Biosimilars: Change, challenge, and accomplishments

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Abstract
Since the first biosimilar product was approved in Europe in 2006, there have been many developments in the global regulatory environment, and the healthcare community's understanding and acceptance of biosimilars. However, there are still a number of challenges in developing, registering, and marketing biosimilar medicines, with the ultimate objective always being to increase competition, drive down costs, and increase access to biologic medicines. This article examines progress to date in the establishment of the biosimilar market, challenges in bringing biosimilars to patients, the impact biosimilars have had, and potential future trends.

Establishment of the biosimilar market
Various terms have been used to describe biosimilar medicinal products: "similar biotherapeutic product" (WHO), "follow-on protein" (US), "subsequent entry biologic" (Canada), and "Similar Biological Medicinal Product (Biosimilar)" (EU). However, this latter term, abbreviated to "biosimilar" captures the essence of both the opportunity and the challenge represented by this type of medicine.[1]

In this context, "Bio" indicates a biological medicinal product. These products are typically complex protein-based molecules, which may also incorporate carbohydrate and lipid moieties as well as other post-translation modifications. They are usually generated by exploiting living organisms as production systems. Biological medicines differ from small molecule medicines in a key respect as they are not produced by a defined chemical synthesis process. This results in any biological medicine having a degree of intrinsic variability. Biologic products will also have a certain amount of batch-to-batch variation, arising from variations in manufacturing process steps e.g., fermentation, cell separation/disruption, purification, filtration.

However, their complex nature also means that biological medicines can be used to treat serious and chronic conditions that are themselves complex, such as cancers and autoimmune diseases. They have the potential to address a range of unmet medical needs and are key enablers of the trend towards increasingly personalised medicine.

At the same time, the cost to develop, register, and manufacture biological medicines, along with the premium that goes with novelty and innovation, means that treatments can come with a high price tag. This is why the highest-selling biological medicines are currently generating worldwide revenues in the multi-billion euro range.

Thus, cost can be a barrier to treatment, and there is a need for enhanced competition in the market for biological medicines, as this traditionally drives down costs and increases accessibility. For small molecule medicines this competition arises from generic products, manufactured using chemically identical Active Pharmaceutical Ingredients as originator products.

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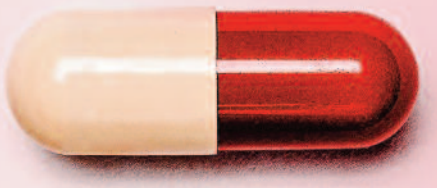

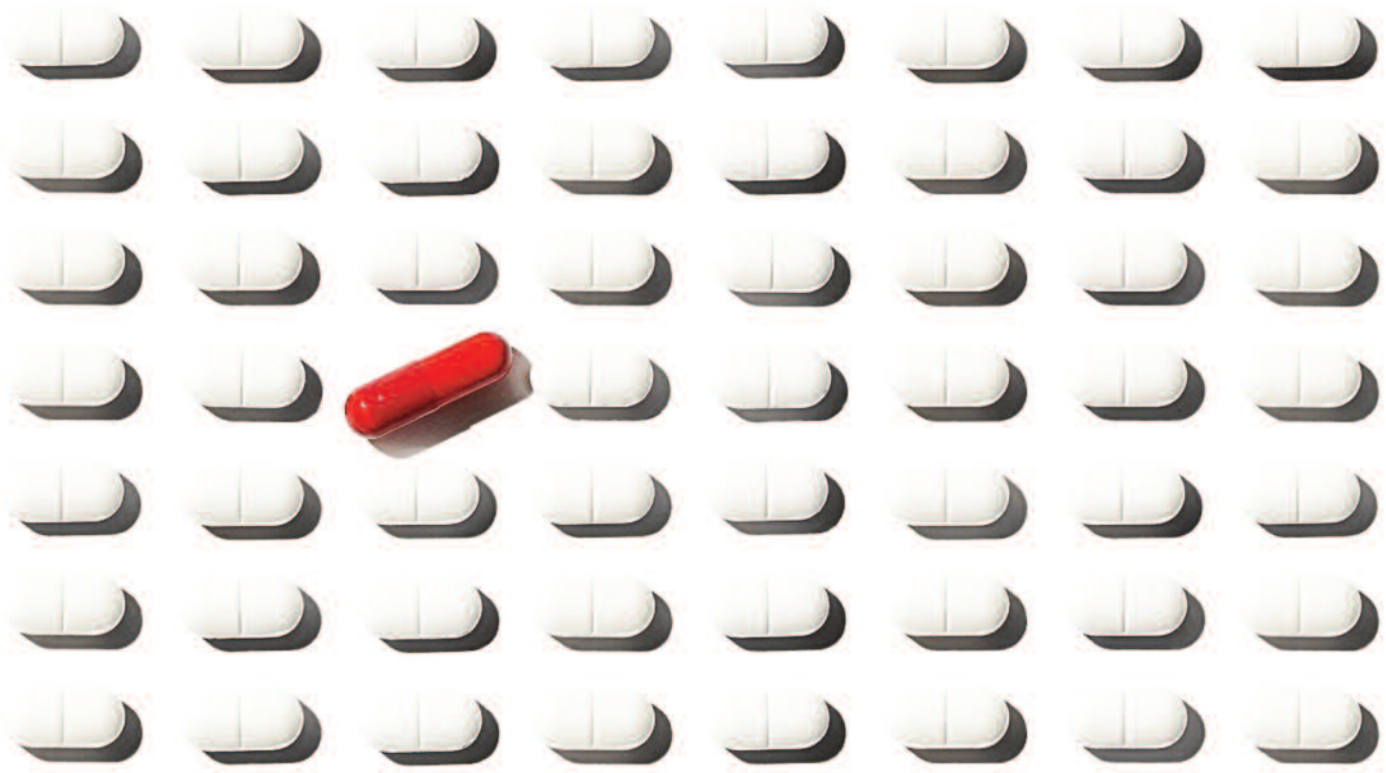

earliest biological products ran out in the early years of this century, biological manufacturers took the opportunity to develop, register, and launch their own versions of these medicines. The regulatory environment around biological medicines was also changing around this time, beginning to provide routes for establishing similarity between these new products and their original counterparts.

In 2005, the European Medicines Agency published guidance on biosimilar products, establishing:

"A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product) in the EEA."[2]

The term "similar", interpreted in line with the WHO definition, thus leads to a requirement to demonstrate "an absence of relevant difference in parameters".

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Since biological products have an inherent variation in their properties, the biologic Active Pharmaceutical Ingredient in a biosimilar cannot be identical to the reference product. This leads to the inevitable position that a biosimilar product cannot be viewed as a "generic biologic" medicine, which has significant implications for their development, regulation, and marketing.

Challenges in bringing biosimilars to patients

The ultimate objective in developing any new medicine is to provide a safe and effective treatment option for patients. However, a number of other stakeholders are involved with different needs and perspectives, which are critical to the successful development, authorisation, and marketing of a biosimilar.

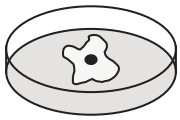
Table 1. Key terminology

Term	Definition
Biological medicine	A complex, protein-based medicinal molecule generated in a biological system
Small molecule medicine	A chemically manufactured medicinal molecule, typically <900 Daltons in size
Active Pharmaceutical Ingredient	The ingredient in a pharmaceutical product that is biologically active
Originator or reference product	An authorised biological medicine used as a reference for developing a biosimilar
Biosimilar	A biological medicine that is highly similar to the originator product in terms of biologic activity, immunogenicity, efficacy, and safety
Non-originator/non-comparable biologic	A biological medicine intended to mimic a reference product that has not been through a rigorous comparability exercise with the reference product

Analytical characterisation

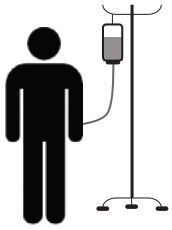
- State-of-the-art validated analytical methods and appropriately qualified characterisation methods must be applied to demonstrate the similarity of the quality attributes of the biosimilar and reference products.
- Addressing the biophysical and biochemical properties of the Active Pharmaceutical Ingredient, the biological activity, assessment of product and process impurities, and (where applicable) immunochemistry.
- Together, these data provide the justification for allowing reduced clinical and non-clinical submissions, so are expected to comprise over and above the amount of data usually submitted for a biological medicine.

Non-clinical evaluation



- The minimum requirement is a head-to-head repeat-dose toxicity study carried out with the final formulated biosimilar product.
- The precise requirements and balance of in vitro to in vivo studies will be driven by the category and complexity of the biosimilar product. However, overall, they must add to the comparability exercise and be designed to show any differences between the reference and biosimilar product.
- Informed by the characterisation data and knowledge of the manufacturing process, more limited studies may be justified compared to a novel biological medicine.

Clinical evaluation



- Clinical data required encompass pharmacokinetics, pharmacodynamics, efficacy, safety, and immunogenicity, generated using the final formulated biosimilar product. Studies must be designed to be sensitive enough to detect any relevant differences between the reference and biosimilar product.
- The volume of clinical information required is usually significantly less than for a novel biological medicine, but similar efficacy to the reference product must be demonstrated in an adequately powered, randomised, controlled trial, with appropriate blinding, and the safety profile data must be characterised in a sufficient number of patients.
- Equivalence study designs (with upper and lower comparability margins) are preferred, but non-inferiority designs (with only one margin) may be considered if appropriately justified. The comparability margins must be justified on the basis of clinical relevance, such that the margin represents the largest difference in efficacy that would not matter in clinical practice.
- Safety data can be expected mainly to detect frequent and short-term adverse events, but further close monitoring of clinical safety is usually necessary in the post-marketing phase.

Figure 1. Key steps in demonstrating comparability of a biosimilar to the reference product

Who are the stakeholders for (biological) medicines and what do they want?

- **Patient**: to receive the most effective treatment with minimal side effects
- **Healthcare professional**: to provide the best clinical outcomes for their patients
- **Payer**: to manage their budgets by selecting the most cost effective, appropriately efficacious treatment
- **Manufacturer**: to provide efficacious treatments for patients at a price level that sustains their business model

Since no two biologic products can be truly identical, a comprehensive comparability exercise is required to demonstrate that the biosimilar has no relevant differences from the originator or reference product in terms of quality, safety, and efficacy, with respect to the same indication. The reference product itself for this exercise must be selected carefully. Some considerations include:[1]

- The dosage of the reference must be identical to the proposed biosimilar.
- The same reference must be used throughout the development of the biosimilar product, therefore a source and supply strategy for the reference is critical.
- The reference and proposed biosimilar product must have a demonstrably similar Active Pharmaceutical Ingredient. Given that the reference will almost certainly only be obtained as the finished drug product, likely with additional excipient materials, this must be factored into the characterisation strategy for the comparison.
- Usually, the reference must be registered in the same territory to which the biosimilar product application will be made, although this requirement does vary across markets.
- The reference product must be established over a sufficient period of time, in a sufficiently high patient population, and have been registered with a full dossier (i.e., it cannot be a biosimilar itself).

A company intending to develop a biosimilar product must therefore be able to make the considerable investment in expertise, facilities, and technology to create a biological medicine manufacturing process, analytical strategy, and clinical study approach. The process design and development must be carried out with the objective of yielding an output that corresponds

to the perceived target product profile of another manufacturer's product – but in the absence of any proprietary information.

This comparability exercise must demonstrate that the biosimilar product and the reference product are highly similar.[1] The key parts of this demonstration are summarised in Figure 1.

Bringing a biosimilar to market

Beyond the technical challenges involved in developing a biosimilar product and generating all the data required for approval, manufacturers must overcome regulatory (and potentially legal) barriers before attempting to gain sufficient market access and uptake to justify their initial investment. Regulatory and legal challenges have been particularly acute in the US market, where the abbreviated application pathway for biosimilar products did not come into force until 2010 and it was 2015 before the first biosimilar was approved. Furthermore, some approved biosimilar products in the US are not yet on the market, due either to ongoing patent litigation, or 'pay for delay' deals, whereby manufacturers agree to delay the launch of their products in the US in return for some benefit, such as earlier access to European markets.[3]

In terms of market access, a number of different factors influence a biosimilar product's progress and there is wide variation in policies and guidelines across markets. For example, in some countries biologic medicines have to go through a Health Technology Assessment, while in others this is not a requirement. Similarly, there are differences in tendering processes, the approach to International Non-proprietary Name prescribing, and substitution.[4]

Ultimately, uptake is dependent on not only the availability of a biosimilar product to prescribers, but also the level of trust and understanding healthcare professionals and patients have in the product. Thus, education and appropriate marketing also play a critical role in ensuring a biosimilar medicine, once authorised, actually reaches patients who can benefit from it, and has the desired impact of driving competitive pricing in a market.

Impact of biosimilars on global markets

Since the ultimate objective of introducing biosimilar medicines is to increase competition, drive down cost, and increase accessibility, the key question is: how successful have biologics been in achieving this objective? In addition, it is important to understand what the future trends may be in biosimilar development. The earliest biosimilar products will soon reach the age that their respective originator products were when used as reference; is there any indication that this coincides with reduced momentum in the introduction of new biosimilar products?

The current biosimilar market

Currently, biosimilars are growing worldwide, with product approvals increasing tenfold in the last ten years. In 2018, the EMA authorised 17 products,[5] the FDA approved seven,[6] taking the total numbers to 59 and 17 respectively. These represent the highest number of approvals in a year, to date.

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Biosimilar products are available to treat a growing range of conditions, with corresponding increasing breadth in types of molecules and modes of action (Table 2).

The regulatory authorities of the larger pharmaceutical markets in the world are broadly aligned with the approaches to biosimilars described by the European Medicines Agency in 2005. Other regulatory authorities have been slower to provide formal guidance, notably in Japan (2009), Canada (2010), Brazil (2010) and the US (2010).[7] China has recently adopted guidance (2015), and although applications are under review, no biosimilar products have yet been approved in this territory. As these regulatory approaches are clarified and harmonised, barriers to biosimilar development and authorisation are reduced, increasing the attractiveness and scale of opportunity to potential manufacturers.

There are also some emerging markets with less mature regulatory environments and more flexible approaches to international intellectual property considerations. Consequently, some countries have seen the development of "non-originator" or "non-comparable" biologic medicines, which have not undergone a rigorous comparability exercise with the reference product. For example, Reditux was approved in India in 2007 as a "similar biologic" without ever having been studied head-to-head versus the anti-CD20 monoclonal antibody reference product (rituximab). The approval was instead based on a single phase II study conducted in 17 patients.[8] This raises obvious concerns regarding the insufficient evidence available on the efficacy and safety; however, products such as these will undoubtedly be impacting on the market in these territories.

As the most mature biosimilars market, Europe provides a good indicator of the impact they may be able to achieve around the world. A recent report identified the following key findings:[9]

- There has been a demonstrable decrease in price when biosimilar products enter the market place.
- The biosimilar product does not need a large market share for a reduction in price in the treatment area to occur.
- There do not need to be multiple biosimilar products available within a class to see price reduction in the total market.
- In some classes, reduction in the price of the originator reference product can reduce the impact of the biosimilar product in terms of market penetration.
- Where multiple biosimilar products are available in the same class, the first to market typically secures the highest market share.

Influencing factors and potential future trends

A number of different factors currently influence, or have the potential to influence, the scale of the continued opportunity for biosimilars and their continued attractiveness to manufacturers and investors. In turn, these trends will influence the future direction of the market and the further impact biosimilars can have on competitiveness, pricing, and accessibility. For example, the potential for combination therapies and personalised medicine, particularly in oncology, encourages manufacturers to develop a portfolio approach in their chosen disease areas. The addition of biosimilars to such portfolios potentially allows for easier development of treatment regimens involving multiple biological medicines, without the need for complex cross-manufacturer collaborations.

Manufacturers of originator biological medicines are adopting a range of tactics to maximise the return on their investments, many of which drive innovation or reduce prices e.g.,:

- Developing a next-generation medicine or 'biobetter' to supersede the reference medicine, such as Amgen's Neulasta, a pegylated version of filgrastim, which is longer-lasting due to decreased renal clearance[10]
- Modifying the reference medicine to differentiate it from the biosimilar, as Roche have done in developing a subcutaneous (SC) formulation of MabThera, which can be administered over five minutes vs. two and a half hours for the IV formulation[11]
- Making market access less favourable for competing biosimilars by methods such as price cuts, negotiating supply deals, and initiating patent litigation.

The concepts of extrapolating new indications, switching patients between reference product and biosimilar, and interchangeability of reference product and biosimilar, are important factors that influence uptake of biosimilars that are not yet fully established in all markets.

Extrapolation is when a biosimilar is approved for use in an indication held by the originator biologic that has not been directly studied in a comparative clinical trial. Regulatory approval of biosimilars for new indications is made on a case-by-case basis after evaluating the totality of evidence. However, this allows substantial scope for interpretation, meaning different regulatory agencies can reach different decisions.[12] It is also worth bearing in mind that once a biosimilar is approved, it embarks upon its own post-approval regulatory life-cycle, distinct from its reference product. So, if the safety profile or Summary of Product Characteristics of either product should subsequently change, does the established biosimilarity remain? It is not currently clear how this would be managed and regulated.

When, how, and why to switch patients from a reference product to a biosimilar is another area where understanding, opinion, and clinical practice are still in flux. A key factor influencing whether a patient switches products is who makes the ultimate decision as to which product the patient receives. The drivers of the decision will vary depending on whether it is in the hands of clinicians or payers and what incentives are in place to encourage a change, which may range from financial benefits to manufacturers providing specific data on the switching process.

Going beyond decisions about switching is the concept of treating a biologic and its reference product as truly interchangeable (much as generic medicines can be) allowing, for example, pharmacy-level substitutions. Interchangeability is a matter of ongoing debate and not yet widely established. However, in 2017, the FDA issued draft guidance[13] outlining the requirements for a biosimilar product to be authorised as interchangeable, such that "the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product".

The conditions that must be met in the application are that the biological product:

- "is biosimilar to the reference product"
- "can be expected to produce the same clinical result as the reference product in any given patient"
- "[if] administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch."

Whilst the FDA "Purple Book" lists 17 approved biosimilar products, currently none of these products has achieved the interchangeable designation,[14] thus, it remains to be seen how the future availability of interchangeable products will influence the US market.

The FDA has also recently issued a statement stressing the importance of biosimilar products in providing patients with "lower-cost, high-quality products".[15] This statement indicated a change in the FDA's guidance on separating the nomenclature of biological and originator medicines, in response to stakeholder feedback. The updated policy "will provide consistency among biologics and will help ensure health care providers and patients have confidence in the safety and effectiveness of any biological product on the market", and is intended to make it easier to monitor the ongoing safety of products. Overall, the statement reflects a positive forward-looking position on the role of biosimilars in providing cost-effective, efficacious, and safe medicines for patients.

Conclusions

The introduction of biosimilars to markets across the globe has had some success in increasing competition and reducing healthcare costs, as evidenced by review of the European market. However, the regulatory environment is still evolving, at different paces in different markets, and achieving a balance between the different needs of the various stakeholders is still a work in progress. Nonetheless, it is clear that there remains significant opportunity for manufactur-

ers, further gains to be made in terms of competition and cost reductions within healthcare systems, and scope for better treatment options to become available for patients.

Conflicts of interest

Martin Mewies is an employee of Woodley BioReg Ltd, which provides services to pharmaceutical industry clients, some of whom manufacture biologic medicines.

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Table 2. Biosimilar categories and examples

Category	Example indications	Example biosimilars
Anti-inflammatory and immune modulators	Rheumatoid arthritis	Amgevita
	Inflammatory bowel disease	Flixabi
	Psoriasis	Solymbic
	Ulcerative colitis	Zessly
Oncology targeted therapies	Wide variety of cancers e.g.,	
	• Breast cancer	Ogivri
	• Leukaemia	Truxima
	• Stomach cancer	Herzuma
	• Lung cancer	Mvasi
Hormones and cytokines	Diabetes	Abasaglar
	HGH deficiency	Omnitrope
	Anaemia	Binocrit

Abbreviation: HGH, Human Growth Hormone

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