

Biosimilars open up new opportunities in chronic diseases

Maria Luisa Brandi

President of the National Observatory on Fragility Fractures

ABSTRACT

The World Health Organization defines a biosimilar product as a biotherapeutic that is similar in terms of quality, safety and efficacy to an already licensed reference product available on the market. To ensure similar efficacy and safety, comparability studies for biosimilars should be carried out at quality, preclinical and clinical level. In this article we provide an overview of biosimilars, looking at the definition of the term biosimilar, the regulatory framework and the future prospects for these drugs. As biosimilar drugs will revolutionize the treatment of osteoporosis, this paper aims to evaluate the pros and cons of choosing the teriparatide biosimilar Movymia®, looking at whether it really can be considered clinically equivalent to the original drug. The benefits of biosimilars may include improving patient access and affordability. Off-patent biologics and biosimilars may also create market competition and stimulate incremental innovation by manufacturers.

KEYWORDS

Biosimilars, biobetters, biological drugs, teriparatide.

Biosimilars: definition

What is a biosimilar? A biosimilar is a biologic product that enters the market after a previously authorized version. It must have demonstrated similarity to a reference (originator or innovator) biologic drug, and must show no clinically meaningful differences from that drug in terms of safety, purity and efficacy. Biosimilar development requires a deep understanding of the reference product^[1]; this must be based on analysis and characterization of the reference product, in order to identify its key characteristics^[2]. While the primary amino acid sequence of a biosimilar is precisely bioengineered, other biologic protein structural features, such as three-dimensional folding, glycosylation, charge and impurity presence, will vary according to the manufacturing process^[3]. Around 40 different analytical methods are used to assess approximately 100 different drug characteristics for similarity between biosimilar candidates and their reference products^[3].

These analytical studies are key to the approval process for biosimilars. Once the biosimilar matches the reference product in all relevant structural characteristics, then live cloned cells are used to develop biosimilar candidates and the chosen cell line is expanded in large bioreactors, in conditions optimized for protein production^[4].

The approval of biosimilars follows the same standards of pharmaceutical quality, safety and efficacy that apply to all biologic medicines, and reference to the originator product is an integral component of the approval. Biosimilars can be manufactured when the original product's patent expires and the demonstration of similarity is based on relevant publicly available information about the reference drug.

The next question is: What is a biologic drug? Biologic products include several molecules (Table I). These products

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Contact

Maria Luisa Brandi; marialuisa@marialuisabrandi.com
Metabolic Bone Diseases Unit Department of Experimental and Clinical
Biomedical Sciences University of Florence, Viale Pieraccini, 6
50139 Florence, Italy
Tel: +39 055 7946304 - Fax: +39 055 7946302

Table I Biologic products.

Vaccines	Cells
Blood components	Monoclonal antibodies
Gene therapy	Cell signaling proteins
Tissues	

generally fall into two categories: rHuDNA-derived peptides and proteins >100 AA and monoclonal antibodies. Unlike most chemical drugs, biologic products generally derive from the metabolic activity of a living organism, either human or non-human (animal, microorganism or yeast) in origin. Biologic products are usually large, structurally complex and difficult to characterize, and inherently more variable than synthetic drugs. They are sensitive to light, temperature and susceptible to contamination. Clinically, biologics are used to treat patients with cancer, kidney diseases, autoimmune diseases and chronic diseases, such as osteoporosis.

Biologics are very expensive (in the range of tens of thousands of € per year) due to costs linked to complicated development and manufacturing processes. Biologics are often distributed through specialty pharmacies.

Biosimilars: regulatory perspectives

Biosimilars are not the same as biologics, only similar to them, as they do not have to be an exact copy of the originator molecule. This is different from the situation regarding small-molecule generics, where differences between these drugs and biologics impose differences in regulatory requirements and strong regulatory oversight (Table II).

Table II Questions about biosimilars from a regulatory perspective.

Do the development and regulatory review processes for innovators and biosimilars differ?
Why are traditional clinical studies not needed in each indication?
Are biosimilars as safe and effective as the originator product?
Are there differences in the different countries on switching and interchangeability?

As regards the development pathway of reference biologic versus biosimilar medicines, while clinical assessments (i.e. pharmacokinetics in humans, efficacy, safety) are more important than pre-clinical assessments (i.e. analytical characterization, structural properties, *in vitro* functional studies) in the development of the originator product, the opposite is true for the development of biosimilars.

Conversely, pharmacokinetic/pharmacodynamic studies in animals and toxicology analyses carry similar weight in the development of both originators and biosimilars. Thus far, in the absence of differences in biophysical properties between biosimilars and their originators, no significant clinical variation has been observed.

The innovator has established efficacy and safety for each indication, while the biosimilar, being very similar in structure and function to a reference biologic drug, does not have to re-establish, *de novo*, the relative benefit/risk balance. The purpose of a clinical program for a biosimilar is to show that any residual uncertainty from the quality assessment does not cause clinically meaningful differences in efficacy and safety and/or immunogenicity in a sensitive population.

A biosimilar sponsor is therefore eligible to apply for the indications and conditions of use that are held by the reference biologic drug, based on the totality of evidence obtained from all comparative analyses.

Taken together, analytical and functional comparisons are the foundation of any biosimilar development process. In addition, pharmacokinetic similarity is an indispensable prerequisite for any biosimilar approval. Efficacy trials should usually be designed as equivalence trials to ensure that the efficacy of the biosimilar is neither decreased nor increased compared with the reference product^[5].

The EMA has been somewhat ahead of the FDA in terms of the number of approved biosimilar products, with the first product approved in 2006, and 46 products approved to date^[6].

Once a biosimilar has been approved by a regional regulatory agency, patients and healthcare professionals can be confident that it will work the same as its reference drug, because the

quality, safety and efficacy profile of the biosimilar is highly similar to that of the originator drug.

The biosimilar approval pathways across highly regulated markets are similar, even though some differences exist. For instance, unlike what happens in the USA, in Europe, the EMA's authorization does not include a recommendation on interchangeability, with substitution policies varying between EU member states.

Pharmacovigilance is mandatory for the EMA. Indeed, pre-clinical data are insufficient to demonstrate the immunologic safety of some biosimilars, as these are derived from microorganisms, and so structural changes in the molecule are expected. One factor to consider with regard to interchangeability is whether switching between originator biologics and biosimilars or between different biosimilars can increase the risk of anti-drug antibodies, which can lead to immunologic reactions (type-I hypersensitivity and injection site or infusion reactions) and decreased drug efficacy (loss of response).

However, uncontrolled substitution can confound accurate pharmacovigilance. Moreover, it is highly possible that the risk-benefit profile established at the time of approval will change over time through expanded use, patient characteristics, and patient exposure. Therefore, awareness among prescribers and pharmacists is necessary and pharmacovigilance should be continued for biosimilars for as long as the product is on the market^[7].

Biosimilars: advantages and future developments

Biotechnologic medicines are an important part of future healthcare. Biosimilars will certainly increase the availability while reducing the direct costs of therapies. In addition, competition between off-patent biologics and biosimilars may stimulate innovation in the formulation and development of next-generation biologics, but in this case the main goal will not be cost savings. Indeed, these medicines may contribute to an expansion of medical treatment options for patients, hence concomitantly contributing to the long-term sustainability of the healthcare system.

One key point is that several large biotech and pharmaceutical companies have already entered this market or formed partnerships with smaller companies. In addition, there are several "new entries" in the areas of manufacturing, drug development and testing. Furthermore, multiple biosimilar products have been approved that will clearly compete for market shares. Moreover, the markets are not restricted to developed and highly regulated countries, but also found in other regions, such as Asia, South and Middle America, and Africa.

On the basis of the increased experience with biologics, major efforts are under way to produce next-generation biologics that have optimized efficacy and safety properties. These products are referred to as biobetters. Biobetters are regulated as new drugs and, as such, require full safety and efficacy assessment. Biobetters have been designed to improve the pharmacokinetics, bioavailability, pharmacologic actions or immunogenicity of existing biologic drug profiles^[8].

Tabella III The evolution of pharmacological treatment of osteoporosis.

1984: Oestrogen	2004: Strontium Ranelate*
1986: Calcitonin (s.c.)*	2005: Ibandronate (oral)
1990: Etidronate*	2006: Ibandronate (i.v)
1995: Alendronate	2007: Zoledronate
Calcitonin (nasal)*	2010: Denosumab
1999: Raloxifene	2011: Bazedoxifene
2000: Risedronate	2017: Abaloparatide**
2002: Teriparatide	2019: Romosozumab
*Not available on the international market; ** Not available on the European market	

Drugs for the treatment of osteoporosis

Several drugs have been developed for treating osteoporosis with the final goal of preventing fragility fractures (Table III). Four of these are biologics. Biologic drugs are highly effective but in general also costly, and thus the clinical benefits of biologic therapy are offset by challenges related to the affordability and accessibility of biologic medicines. In short, the high price of original drugs limits access to treatment, especially in low-income EU countries. The widespread use of biosimilars might significantly reduce the cost of biologic treatments, also for individual patients.

Movymia®: differences from the originator

The first biosimilar in the field of osteoporosis was developed from the biologic drug teriparatide PTH (1-34). Teriparatide - this is its international non-proprietary name - is the biologically active 34-amino acid N-terminal fragment of the 84-amino acid native parathyroid hormone, PTH (1-84). Teriparatide is a relatively simple molecule, as it is a synthetic 34-amino acid monomer and contains no glycosylation or other post-translational modifications. There exist both synthetic and genetically engineered versions of teriparatide, which show identical affinity for the PTH membrane receptors, as well as the same biologic activity.

The active substance in Movymia®, a biosimilar teriparatide, also referred as RGB-10, is produced in *E. Coli* using recombinant DNA technology; the same also applies to its reference medicinal product, Forsteo®.

In order to claim the similarity of a biosimilar teriparatide to its reference product, a thorough physical, chemical, structural and biological characterization, as well as impurity profiling, was performed^[9].

Physical, chemical, structural and biologic characteristics were analyzed, through side-by-side comparison, on three batches of the proposed product. Additionally, comparability was also demonstrated during stability and stress testing studies. The robust biosimilarity exercise allowed it to be concluded that Movymia® is biosimilar to Forsteo® from a quality perspective. The results of the quality comparability exercise

laid the foundations for the specifically designed clinical development program. The clinical development program consisted of a single-dose comparative PK study in 54 healthy premenopausal women and a multi-center phase III study conducted in Japan in patients with osteoporosis at high risk of fragility fractures. The predefined equivalence range of 80-125% for the relative bioavailabilities was met^[10]. Movymia® and Forsteo® were considered to be similar from a pharmacologic, pharmacokinetic and pharmacodynamic perspective. The design of the Japanese study was adequate to provide meaningful efficacy and safety data, including immunogenicity results^[11]. On the basis of all the findings, it was agreed that the safety profile of Forsteo® and Movymia® can be considered comparable, and therefore acceptable.

In November 2016, the EMA positively evaluated the overall benefit/risk balance of Movymia® 20 µg/80 µL solution for injection, recommending the granting of a marketing authorization for the medicinal product Movymia®, intended for the treatment of osteoporosis in adults.

Recommendations and precautions to be followed by healthcare professionals and patients for the safe and effective use of Movymia® have been included in the summary of product characteristics.

Movymia®: new opportunities

Biosimilars have significantly influenced the reimbursement system in the EU countries, as shown by increased levels of investment in the reimbursement of biosimilars. However, due to the modest cost savings with biosimilars versus generics, differences in reimbursement practices and incentives, as well as in medical practices, are observed across countries. Benefits include moving biologics to an earlier line of treatment.

Cost savings from the introduction of Movymia® in European countries have been tempered by the fact that competition has been limited to the first-generation reference product. Dynamic competition through the market entry of new teriparatide biosimilars may have an important impact in the expansion of medical treatment options for patients, hence concomitantly contributing to the long-term sustainability of the healthcare system. These benefits, when transferred to real-life scenarios, could result in wider use of biologics than the standard of care in osteoporosis.

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