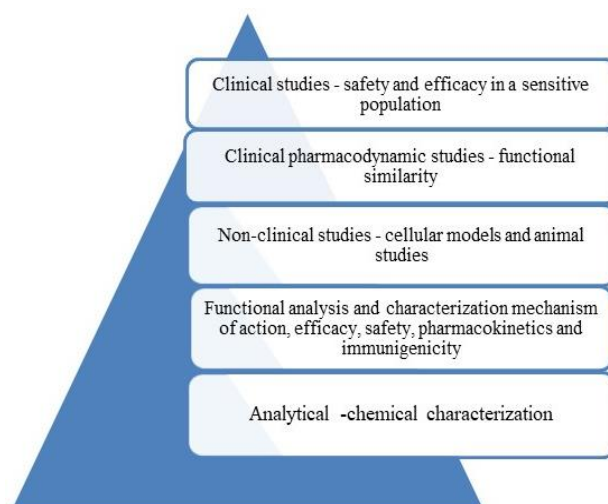
biosimilar are required in extensive detail. Evaluations include the amino acid sequence of the molecule, structural conformation, and target binding factors and nonclinical evaluation of activity, clinical assessment of pharmacokinetic and pharmacodynamic properties, and evidence of comparable clinical efficacy and safety with the original product. Based on the combination of this evidence, supporting structural and functional similarity and equivalent pharmacologic properties and efficacy, biosimilar

medications, including those for the reference trastuzumab, have been approved for use in multiple indications.

Trastuzumab is a monoclonal antibody that targets HER2 on the surface of breast cancer cells and inhibits dimer dependent HER2 signaling and induction of antibody-dependent cellular toxicity, among other potential mechanisms of action. Since its initial approval in 1998 for the treatments of metastatic breast cancer, trastuzumab has been studied in multiple settings for the treatment of HER2-overexpressing breast cancers. In 2005 interim analysis of combined results for NSABP B31 and NCCTG N9831 were published. Both of the included studies compared the efficacy of typical doxorubicin/cyclophosphamide therapy followed by paclitaxel given with or without trastuzumab in early stage breast cancer. Results of this study noted median follow-up of 2 years with disease free survival (DFS) hazard ratio (HR) 0.48 (CI 95% 0.39– 0.59) and OS HR 0.67 (CI 95% 0.48–0.93).8 Subsequent analysis noted a long-term DFS (HR 0.60) and OS (HR 0.63) advantage when adjuvant chemotherapy was given in combination with trastuzumab. These trials, combined with others, confirmed trastuzumab as standard

of care in combination with chemotherapy followed by trastuzumab alone to complete 1 year of therapy. In the metastatic setting, trastuzumab was shown to produce a large increase in objective response rate, time to progression, and OS when given in combination with chemotherapy, either doxorubicin and cyclophosphamide or paclitaxel. The response rate in the group treated with chemotherapy plus trastuzumab was 50% versus a response rate of 32%

in those treated with chemotherapy alone. The median time to progression was 7.4 months with chemotherapy plus trastuzumab compared with 4.6 months with chemotherapy alone. Similarly, OS was increased to 25.1 months with the addition of chemotherapy versus 20.3 months with chemotherapy alone.



**Figure 3:** (Biosimilar Development And Approval Schematic leading to ‘Totality Of Evidence’)

**Table 5:** Five Trastuzumab Biosimilar Medications Approved Currently)

S. no.	Name of drug	Approval year	Brand name	Treatment
01	Trastuzumab-dkst (MYL-14010)	In Dec 2017 by US FDA	Ogivri	HER2-overexpressing metastatic setting and HER2-overexpressing metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma.
02	Trastuzumab-pkrb (CT-P6)	In Dec 2018 by US FDA	Herzuma	HER2-overexpressing breast cancers in the adjuvant and metastatic setting.
03	Trastuzumab-dttb (SB3)	In Jan 2019 by US FDA	Ontruzant	HER2-overexpressing metastatic breast cancer and g metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma.
04	Trastuzumab-gyyp (PF-05280014)	In March 2019 by US FDA	Trazimera	HER2-overexpressing metastatic setting and HER2-overexpressing metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma.
05	Trastuzumab-anns (ABP980)	In June 2019	Kanjinti	Similar to Trastuzumab

**Methods**

The five trastuzumab biosimilar medications currently approved for the US market with consideration of data leading to overall evidence supporting similarity to

trastuzumab. Additional trastuzumab biosimilars are in development in both Europe and the US, however, these have not yet gained approval for utilization. Of note, the clinical comparison of biosimilar trastuzumab with the originator product was based on demonstrating statistical





equivalence in well-established endpoints derived from meta analyses of prior clinical trials. Such endpoints included overall response rate (ORR) and progression free survival (PFS) in advanced HER2-positive breast cancer and pathological complete response (PCR) rate in the neoadjuvant setting for primary HER2-positive breast cancer. Safety was assessed by measuring adverse events (AE) and immunogenicity was evaluated during and after the trial.

## DISCUSSION

Trastuzumab is a monoclonal antibody that binds to HER2 to inhibit cellular proliferation and activate antibody-dependent cell mediated toxicity thereby exerting antitumor activity. This mechanism of action is preserved across trastuzumab's indications for HER2-overexpressing early stage breast cancer, HER2-overexpressing metastatic breast cancer, and HER2-overexpressing metastatic gastric or GEJ adenocarcinoma, in all cases, HER2 remains the target.

The approval of biosimilars is based on the totality of evidence demonstrating similarity to the reference medication, clinical data is only typically available for one indication of the reference production. Therefore, biosimilars are often approved for multiple indications, that are held by the reference product, without available clinical evidence for all indications. This is probably the most unfamiliar concept in the approval process for biosimilars. This unique aspect of approval does create a significant barrier to the utilization of biosimilars because of the misconceptions of the level of evidence. However, given the evidence required to establish a product as a biosimilar, the scientific evidence to support such extrapolation is typically available. In order to establish a product as a biosimilar of trastuzumab, it must undergo analytical testing to establish structural and functional similarity. For each of the approved trastuzumab biosimilars, these analytical factors have been found to be the same or highly similar to the reference trastuzumab. Structural similarity requires that preclinical data demonstrates that the biosimilar structure is virtually identical to the original product with regard to amino acid sequence, final protein product including the three-dimensional structural confirmation, and Fc binding regions. Once established as being structurally similar to trastuzumab, biosimilars are then subjected to HER2-binding assays, inhibition of proliferation assays, and antibody-dependent cellular cytotoxicity assays in order to establish functional similarity to trastuzumab prior to any clinical testing. The rigorous establishment of similarity allows for utilization of clinical trials designed with short term primary endpoints, including OR as seen in the HERITAGE study and CR as seen in studies for CT-P6, and secondary end points such as PFS and DFS that can be measured at long-term follow-up.<sup>12,16</sup> The clinical trials discussed have all provided similar outcomes for the respective biosimilars tested against trastuzumab. In combination, the analytical establishment of these

biosimilars as structurally and functional similar to trastuzumab and the clinically proven equivalent efficacy allows for the extrapolation that these biosimilars will also perform in an equivalent manner in other settings when HER2 is the target. For this reason, MYL-14010, SB3, PF-05280014, and ABP-980 gained approval for all of the indications originally proven for trastuzumab. Only CT-P6 (Herzuma) is not approved for use in metastatic gastric cancer because this indication was not sought in the amended FDA approval application. The FDA has recently provided guidance on the extrapolation of biosimilars to indications not formerly studied. In the context of biosimilars, extrapolation is not based on the assumption that the data from one study or population is sufficient to support approval for multiple, non-studied, indications. However, in keeping with the abbreviated approval process supported by the overall evidence, extrapolation is based on all of the available data on the biosimilar, previous findings of safety and efficacy for other approved indications of the reference product, and the knowledge of various scientific factors for each indication. The scientific factors that are studied during establishment of bio similarity include mechanism of action, pharmacokinetics, pharmacodynamics, and immunogenicity and allow for the FDA to extrapolate safety and efficacy of a biosimilar to indications or populations not formerly studied. Safety and efficacy have been established for trastuzumab in neoadjuvant, adjuvant and metastatic breast cancer, and metastatic gastric and GEJ tumors. Based on the FDA's guidelines for extrapolation, additional indications not based on clinical trials were approved for the discussed trastuzumab biosimilars. Clinically, it can be a challenge to approve the use of an oncological medication without well-established efficacy that is based on clinical trials. The traditional model would have clinical trial evidence to support each individual indication. However, reviewing the experiences with previously marketed biosimilar medications, it is reassuring that extrapolated indications have later been supported by trial data.<sup>20</sup> For example, INN filgrastim (Zarzio, Kundl, Austria) was approved in Europe for all indications of the reference filgrastim based on analytic data in combination with a study of patients with breast cancer who had chemotherapy-induced neutropenia. Following release in the European market, additional studies have demonstrated safety and efficacy in extrapolated indications including stem cell mobilization. It is possible that similar comparison studies will be conducted, to confirm the efficacy of trastuzumab biosimilars for the extrapolated indications. Interchangeability, switching from the reference trastuzumab to a biosimilar or vice versa, is a separate issue. In the US, establishing a product as a biosimilar to the reference product does not mean it is interchangeable. Following FDA guidelines, to establish interchangeability a biological product must be a biosimilar of the reference product, it is expected to have the same clinical results as the reference product in any given patient and, if the product is administered over time, the risk of safety or diminished efficacy of alternating or switching between



the reference and biosimilar products must not be greater than the risk of using the reference product without switching. Of note, in the US, interchangeable products can be substituted for the reference product without prescriber involvement, although this is regulated at the state level. Normally, establishing a biological product as interchangeable requires scientific evidence based on a 'switching study' where the pharmacokinetic, pharmacodynamics, and immunogenicity are compared between the reference product and a group that switches between the reference product and the proposed biosimilar. Currently, to the best of our knowledge, none of the US-approved trastuzumab biosimilars are labeled as interchangeable. Despite approval of five trastuzumab biosimilars by the US FDA, market launch and availability has been halted due to remaining patents on Herceptin, the trastuzumab originator drug marketed by Genentech, South San Francisco, CA, USA. The trastuzumab patent is set to expire mid-2019 making it very likely that trastuzumab biosimilars will be launched shortly after this in the US. Sales of trastuzumab biosimilars are expected to lead to cost savings overall. Herceptin has previously been the only available trastuzumab on the market with a cost of approximately US\$70,000 for 1 year of treatment, the standard treatment duration for early stage HER2 breast cancers. For many patients, high copays, or out-of-pocket expenses, make this standard of care treatment cost prohibitive. While biosimilars are expensive to develop and market, the addition of alternatives to branded trastuzumab will introduce market competition and a projected cost savings of 20–30%. This cost savings appears modest in comparison with the 80–90% cost savings of typical generic medications. The development costs of a biosimilar are markedly different than those involved in bringing a generic small molecule drug to market. Of note, in many markets, the utilization of branded trastuzumab has been historically limited due to cost. Therefore, a competitive market combined with modest cost savings is expected to allow for greater access to HER2 monoclonal antibodies in the US and globally. Ultimately, the economic impact and access expansion will depend on the market price of biosimilars, provider utilization, and insurance acceptance. We remain optimistic about overall cost effectiveness allowing for improved patient access and savings over time. While the utilization of trastuzumab has revolutionized the treatment of HER2-positive breast cancers over the years, some limitations remain. For instance, HER2-targeted antibodies do not cross the blood brain barrier and tumor resistance to trastuzumab is well described. In addition, they traditionally lack efficacy as a monotherapy and are instead given in combination with chemotherapy which limits utilization in certain patient populations. Trastuzumab biosimilars will have similar limitations. Studies investigating both bispecific and trifunctional antibodies are ongoing in attempts to overcome resistance. In addition, future alterations in the Fc binding regions may allow for expanded utilization of trastuzumab. These investigations allow for future areas of investigation

for trastuzumab biosimilars. There are five currently approved trastuzumab biosimilar medications available in the US for use in both HER2-overexpressing adjuvant breast cancer and metastatic breast cancer treatment (Table 1). The development and testing of these medications included rigorous analytical testing of the structure and binding function in order to establish them as biosimilars of trastuzumab. In gaining approval this data, along with clinical data, demonstrating similar efficacy and safety compared with trastuzumab was reviewed. These characteristics of biosimilars allow for more rapid approval and the potential for significant cost savings and expanded patient access to targeted therapy for breast cancer.

## RESULTS

The utilization of trastuzumab biosimilar medications is of particular interest in HER2-positive breast cancer as these drugs have the potential for cost savings and increased utilization/access to HER2 targeted therapy in both early stage and metastatic HER2-positive breast cancers. Five trastuzumab biosimilars: MYL-1401O (Ogivri), CT-P6 (Herzuma), SB3 (Ontruzant), PF-05280014 (Trazimera), and ABP980 (Kanjinti), have now been approved by the US Food and Drug Administration (FDA) for use in HER2-positive breast cancers. This review provides an overview of these agents with special consideration of the development and approval process, including available clinical data results for these trastuzumab biosimilars.

## CONCLUSION

The production of biopharmaceuticals involves complex processes and includes the development of an engineered cell line, the production of the active substance through large scale culturing of cells, the purification of the protein including a wide variety of downstream processing steps, and its formulation. Consequently, any two independently developed biopharmaceuticals starting from the same DNA sequence will be characterised by particular differences in composition. Approval of biosimilars is contingent upon a full and detailed demonstration of pharmaceutical quality, a comparative analysis with a reference product, limited non-clinical and clinical evaluations, and a post-approval follow-up. In the absence of specific data concerning interchangeability, any measures taken, e.g. by health insurance companies and/or reimbursement authorities, to control budgets by stimulating the use of less expensive biopharmaceuticals should contain a mechanism that prevents switching between products in a patient. There are five currently approved trastuzumab biosimilar medications available in the US for use in both HER2-overexpressing adjuvant breast cancer and metastatic breast cancer treatment. The development and testing of these medications included rigorous analytical testing of the structure and binding function in order to establish them as biosimilars of trastuzumab. In gaining approval this data, along with clinical data, demonstrating similar efficacy and safety compared with trastuzumab was reviewed. These



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**Source of Support:** The author(s) received no financial support for the research, authorship, and/or publication of this article.

**Conflict of Interest:** The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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