

## An Analysis on Biosimilars

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**ABSTRACT:** Production of biosimilars, similar to the original pharmaceuticals that faces certain challenges like possible need for unique naming to differentiate the various biopharmaceutical products, regulatory framework and commercial opportunities have made the researchers in head over heels to design the appropriate one. Clinical applications have to be the main target that relies on cost-effectiveness and market value.

**KEYWORDS:** biosimilars, biopharmaceutical products, clinical applications, market value.

### 1 INTRODUCTION

Given that biosimilars are agents that are similar but not identical to the reference biopharmaceutical, this study aims to introduce and describe specific issues related to the economic evaluation of biosimilars by focusing on the relative costs and effectiveness of biosimilars.

A biosimilar product is defined in the US as one that is “highly similar to the reference product notwithstanding minor differences in clinically inactive components” and for which there are “no clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency.”

biosimilars are “similar but not the same” or in other words biosimilars are “the twin but not the clone” to the original biologic innovator product.

#### 1.1 CHALLENGES IN BIOSIMILARS

- i) Verification of the similarity,
- ii) The interchangeability of biosimilars and innovator products,
- iii) The possible need for unique naming to differentiate the various biopharmaceutical products,
- iv) Regulatory framework,
- v) Commercial opportunities as well as guidelines to assist manufacturers in product development,
- vi) Intellectual property rights, and
- vii) public safety.<sup>2</sup>

### 2 PHARMACOVIGILANCE OF BIOSIMILARS

Pharmacovigilance, as part of a comprehensive risk management programme, will need to include regular testing for consistent manufacturing of the drug. The most critical safety concern relating to biopharmaceuticals (including biosimilars) is immunogenicity.<sup>2</sup> Pharmacovigilance is important in the biosimilars market because of the limited ability to predict clinical consequences of seemingly innocuous changes in the manufacturing process and the scientific information gap.<sup>2</sup>

### 3 FUNDAMENTAL DIFFERENCES FROM GENERICS AND ASSUMPTIONS FOR BIOSIMILARS

Webber defines follow-on (protein) biologics as products that are intended to be sufficiently similar to an approved product to permit the applicant to rely on existing scientific knowledge about safety and efficacy of the approved reference product.<sup>10</sup>

As a number of patents for biologic products are to expire in the next few years, the subsequent follow-on products have generated considerable interest within the pharmaceutical/biotechnological industry as biosimilar manufacturers strive to obtain part of an already large and rapidly growing market.<sup>10</sup>

### 4 CURRENT REGULATORY REQUIREMENTS EMA

For approval of biosimilars in Europe, the EMA has issued a new guideline describing general principles for the approval of similar biological medicinal products, or biosimilars.<sup>10</sup>

Specifically, the concept papers discuss approval requirements for four classes of human recombinant products containing erythropoietin, human growth hormone, granulocyte-colony stimulating factor, and insulin. The guideline consists of a checklist of documents published to date which are relevant to data requirements for biological pharmaceuticals. In the United States, current approval pathway for follow-on biologics depends on whether the biologic product is approved under the United States Food, Drug, and Cosmetic.<sup>10</sup>

The first biosimilar molecule approved in April 2006 in Europe by the European Medicines Agency (then EMEA, now EMA) was Omnitrope, a version of somatropin. This was closely followed by another HGH, Valtropin two weeks later. To date, the EU has approved 14 biosimilars, all of which are versions of somatropin, epoetin (EPO) or more recently, filgrastim. Some early applications, (e.g. interferon alpha-2a and insulin) were not successful; either rejected or withdrawn voluntarily.<sup>4</sup>

### 5 CLINICAL APPLICATIONS

#### 5.1 APPRAISAL OF BIOSIMILAR FILGRASTIM (NIVESTIM™)

A series of rigorous analyses have now demonstrated the bioequivalence of Nivestim and Neupogen in terms of their physicochemical properties, pharmacokinetic, and pharmacodynamic characteristics, as well as their clinical efficacy and safety profiles.<sup>3</sup>

Nivestim may become a valuable and cost-effective treatment option for clinical scenarios, other than chemotherapy-induced neutropenia, where Neupogen is currently used, including severe chronic neutropenia and peripheral blood progenitor cell mobilization.<sup>3</sup>

#### 5.2 RITUXIMAB AND BIOSIMILARS

Rituximab, a chimeric IgG1 anti-CD20 MAb, is a breakthrough MAb for cancer, rheumatoid arthritis, and a wide range of immunologic illnesses. It has received formal FDA regulatory approvals for treatment of non-Hodgkin lymphoma and chronic lymphocytic leukemia and, in combination with methotrexate, as second-line therapy for adult patients with moderate to severe rheumatoid arthritis.<sup>12</sup>

Reditux, the world's first biosimilar MAb for rituximab is a special initiative. Dr Reddy's was the first to gain approval for a rituximab biosimilar in Asia, Latin America, and the Middle East. In the case of rituximab, within 3 years of launch of Reditux, the number of patients receiving this therapy increased more than six-fold in India.<sup>12</sup>

#### 5.3 CANCER IMMUNOTHERAPY

Metastasis occurs in the late stages of cancer development and partly represents the failure of both the innate and adaptive immune systems. Stimulation of the innate immune system may lead to short-term benefits, to have a long-term benefit it must be followed by DC, IL-2/LAK or similar cytotoxic cell infusion. There are many exciting mAbs and drugs developed against various immune-related receptors such as Ipilimumab or PD-1, and for controlling Treg cells and MDSCs.<sup>6</sup>

## 6 FUTURE STUDIES TO DEMONSTRATE SIMILARITY

- choose a sensitive experimental human model whereby the clinical impact of the originator product is large; thus, by comparing two large impacts, small differences can be easily appreciated
- use a homogeneous cohort of patients that eliminates the intersubject variability and allows variability to be more noticeable between the candidate biosimilars and the originator product
- choose younger patient populations to eliminate the noise from comorbid conditions in older patients;<sup>34</sup> this can lead to a smaller sample size.

There may be strategies that allow a “fingerprint”-like identification of highly similar patterns in two different products, which might be used to reduce the scope and extent of the currently required clinical studies.<sup>5</sup>

## 7 BIOSIMILAR MEDICINES

To date, biosimilars of recombinant human erythropoietins (epoetin alfa and epoetin zeta), G-CSFs (filgrastim), and human growth hormones (somatropin) have entered the European market. In the coming years, patents will expire on some major biopharmaceuticals such as interferons and insulins. Probably, this will lead to the market entry of a number of biosimilars in the near future.<sup>11</sup>

## 8 INDIAN MARKET

At present, India is one of the leading contributors in the world biosimilar market. India has demonstrated the greatest acceptance of biosimilars, which is reflected from over 50 biopharmaceutical brands getting marketing approval. The Indian biotechnology industry is also gaining momentum, with revenues of over U.S. \$ 2.0 billion in 2006, 70% of which is biopharmaceuticals. These are projected to reach up to \$580 million by 2012.<sup>8</sup>

**Table I** Approved biosimilars in Europe as of July 2012

International nonproprietary name	Indication	Reference product	Biosimilar	Price (in Belgium)	Year of approval
Somatropin	Treatment of growth hormone deficiency	Genotropin®		€28.7 per mg	1987
			Omnitrope®	€22.4 per mg	2006
Somatropin	Treatment of growth hormone deficiency	Humatrope®		€23.7 per mg	1990
			Valtropin®	–	2006
Epoetin alfa	Treatment of anemia and reduction of transfusion requirements	Eprex®		€101 (10,000 IE/1 mL)	1990
			Binocrit®	€42.49 (1000 IE/0.5 mL)	2007
			Epoetin alfa Hexal®	–	2007
			Abseamed®	–	2007
Epoetin zeta	Treatment of anemia and reduction of transfusion requirements	Eprex®		€101 (10,000 IE/1 mL)	1990
			Silapo®	–	2007
			Retacrit®	€42.49 (1000 IE/0.5 mL)	2007
Filgrastim	Prevention or reduction of neutropenia	Neupogen®		€279.3 per mg	1991
			Biograstim®	–	2008
			Filgrastim Ratiopharm®	–	2008
			Ratiograstim®	–	2008
			Tevagrastim®	€223.4/ mg	2008
			Zarzio®	€223.4/ mg	2009
			Filgrastim Hexal®	–	2009
Nivestim®	–	2010			

The above table shows the approved biosimilars in Europe as of July 2012

(Paul J Declerck, Steven Simoens, 'A European perspective on the market accessibility of biosimilars')<sup>9</sup>

## 9 COST-EFFECTIVENESS

Biosimilars have been developed for older biopharmaceuticals, for which second-generation biopharmaceuticals are now marketed and have become the standard treatment (eg, second-generation erythropoietins and second-generation G-CSFs). This implies that the cost-effectiveness of the first-generation biosimilar needs to be determined relative to the second-generation biopharmaceutical.<sup>11</sup>

The first biosimilar monoclonal antibody is likely to be a copy of the cancer drug rituximab. Initially developed by Biogen Idec in Cambridge, Massachusetts, rituximab is expected to be one of the first monoclonal antibody therapies to go off patent, which Malecki says it may do in Europe as early as 2013. It is also one of the best-sellers: in 2009 the drug earned about \$5.61 billion worldwide. In May 2011, the Israeli generics maker Teva Pharmaceuticals announced that its biosimilar version of rituximab is ready for clinical trials.<sup>7</sup>

## 10 BIOSIMILAR THERAPEUTIC ANTIBODIES

Bio-better antibodies are antibodies that target the same validated epitope as a marketed antibody, but have been engineered to have improved properties.

Second-generation antibodies are panitumumab (Vectibix; Amgen), which followed cetuximab; ofatumumab (Arzerra; Genmab/GlaxoSmithKline), which followed rituximab and adalimumab (Humira/Trudexa; Abbott), certolizumab pegol (Cimzia, UCB) and golimumab (Simponi; Centcor), all of which followed infliximab. The third-generation CD20-specific antibody obinutuzumab (GA101; Glycart/Roche/BiogenIdec) is less immunogenic than rituximab.<sup>1</sup>

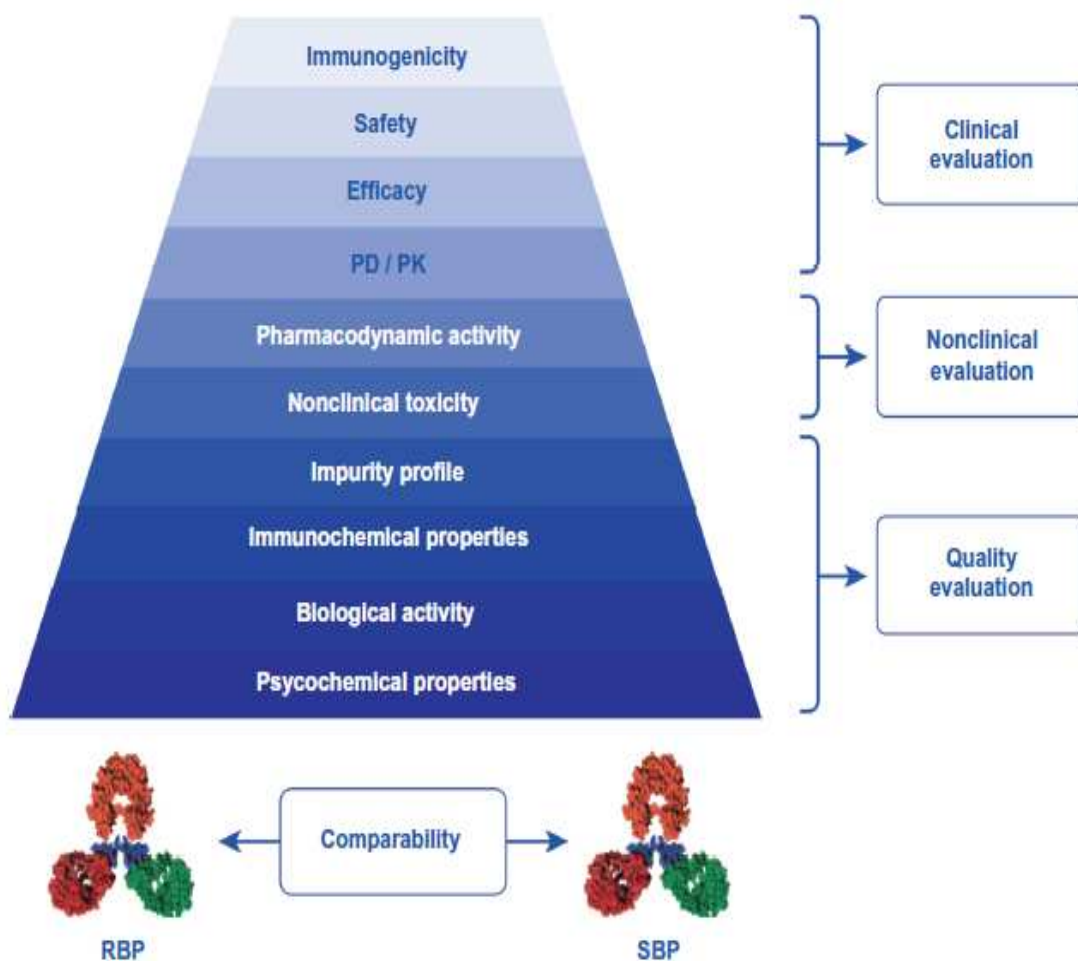


Figure 1 Comparability exercise.

Abbreviations: SBP, similar biotherapeutic product; RBP, reference biotherapeutic product; PK, pharmacokinetics; PD, pharmacodynamics.

**FIG COURTESY:** Zayrho Desanvicente-Celis, Julian Caro-Moreno, Mateo Enciso-Zuluaga, Juan-Manuel Anaya, 'Similar biotherapeutic products in Latin America. Regulation and opportunities for patients with autoimmune diseases'<sup>13</sup>

## 11 CONCLUSION

Biosimilars differ from generic drugs because their active ingredients are huge molecules with intricate structures. Such molecules are nearly impossible to replicate in every detail even in the hands of the original manufacturer, minute variations in production yield slight differences. Unlike the relatively simple construction of a small-molecule drug, making a biosimilar is more like placing a complicated family recipe in the hands of a new chef. The overall result may be roughly the same, but it is not exactly how mother used to make it and it may not precisely match the safety and therapeutic effects of the original.<sup>7</sup>

"Not a day goes by when you don't read a press release saying some company is getting into biosimilars," says Michael Malecki "The revolution in Pharmaceutical industries is going to be only Biosimilars by overcoming the challenges.Way to change the world with goodness.

## REFERENCES

- [1] Alain Beck, 'Biosimilar, biobetter and next generation therapeutic antibodies', *MAbs*. 2011 Mar-Apr; 3(2): 107–110.
- [2] Bhupinder Singh Sekhon, Vikrant Saluja. 'Biosimilars: an overview', *Dove Medical Press*, 2011:1 1–11.
- [3] Cornelius F Waller, 'Critical appraisal of biosimilar filgrastim (Nivestim™) for febrile and chemotherapy-induced neutropenia' *Dove Medical Press*, 2012:2 1–11.
- [4] Fiona M Greer, 'Biosimilar development: from science to market', *Life science technical bulletin- issue n°47 / july 2011*.
- [5] Ghaith Noaiseh, Larry Moreland, 'Current and future biosimilars: potential practical applications in rheumatology', *Dove Medical Press*, 2013:3 27–33.
- [6] Gianfranco Baronzio, Gurdev Parmar, Irina ZH Shubina, Valter Cassutti, Sergio Giuli, Marco Ballerini, Mikhail Kiselevsky, 'Update on the challenges and recent advances in cancer immunotherapy', *ImmunoTargets and Therapy* 2013:2 39–49.
- [7] Heidi Ledford, 'Biosimilar' drugs poised to penetrate market, *Nature* 468, 18-19 (2010).
- [8] Monika Misra, 'Biosimilars: Current perspectives and future implications', *Indian J Pharmacol*. 2012 Jan-Feb; 44(1): 12–14.
- [9] Paul J Declerck, Steven Simoens, 'A European perspective on the market accessibility of biosimilars', *Dove Medical Press*, 2012:2 33–40.
- [10] Shein-Chung Chow, Laszlo Endrenyi, Peter A Lachenbruch, Lan-Yan Yang, Eric Chi, 'Scientific factors for assessing biosimilarity and drug interchangeability of follow-on biologics' *Dove Medical Press*, 2011:1 13–26.
- [11] Steven Simoens, 'Biosimilar medicines and cost-effectiveness', *Dove Medical Press*, 2011:3 29–36.
- [12] Zaina P Qureshi, Jametta S Magwood, Sarveshwari Singh, Charles L Bennett, 'Rituximab and biosimilars – equivalence and reciprocity' *Dove Medical Press*, 2013:3 19–25.
- [13] Zayrho Desanvicente-Celis, Julian Caro-Moreno, Mateo Enciso-Zuluaga, Juan-Manuel Anaya, 'Similar biotherapeutic products in Latin America. Regulation and opportunities for patients with autoimmune diseases', *Dove Medical Press*, 2013:3 1–17.