

Journal of Generic Medicines: The Business Journal for the Generic Medicines Sector

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Journal of Generic Medicines: The Business Journal for the Generic Medicines Sector 2012 9: 187

DOI: 10.1177/1741134312470444

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Overview of the biosimilars: Strategic considerations of various issues

Alex Kudrin

Abstract

Compared to well-established generic medicines that are routinely developed using the bioequivalence approach and identical drug substances, biosimilars are developed using a step-wise comparability exercise aimed at demonstrating similar but not identical quality, non-clinical and clinical attributes. Biosimilar development is not intended to demonstrate the clinical benefits of the product as millions years of exposure data are currently available for the many originator monoclonal antibodies but rather to demonstrate a high degree of similarity against the reference using analytical and non-analytical state-of-the-art quality, non-clinical and clinical tools. It is therefore assumed that biosimilar development will be strongly based on the well-studied safety profiles of the originator product. The scope and size of the biosimilar safety database will be propelled by a risk-driven evaluation of biosimilarity and immunogenicity-attributed risks. The first driver for biosimilars is the expiry of patents for several originator biologic products with a significant revenue stream. Secondly, many stakeholders, especially payers and patients, need earlier and expanded access to affordable biologics, and biosimilars could provide substantial budget savings. With a more mature and defined regulatory framework surrounding biosimilars, a number of biosimilar players have emerged in the last few years including contract research organizations (Parexel, Quintiles), generic (Sandoz, Teva, Hospira), innovative companies (Merck Ventures, Merck & Serono, GSK, Pfizer, etc.) and even some companies with no prior pharmaceutical expertise who are moving into the biosimilar business (Samsung, LG Life Sciences, Fuji Pharma). The objective of this article is to highlight some important commercial, regulatory and developmental trends relating to biosimilars, across developed and emerging markets.

Keywords

Biosimilar, extrapolation, immunogenicity, market access, pipeline

Definition of biosimilars

The objective of this review is to provide with some analysis of values that biosimilars could deliver to worldwide clinical communities beyond those often associated with cost reductions. We should commence the discussion with appropriate definitions and setting the boundaries around what is considered “biosimilar”. Biosimilars is a biological medicine that is developed to be similar to an existing biological medicine (the ‘reference medicine’). The active substance of a biosimilar and its reference medicine is essentially the same biological substance, though there may be minor differences due to their complex nature and production methods. Like the reference medicine, the biosimilar has a degree of natural variability. When approved, its variability and any differences between it and its reference medicine will have been shown not to affect safety or effectiveness. An authorised biosimilar is generally administered via the same route of administration and

used at the same dose (posology) as the reference products in indications approved for a reference medicinal product. If there are specific precautions to be considered when taking the reference medicine, the same will generally apply to the biosimilar.

Important is that nascent biosimilar products are developed via biosimilarity development pathways and they are also approved through regulatory routes in which such a biosimilarity has been carefully evaluated using appropriate WHO and ICH (EU, US and Japan) biosimilar guidelines.

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In summary, most appropriate definition of biosimilars include the following:

1. Product with primary structure identical to the reference biological product;
2. Biosimilarity development pathway involving relevant orthogonal analytical comparability methods, non-clinical and clinical models has been utilised from the outset rather than in opportunistic fashion;
3. Quality, non-clinical and clinical attributes are sufficiently similar yet might not be identical between the biosimilar and the reference product;
4. Products that are approved by national or regional authorities using the same product label as a reference product (subject to full extrapolation of indication claims). Strictly speaking, products approved via "stand-alone" application route in absence of approved reference in the concerned country, cannot qualify as a biosimilar but can be classed as new biological product for these regions.

Based on criteria listed above, any other products developed not in accordance with biosimilarity pathways are not covered by this review. Those include products approved in pre-biosimilar legislation era or often in countries where even now there is no established biosimilar legislative framework. In addition, term "biobetter" has been confusingly used in various discussions. Because biobetters potentially may exhibit dramatically different features to those known with reference products, such as enhanced efficacy, different pharmacokinetic properties, different posology or route of administration, these products would not fall under biosimilar category and would have to follow "stand-alone" pathway for regulatory approval. Hence, inappropriate use of "biosimilar" term around products that would be normally classified as "new biological substances" can be damaging to nascent biosimilar industry striving to develop high-quality and highly similar products. Despite that the landscape of biosimilar industry nowadays is extremely complex with both biosimilar and reference companies developing biosimilar products, by setting appropriate boundaries, we could isolate values and different considerations for biosimilar products. In summary, this review is focused around biosimilars and set by our definition boundaries will exclude new biological substances, so called me-too (but not similar) biologics and "biobetters"

Value of biosimilars

The total world market for biologics was estimated to be around \$157 bn with forecast figures of \$200-210 bn

biologic sales in 2016.¹ Approximately 270 monoclonal antibodies are currently in phase II-III development phase. With improved quality and yield of cell culture production, almost 80 tonnes of monoclonal antibodies are expected to be produced by 2020. Biosimilar monoclonal antibodies will represent at least 10% of that volume. Biologic sales are expected to grow at a compound annual growth rate (CAGR) of 4.3% during 2010-16, with \$89.9 bn worth of biologic drugs due to have expired by the end of 2016, providing a significant opportunity for biosimilar manufacturers. Global biosimilar sales have doubled each year since biosimilar somatropin was first launched in Europe in 2006, growing from \$10.6 m in 2007 to \$311-693 m in 2010-2011, with the world market forecast to exceed \$2-4 bn in sales by 2015.¹⁻³ Nevertheless, the biosimilar market will constitute only around 2% of the total biologic spending in 2016 (Figure 1). Modest growth is explained mainly by remaining patent protection legislation, market exclusivity and lack of flexibility around substitution/interchangeability.

The colossal growth of healthcare expenditure on biologics will reach \$210 b by 2016 and long-term this is deemed to be unsustainable in a cost-conscious world. Despite the fact that the high cost of biologics is one of the key drivers for biosimilar growth, there are various additional factors that assist biosimilar opportunities.

Savings that can be achieved by use of biosimilars are projected to range between a conservative lower estimate of \$3.6 bn⁴ to an upper estimate of \$71 bn⁵ over the next 10 years. Emergence of both domestic and global biosimilars is accompanied by values that could be arbitrary divided in two groups:

1. Values for a global community, including patients, physicians and other stakeholders
2. Values for biotechnology industry and drug innovation.

Whilst such a division can help to appraise immediate and short-term benefits for different stakeholders, in the long-term these differences become blurred as enhancing drug innovation will invariably aid public health and the wider community.

Apart from the well-known cost-reducing benefits of biosimilar products, there are other potential scientific and commercial values (see Figure 2):

- In order to accomplish a biosimilarity exercise successfully, developers are forced to research carefully all quality and clinical features, and risks associated with the reference product.
- Need for global biosimilars has allowed for the strengthening of the legislative, regulatory and

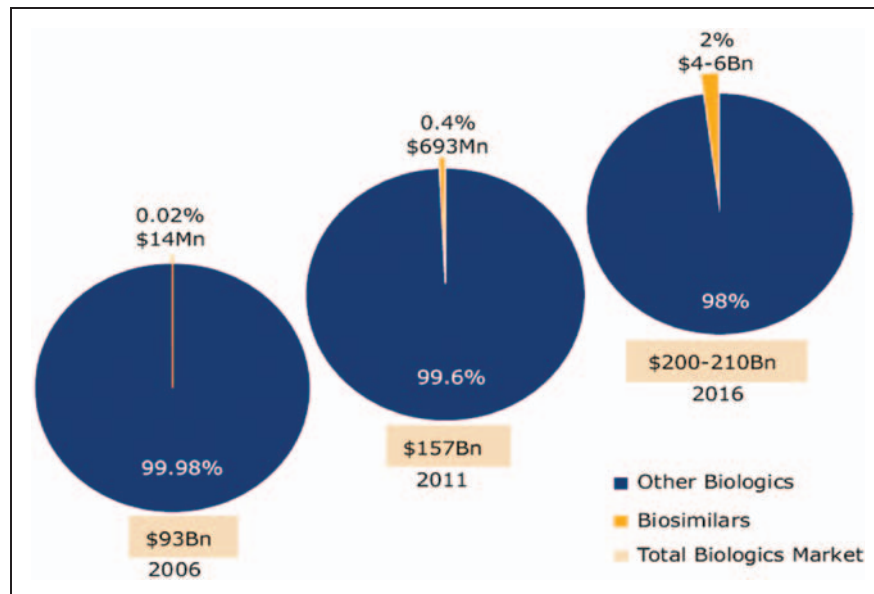


Figure 1. Global biologics spending.¹

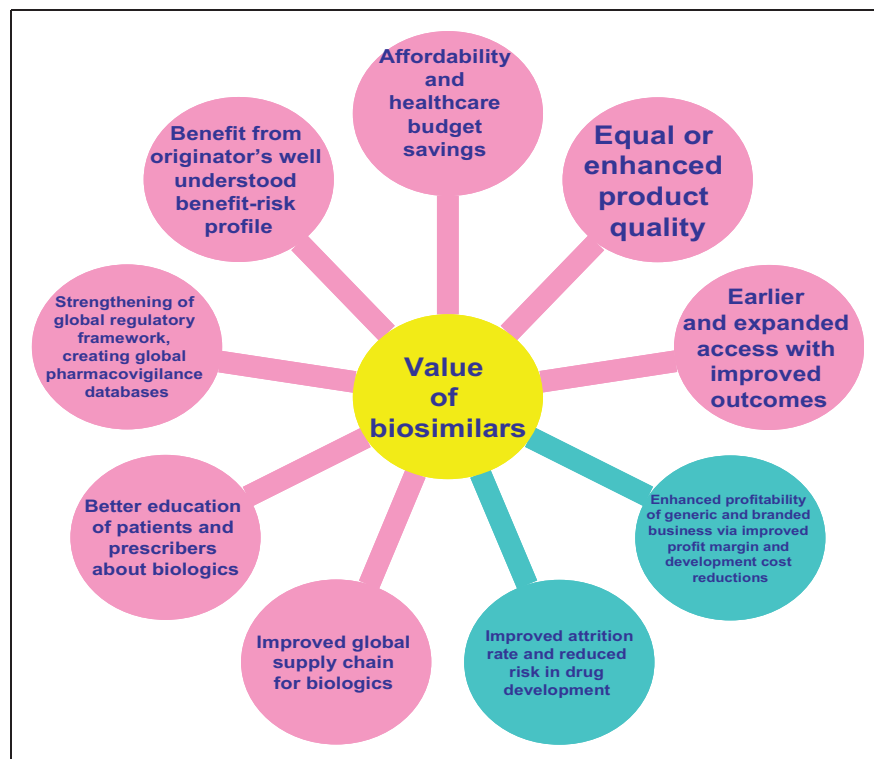


Figure 2. Values of biosimilar products for patient and industry stakeholders.

research framework at WHO, and at regional (FDA, PMDA and EMA) and country-specific levels, opening up opportunities for creating biosimilar regulatory pathways;

- Biosimilars will inevitably help regulators, industry, prescribers and patients to understand the safety and immunogenicity risks associated with biologics, opening up avenues for the earlier use of biologics

and eventually allowing for switching and interchangeability.

- There is an opportunity for biosimilar developers to create global biosimilar databases, e.g. pharmacovigilance and immunogenicity databases.
- Biosimilar developers will need to drive a global educational campaign on the use of both biologics and biosimilars especially in emerging markets where the use of biologics was, until recently, relatively uncommon.
- Significant scientific and technical progress might be made around the development of new and more convenient delivery devices. It is noteworthy that the biosimilar involvement of companies such as Samsung, LG Life Sciences and Fuji Pharma may assist in advances in this area. For example, future delivery devices may not only provide convenient and painless administration but may also allow for safety data collection and transmission as well as compatibility with other gadgets.
- Creation of a global biosimilar markets could help re-design and strengthen supply chains for all biological products.

With sales for the top 50 pharma companies' forecast to decline by 1.6% during 2010–16, many pharmaceutical companies are looking to expand into markets which offer low development costs, long-term growth, limited competition, and are of relatively low risk. One such area is biosimilars, which has attracted both innovative biologics players and generics players alike. According to Datamonitor, an average operating margin of leading branded biologics manufacturers was 28%, which is achieved due to the high value of branded biologics. In contrast, the operating margin for generics manufacturers is only 15%, due to the severe price competition which limits overall sales, despite the cost-consciousness of generics players. It is predicted that, taking into account discounted (20–35% discount) yet considerably higher than average generic pricing (80% discount) and lower development costs than those for branded products, biosimilars could provide an average profit margin of around 21%. Commercially this is attractive to generic manufacturers and this type of return can appeal to developers of originator brand products as well.

It is estimated that the total cost of developing a biosimilar is \$100 m–200 m,^{6,7} with development abbreviated to approximately 8 to 10 years compared with the 10–12 years required to develop a new biologic at a cost ranging between \$ 400 m–1.3 bn.³ Importantly, whilst there are comparability and development risks, biosimilars can benefit considerably from the well-defined risk-benefit framework

surrounding the originator products, thereby alleviating regulatory barriers. Nevertheless, demonstrating “biosimilarity” is an exercise in proving that any differences identified amongst quality, non-clinical and clinical attributes do not preclude the product qualifying as a biosimilar.

Whilst the internal attrition rate for biosimilars pipelines has yet to be determined and disclosed, the probability of technical, regulatory and commercial success is thought to be on average higher than those values with novel biologics. According to some estimates, the probability of success for a biosimilar is projected at 65% compared with an estimated 25% for a novel biologic.³

Following a stepwise biosimilarity comparability exercise, developers can alleviate the risk of failure during the clinical phase, as opposed to facing a higher level of risk with new biological products during phase III. Apart from providing patients and prescribers with high-quality affordable medicines, biosimilar products are also expected to reduce overall R&D obsolescence and increase the versatility of R&D pipelines. This is mainly because reduced development costs could free up resources to fund the development of new innovative medicines. The reduction in R&D waste is proportional to improved attrition rate, reduced regulatory, developmental and commercial risks, optimized development costs and the enhanced performance of the company in line with a low-cost R&D strategy.

Therefore, the presence of biosimilar products in the portfolio of both generic and innovative companies can complement the portfolio, enhance the diversity of developed candidates and potentially reduce the company's overall risk. Consequently, the total net benefit from biosimilars translates not only into expanded access of the patient populations to affordable biologics but also may reinvigorate R&D innovation. Interestingly, the utilization of a mixed R&D model (biosimilar and originator products) could help develop a low-cost development framework at corporate level and may assist with cost containment in the development of innovative medicines as well.

One of the interesting and long-term effects of emerging biosimilars is a “virtuous cycle” phenomenon which is conceded by reference product companies as a drive to develop new generations of highly priced super biologics with completely new efficacy and safety attributes. For example, the development of pertuzumab and trastuzumab-DM1 in breast cancer indications by Roche-Genentech could have been prompted by looming patent expiry for trastuzumab. Ultimately, continuous innovation and development of novel biological products will optimise treatment paradigm and improve clinical outcomes

shaping the future healthcare where biosimilars and novel biologics will constantly co-exist with each other.

To make the most of the biosimilar opportunity, companies will need to revise their existing business models and learn how to work in multiple partnerships adhering to a low-cost approach. It is not clear what will be considered a sustainable portfolio for the company which focuses entirely on biosimilar products.

However, due to the highly competitive nature of the market, it is thought that any new successful entrant should have at least one product registered in one geographical territory in order to generate cash and keep pace with the commercial competition of other rivals. In addition, the portfolio should contain several products at different stages of pre-clinical and clinical development with some programmes accelerated by means of co-development partnerships and alliances. Such a portfolio could diversify and reduce the risk and allow for prioritisation of programmes in accordance with the highly dynamic and competitive biosimilar landscape. Therefore, stand-alone biosimilar companies and generic companies with some biosimilar sales will find life very difficult. The economics of the generics markets and the issues specific to biosimilars suggest that the larger players are likely to be those which will succeed in the sector. It is consequently not surprising that many innovative companies have decided to enter the biosimilar business in pursuance of a low-cost and low-risk approach due to constraints in their financial and operational resources.

In the short- to medium-term, biosimilar players will need to have a presence in the EU and emerging market territories. The USA has a much larger potential addressable market for biosimilars than Europe in almost all product classes. However, due to the relative immaturity of regulatory pathways for biosimilars in the USA, the size of US biosimilar market is difficult to quantify with modest growth predicted over the next few years before the first complex biosimilar monoclonal antibodies (mAB) products are approved by FDA.

Monoclonal antibody biosimilars in the treatment paradigm of autoimmune diseases and cancers

Apart from cost considerations, other features resisting the growth of biologics include safety and immunogenicity considerations. The immunogenicity against mABs such as infliximab was reported in up to 60% of patients.⁸ The emergence of unwanted immunogenicity may result in the loss of efficacy and stepping up in treatment modality options. In some forms of autoimmune disease, such as inflammatory bowel disease, this means that patients will undergo surgery with

partial or total bowel resections. Hence, a significant burden of disability and impaired quality of life can arise as a consequence of immunogenicity. However with multiple disease-specific factors there is no clear evidence that loss of response is always linked to immunogenicity and therefore trough levels or circulating product levels are often recommended as a best measure of immunogenicity and concentration-guided treatment escalation. Development of humanized (alemtuzumab) and fully human mABs (adalimumab and denosumab) as opposed to chimeric products (infliximab) considerably alleviated immunogenicity but did not completely solve the problem. Biosimilar developers have an opportunity to develop products with equivalent clinical efficacy but reduced immunogenicity features. Even a slight advantage of the product in terms of immunogenicity might be accompanied with improved long-term efficacy outcomes. Importantly, the usual duration of biosimilar phase III studies (6–12 months) is unlikely to show these improved outcomes in the presence of modestly improved immunogenicity rates. Therefore, larger observational studies (registries) of longer duration may assist in gaining further insights on clinical read-outs of reduced immunogenicity.

A considerable body of clinical evidence has emerged in the last few years to support the so-called “top-down approach” in therapeutic management of autoimmune diseases. Early treatment (top-down therapy) with infliximab has also been compared with a conventional approach (steroids + immunomodulators, step-up therapy). A total of 130 steroid-naïve patients with recent-onset Crohn’s disease (CD) were randomized to initial therapy with infliximab and azathioprine, or to steroids and later azathioprine. Although remission rates at 1 year were similar (77% vs 64% respectively, $p = 0.15$), 19% on step-up therapy were still on steroids, compared to 0% given top-down therapy ($p < 0.001$). Endoscopic healing was higher using the top-down approach.⁹ The SONIC study randomized 508 CD patients in a head-to-head, blinded, double dummy comparison of infliximab with and without azathioprine to azathioprine alone. Infliximab 5 mg/kg at 0–2 and 6 weeks and every 8 weeks thereafter with azathioprine (2.5 mg/kg) was superior to infliximab alone for the induction of steroid-free remission after 26 weeks (57% vs. 45%, $p < 0.05$). Azathioprine monotherapy was the least effective therapy (30% steroid free remission after 26 weeks, $p < 0.01$ vs. both infliximab-based regimens). Mucosal healing (defined as the disappearance of ulcers) was higher in the combined infliximab + azathioprine treatment group compared to the two other groups.¹⁰ In contrast, preliminary data from the recent Canadian COMMIT trial showed no benefit of adding methotrexate to a combination of steroids and

infliximab for the induction of clinical remission but high remission rates were achieved in both groups.¹¹ Compared to infliximab, sufficient clinical evidence on the earlier use of adalimumab in inflammatory bowel disease (IBD) is still lacking.

Similarly, early institution of biologics in combination with conventional immunomodulatory therapies in rheumatoid arthritis has been shown to provide improved remission rates, reduced joint disfigurement and disability, enhanced quality of life and reduced probability of developing unwanted immunogenicity.¹²

Increasingly, prescribers of biologics opt for using a biologic in treating especially aggressive and severe forms of rheumatoid arthritis (RA). At present, in line with the current licensed indication, rituximab may be used in adult patients with RA who qualify for treatment with biological agents and have had an inadequate response or intolerance to one or more TNF inhibitors; patients with a contraindication to TNF inhibitors have not yet been adequately studied. However, registry and non-interventional studies have reported 17–20.5% of patients receiving rituximab as their first biological disease-modifying anti-rheumatic drug (DMARD). The current recommendation of the official rheumatology bodies is to institute biologics only upon careful optimisation of patient response to conventional DMARDs, anti-TNF agents and after completion of all comprehensive screening algorithms (e.g. excluding pre-existing Hepatitis B, C and tuberculosis) and vaccinations.¹³ Nevertheless, careful escalation of treatment in well selected patients in order to achieve more lasting remission and prevent long-term disabilities arising from sub-optimally controlled disease is an acceptable treatment approach.

As a consequence, the American College of Rheumatology (ACR)¹⁴ and the European Crohn's Colitis Organization (ECCO)¹⁵ updated their recommendations to include biologics for patients with intermediate and longer-duration RA and patients with moderate-to-severe IBD with poor prognosis and inadequate response to conventional immunomodulatory therapies. ECCO guidance on treatment of CD (2010) specifically states that "the therapeutic goal should be to induce clinical remission for every patient, but even at diagnosis it is essential to keep in mind how remission will be maintained after medical induction therapy. In clinical practice, a 'step-up' approach of adding therapies if first-line or less toxic approaches are unsuccessful within an appropriate period, is commonly used. However, decisive treatment with a potent agent ('top-down' approach) at an early stage may be preferred by the patient suffering symptoms from active disease. The choice of an induction agent depends on published efficacy, side-effect profile and familiarity, as well as the patient's views

in conjunction with the activity, location and behaviour of disease".¹⁵

In oncology, rituximab, administered intravenously in combination with other chemotherapy was demonstrated to improve overall survival compared to chemotherapy alone for patients with newly diagnosed or relapsed follicular lymphoma. An earlier inclusion of rituximab into combination regimens for treatment of follicular lymphoma and chronic lymphocytic leukaemia has been shown to extend progression-free survival, time to disease progression and increase overall survival at a 3- and 4-year period. In addition, lymphoma treatment guidelines recommend rituximab as a part of combination regimens for non-bulky stage I and bulky stages I–IV of diffuse B-cell lymphomas.¹⁶

In line with the "top-down" approach, biosimilars could assist with expanded access of newly diagnosed patients with severe and aggressive forms of autoimmune diseases and cancers to more affordable biological agents in order to achieve better long-term treatment outcomes, prevent disease-related complications, improve quality of life and reduce disability. The rivalry of numerous biosimilars will assist in further price reductions and, with improved understanding of these products, the use of biosimilars is likely to revolutionise oncology and autoimmune disease care benefiting from expanded market of biologics and "top-down" approaches (Figure 3).

Global regulatory framework

The European Medicines Agency has pioneered the legal, regulatory and scientific framework for approval of biosimilars with considerable number of scientific advice procedures on biosimilar products carried out so far, 14 products approved (as of 2011) and other ongoing assessments of biosimilar products. WHO enacted biosimilar guidelines in 2009 and its framework has been put forward into regional and national biosimilar legislation.¹⁷ The Japanese PMDA enacted biosimilar guidelines in 2009.¹⁸ Recently the FDA published a draft of new biosimilar guidelines which highlighted a step-wise comparability and case-by-case evaluation approach with biosimilars.¹⁹ Biosimilarity, as defined by the FDA, is when: "The biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components. . . [and] there are no clinically meaningful differences between the biological product and reference product in terms of safety, purity and potency of the product." In making this assessment, the biosimilar sponsor needs to realize that the assessment is made on a case-by-case basis. However, the interchangeability has not been defined by the FDA and the guidance only alludes to the fact that, in case of high similarity,

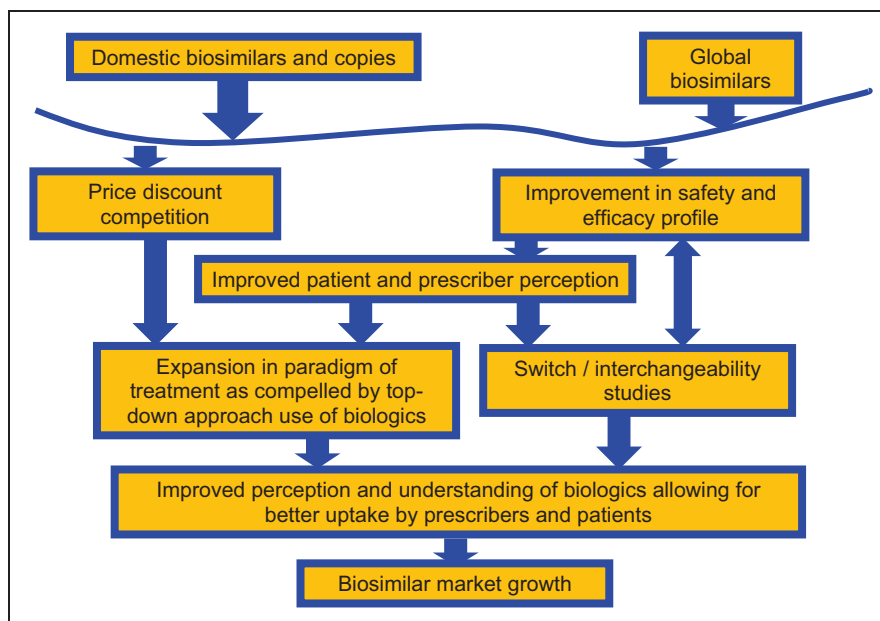


Figure 3. Why do we need many biosimilars? Note: Domestic biosimilars and copy products are defined as products developed for local markets not in accordance with appropriate state-of-art biosimilarity legislation and often in absence of locally approved reference products.

the biosimilar could qualify for interchangeable status albeit supplemented by a pharmacovigilance program required to monitor various risks emerging during post-marketing period.

Up to February 2012, the FDA had received 35 requests, held at least 21 pre-IND meetings with biosimilar sponsors and received 9 INDs for biosimilar programs.²⁰ Development program proposals included prospective global programs (including US population subsets) and “retrospective” programs proposed for products already licensed outside the US.

Specific considerations of various biosimilar guidelines were well covered elsewhere.²¹ A number of countries from emerging economies have reviewed their national legislative path for biosimilars and enacted appropriate guidance documents. Remarkably, China and Russia have not issued biosimilar guidelines and their approval follows a route established for any novel biologics (Table 1).

The cornerstone of EU and US biosimilar guidelines is a risk-based approach which is driven by a level of prior unique knowledge of reference product risk-benefit profiles on the one hand and the robustness and comprehensiveness of analytical orthogonal and fingerprint-like methods and non-analytical quality, non-clinical and clinical (PK/PD, efficacy, safety and immunogenicity) comparability data generated with biosimilar products on another hand. A biosimilarity exercise is completed pre-approval with both biosimilar and reference product destined for independent life-cycle management. However pharmacovigilance

activities with biosimilars will continue during post-marketing period including both passive surveillance and various post-marketing safety studies and registries designed to evaluate safety and immunogenicity related signals. In line with this paradigm, the approach to the evaluation of biosimilar natalizumab will be different to the one with biosimilar etanercept due to the close link between natalizumab use and the risk of progressive multiple leukoencephalopathy (PML), a life-threatening drug-related adverse reaction which can affect between 1 and 9 persons in 1000 treated patients.²² The concern from a prior knowledge perspective is whether the biosimilar developer will produce a convincing safety monitoring and risk management network which will be in line with the system established for a risky reference product, such as natalizumab.

Development Pipeline

The precise situation with the biosimilar development pipeline is difficult to evaluate with a high degree of accuracy due to fragmentary data available in the public domain. Critically and as per original definition given at the beginning of this paper, not all products included in this analysis could be regarded as true biosimilars because of differences seen in qualitative, non-clinical and clinical domains against the reference products. However, considering the original intent of the manufacturer to develop biosimilar products via the comparability approach and taking into account

Table 1. National and regional biosimilar legislation.^a

Region	Biosimilar approval pathway
EU	EMA/CPMP/BWP/3267/00; effective December 2003. Guideline on comparability of medicinal products containing biotechnology-derived proteins as active substance. Quality issues. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC_500003573.pdf EMA/CPMP/3097/02; effective June 2004. Guideline on comparability of medicinal products containing biotechnology-derived proteins as active substance. Non-clinical and clinical issues. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC_500003963.pdf CHMP/437/04; effective October 2005. Guideline on similar biological medicinal products. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC_500003517.pdf EMA/CHMP/BWP/49348/2005; effective June 2006. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC_500003953.pdf EMA/CHMP/BMWP/42332/2005; effective June 2006. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC_500003920.pdf EMA/CHMP/BMWP/14327/2006; Draft (deadline for comments July 2007). Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC_500003947.pdf EMA/CHMP/BWP/157653/2007; effective July 1, 2009. Guideline on development, production, characterization and specification for monoclonal antibodies and related products. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC_500003074.pdf EMA/CHMP/BMWP/86289/2010; Deadline for comments May 31, 2011. Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use. www.cma.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/11/WC500099362.pdf EMA/CHMP/BMWP/403543/2010; Deadline for comments May 31, 2011. Guideline on similar biological medicinal products containing monoclonal antibodies. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/n/WC500099361.pdf EMA/CHMP/BWP/617111/2010; Deadline for comments May 31, 2011. Concept paper on the revision of the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/02/WC500102285.pdf Notes: BWP, Biologies Working Party; BMWP, Biosimilar Medicines Working Party; CHMP, Committee for medicinal products for human use; CPMP, Committee for proprietary medicinal products; EMA, European Medicines Agency. EMA/CHMP/BMWP/94528/2005; effective June 2006. Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Guidance on similar medicinal products containing somatropin. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC_500003956.pdf EMA/CHMP/BMWP/32775/2005; effective June 2006. Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Guidance on similar medicinal products containing recombinant human soluble insulin. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC_500003957.pdf EMA/CHMP/BMWP/3B29/2Q05; effective June 2006. Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Guidance on similar medicinal products containing recombinant granulocyte-colony stimulating factor.

(continued)

Table 1. Continued.

Region	Biosimilar approval pathway
	www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC_500003955.pdf EMA/CHMP/BMWP/94526/2005; effective July 2006. Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Guidance on similar medicinal products containing recombinant erythropoietins. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC_500003921.pdf EMA/CHMP/BMWP/170734/2008; Deadline for comments October 2008. Concept paper on the revision of the guidance on similar biological medicinal products containing recombinant erythropoietins. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC_500003914.pdf EMA/CHMP/BMWP/102046/2006; Draft (deadline for comments April 2008). Guideline on similar medicinal products containing recombinant interferon alpha. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC50000393L.pdf EMA/CHMP/BMWP/118264/2007; Draft (deadline for comments October 2008). Guideline on similar biological medicinal products containing low-molecular-weight-heparins. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC_500003928.pdf EMA/CHMP/BMWP/403543/2010; Deadline for comments May 31, 2011. Guideline on similar biological medicinal products containing monoclonal antibodies. (Draft) www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/04/WC500099361.pdf EMA/CHMP/BMWP/94599/2010; End of consultation June 1, 2010. Concept paper on similar biological medicinal products containing recombinant follicle stimulation hormone. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/04/WC500089208.pdf EMA/CHMP/BMWP/86572/2010; End of consultation June 11, 2010. Concept paper on similar biological medicinal products containing recombinant interferon beta. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/04/WC500089210.pdf Notes: BWP, Biologies Working Party; BMWP Biosimilar Medicines Working Party; CHMP, Committee for medicinal products for human use; CPMP, Committee for proprietary medicinal products; EMEA, European Medicines Agency.
Country	Biosimilar approval pathway
USA	February 2012 Draft guidance on biosimilar development; Quality and scientific considerations in demonstrating biosimilarity to a reference product
Japan	March 2009 Biosimilar guidance by PMDA
Argentina	September 2009 Administracion Nacional de Medicamentos, Alimentos y Tecnologia (ANMAT) published biologics and biosimilar approval guidance
Australia	August 2008 Australian TGA Adopted EU biosimilar guidelines
Brazil	December 2010 Resolution 55/2010 regulates all biologic products
Canada	April 2009 Guidance on "subsequent entry biologics"
China	– All biologics, original or copy-biologics, undergo the same pathway
Colombia	– License for Manufacturing Facilities of Biological Products
India	July 2012 Department of Biotechnology issues guideline for pre-clinical and clinical evaluation of biosimilars
Malaysia	July 2008 Guidance Document for Registration of Biosimilars in Malaysia
Mexico	June 2009 Article 222 of the General Health Law
Russia	– Biosimilars are subject to the same regulations as generics

(continued)

Table 1. Continued.

Region	Biosimilar approval pathway
Saudi Arabia	December 2010
Singapore	April 2010
South Korea	September 2010
Taiwan	November 2008
Turkey	August 2008
Venezuela	August 2000
Guidelines on Biosimilars version 1.1 Appendix 17 of the Guidance on Medicinal Product Registration in Singapore Guidelines on the Evaluation of Biosimilar Products Review Criteria for Registration and Market Approval of Pharmaceuticals-Registration and Market Approval of Biological Products Instruction Manual on Biosimilar Medical Products SRPB-R Guidelines: application for Health registry of DNA recombinant products, monoclonal and therapeutic antibodies	

^aAvailable EMA concept papers are temporary documents and are normally replaced by fully-developed guidelines.

national differences in regulatory acceptance of such a product as a “follow-on or similar version”, the total figure will constitute a large number of heterogeneous products.

According to Citeline, there are currently over 300 biosimilar mAb products in development in over 200 indications including oncology, inflammatory and autoimmune diseases, metabolic and central nervous system disorders, infectious and cardiovascular disease and transplant rejection. Around 100 companies are involved in mAb development, which includes label expansion of existing therapies as well as new therapy areas.²³ Reportedly, there are around 400 biosimilar developers in China alone covering first and second generations of biosimilars and mAb biosimilars.

The vast majority of currently developed mAbs biosimilars (81%) are in preclinical development, five are currently in phase 1 or 2 and nine are in phase 3 development. According to Citeline, as of March 23, 2012, there were 31 clinical trials worldwide. The top three indications tested in pivotal trials for the corresponding reference mAbs were NHL (19%), rheumatoid arthritis (19%) and breast cancer (16%). These are essentially the same as for the biosimilar versions²³ (Figure 4).

The first biosimilar infliximab from Celltrion was recently approved in South Korea and there are plans for the submission of several applications in the EU.²⁴ Parallel regulatory submissions for this product were made in other countries and regions. Lessons learned from this first global biosimilar will validate the biosimilar regulatory framework and will guide other regulatory agencies in fine-tuning their approach to complex biosimilars.

Two domestic biosimilar mAbs are already launched, Dr. Reddy's rituximab, Reditux was approved in India in 2007, and Clotinab, Isu Abxis' biosimilar form of abciximab, was first approved in South Korea in 2006 and subsequently in Brazil, India and Jordan in 2007. However, these products are unlikely to be regarded as true biosimilars from an international point of view.

There are several global biosimilar players that already hold approved EPOs, growth hormones and G-CSF products and are currently developing a whole range of mAb biosimilars: Sandoz (with biosimilar rituximab in phase III), Hospira in alliance with Celltrion (submitted application for biosimilar infliximab and completed phase III for trastuzumab, ongoing phase II-III for rituximab and cetuximab); and Teva in partnership with Lonza and Hualida (different stages of clinical development of mAbs and interferon alfa). There are also a number of partnerships and alliances that have been created between some of the larger pharma players and domestic biosimilar developers (see Figure 5).

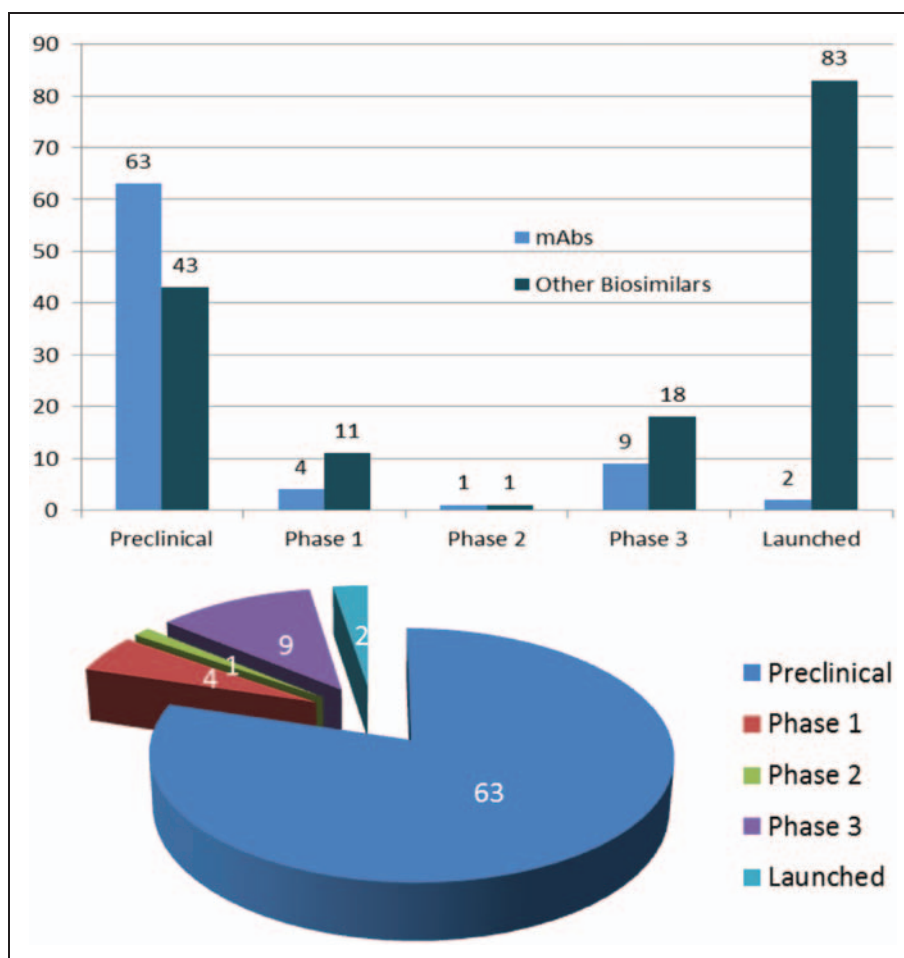


Figure 4. Biosimilar monoclonal antibodies (mAbs) by development phase.²³ Note: The statistics on biosimilar pipeline should be interpreted with caution since the dataset may contain products that are developed not in accordance with typical biosimilarity exercise or do not fall into definition boundaries set out in this article.

The biosimilar market in China has become very crowded. It is believed that, in 2010, domestic “copies” (although with most of them not regarded as biosimilars) constituted around 40% of the \$1.5 bn biologics market in China (\$670 m). These products mainly included insulins, growth hormones, erythropoietins, GM-CSF, etanercept and interferons. Over 20 companies market erythropoietins at 30% of the originators’ price, with 3SBio claiming to hold a 30% market share. The significant biosimilar market potential in China is emphasized by the large proportion of treatment-naïve patients, progress made in national medical insurance coverage and wealth growth. The first wave of products was launched often before the originator products and those include Jintropin (somatropin; Changchun GenSci), Yi Sai Pu (etanercept; CP Guojian), Qiangke (etanercept; Shanghai Celgen) and Yi Bi Ao (rhEPO; 3SBio). The second wave of complex biosimilars are advanced through phase III studies and NDA submissions in

China (trastuzumab from CP Guojian, infliximab and cetuximab from Biomabs). In the absence of biosimilar guidance in China, a number of often non-comparable biosimilar-like products were able to reach local markets with developers pursuing a primarily “China for China strategy”. Domestic players are limited in volume and quality capability in production (low yield, low commercial scale, lack of analytical skills, consistency in master cell banks and quality assurance). Some of these products were developed without direct comparison to their reference but were nevertheless approved by the Chinese FDA as stand-alone bionovels.

Biocon in alliance with Mylan, Ranbaxy, Dr Reddy’s with Merck Serono and Reliance Life Sciences are key biosimilar players on the Indian market. Celltrion, Arogen, LG Life Sciences, Fuji Pharma, Samsung, Isu Abxis, Hanwah Chemical, Green Cross and Binex are key South Korean players. A diverse range of domestic biosimilar players emerged

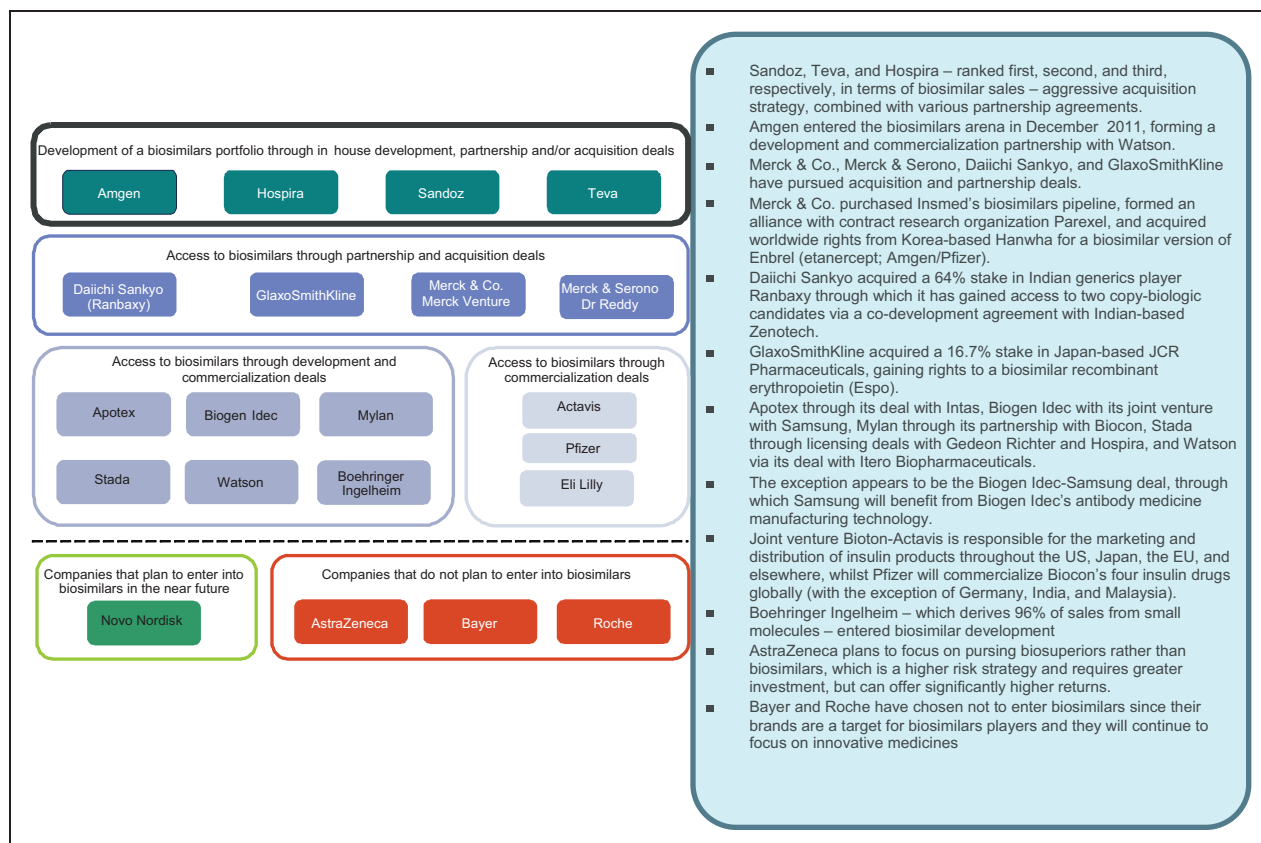


Figure 5. Global biosimilar landscape.²

in Eastern Europe, Russia (Stada, Gedeon Richter, Biocad) and Brazil (PharmaAxis and Vital Instituto). Domestic players are harnessing both domestic plans and strategies covering developed and other emerging markets. For example, whilst Embrel's patent life has been now extended in the US, many biosimilar companies (Mycenax Biotech (Taiwan), Avesthagen (India), Hanwha Chemical (South Korea), LG Life Sciences (South Korea), Daewoong/Binx (South Korea) in the emerging markets are developing biosimilar versions of etanercept to satisfy the growing demand of patients from ex-US markets for self-injectable treatments for autoimmune diseases.

Analysis of the pipeline illustrates that biosimilar space is becoming crowded with multiple products tested in the pre-clinical and clinical phase of development. A large proportion of these products are currently developed outside developed markets with the ultimate focus of positioning them in the US and the growing markets of Asia and Latin America. Most of biosimilar clinical trials are currently conducted outside of the EU and US in South Korea, India, former CIS countries, etc. reflecting a strategy of achieving approval for these products in multiple countries and containing development costs by reducing the US and EU subsets of patients.²³ Most of the companies

disclosing biosimilar mAb development plans publicly are located in South Korea and India. Given the lack of guidance for the development of biosimilars in the US over the past few years, it is not surprising that only a few US companies have publicly announced biosimilar mAbs in development. However, this will change as the US biosimilar framework takes shape.

It is clear that, in next few years, more domestic and global candidates will reach the phase III study stage with subsequent regulatory submissions made both regionally and across the globe.

Development considerations

General principles

The risk-based approach is the cornerstone of biosimilar development strategy. The scope, breadth and amount of non-clinical and clinical data are dictated by the magnitude of differences identified during CMC development and product characterisation. Principles for biosimilar development are outlined elsewhere.²¹ In brief, using prior information on reference product coupled with the outcome from analytical comparative studies, the level of toxicology and clinical data required will be assessed and determined.

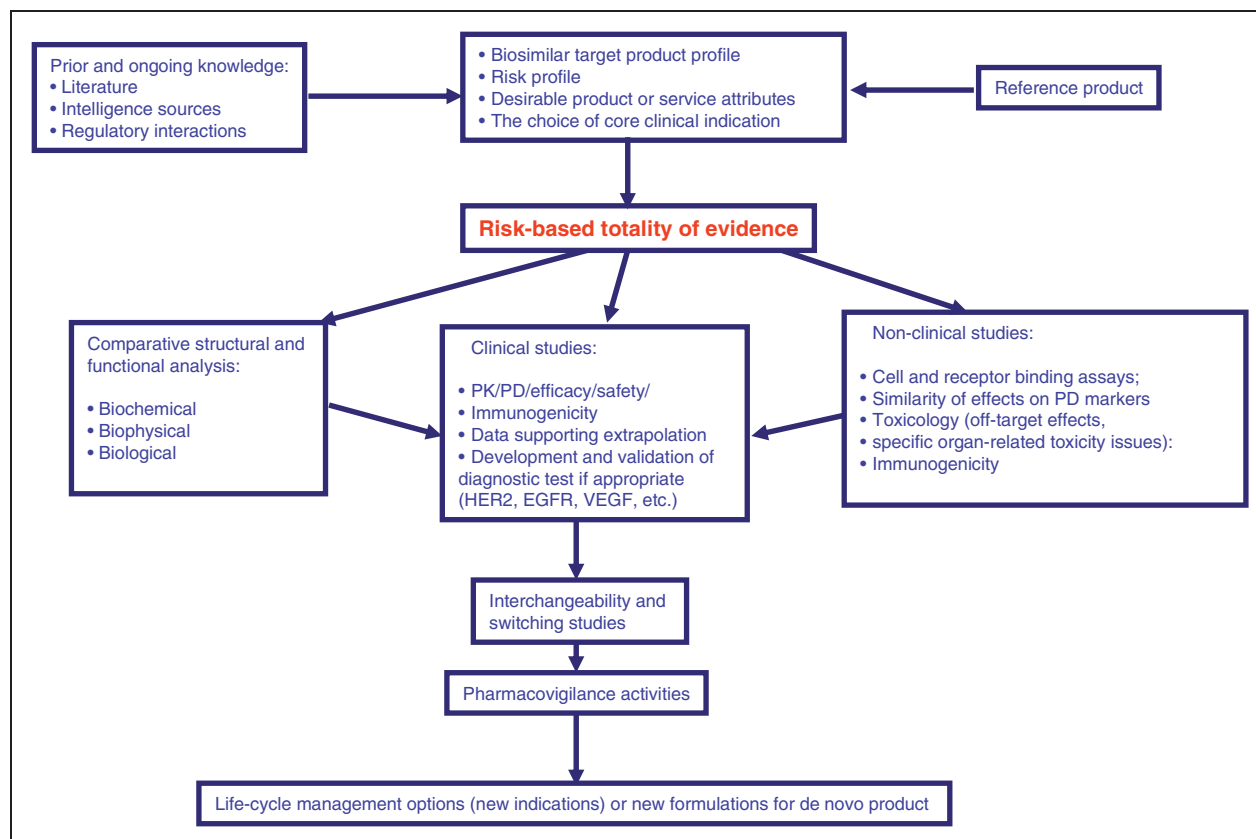


Figure 6. Roadmap for biosimilar development.

At a minimum, pharmacokinetics/pharmacodynamics (PK/PD), efficacy, safety and immunogenicity data will need to be provided in support of biosimilarity; however, other more extensive toxicology and/or clinical studies may be required, depending on prior knowledge or identified differences, especially in reference to the need to address residual uncertainties regarding biosimilarity (Figure 6).

Risk-based evaluation of the scope and amount of required non-clinical and clinical data is driven by prior knowledge and by the extent of understanding of the reference product. Target product profile and the extent of difference will determine the risk profile of the biosimilar. Non-clinical studies should be built around addressing established differences, off-target and atypical safety signals, and various data to support extrapolation of indications. The choice of core clinical indication may have an impact on biosimilar positioning as the majority of prescriber are unfamiliar with extrapolation methodology. Clinical studies may also include validation of own delivery devices and diagnostic tests. A high degree of similarity will minimise or obviate the need for interchangeability data (specifically in the US). It should be noted that interchangeability issues in the EU are subject to national authorities' legislation and reside outside of EMA

remit. Therefore EMA biosimilar path does not impose requirements for switching studies or proof of interchangeability. From FDA perspective, switching data and evaluation of switch-related immunogenicity during the post-marketing period are more likely to be required on case-by-case basis. Finally, there is nothing to prohibit biosimilar developers pursuing novel indications or new formulations which have not been explored by reference product companies. Those can be introduced onto the market as new branded products.

Most of the currently ongoing clinical programs conducted with complex biosimilars consist of one or two single-dose PK studies in normal human volunteers (designed to evaluate any trends in PK behaviour of the biosimilar analogue) and a large phase III equivalence study conducted in patients and powered for appropriate PD/efficacy endpoints or PK parameters (such as AUC/Cmax at steady-state) and incorporating various PK, safety and immunogenicity evaluations. The cost of such a program depends on the complexity and need for additional studies (e.g. separate studies for rituximab in patients with rheumatoid arthritis and lymphoma) was estimated to vary between \$0.1 and 0.5 B and would require between 1 and 4 years to complete.³

Learning lessons from the development and regulatory approval of biosimilars, the focus of scientific debate in the near future will be dedicated to the following topics:

- The acceptance and utility of non-inferiority studies in proving biosimilarity;
- Extrapolation of clinical indications for products with less understood-mechanism of action (e.g. Rituximab in autoimmune and oncology indications, Palivizumab in viral diseases, Omalizumab in asthma and other IgE related allergic diseases, and interferons in viral, autoimmune and oncology indications);
- Approach to evaluation of immunogenicity;
- Interchangeability data;
- Pharmacovigilance of biosimilars.

An overarching biosimilar guideline by the EMA is currently under revision and, as the concept paper details, the position on non-inferiority studies might be further fine-tuned in the new draft. There might be scenarios where due to the heterogeneity of the clinical condition and the highly variable performance of clinical outcomes, the conduct of equivalence studies will not be feasible. These scenarios include evaluation of overall response rates and disease-free or overall survival in oncology indications (anti-VEGF or anti-EGFR mAB) or assessment of multiple sclerosis activity (for natalizumab or interferons). In some of these complex cases, the PK-based equivalence may not be straightforward as PK/PD relationships with disease activity are not very clearly defined. Therefore, in some cases, non-inferiority studies might be allowed in the future, provided the non-inferiority margin and PK/PD/efficacy rationale are well justified.

Extrapolation of indications

According to EMA and FDA biosimilar guidelines, extrapolation of indications will be possible in some cases, if the mode of action and receptor-mediated pharmacodynamic effects are well understood and shared between several target indications. In Japan, PMDA proposed a more conservative approach to extrapolation of biosimilarity with additional indications granted only after successful re-evaluation of the post-marketing efficacy and safety data upon completing a 6-year marketing of the product in the core comparability indication. Prudently, a number of issues need to be addressed in some of the extrapolation scenarios. For example, in the absence of overall survival data with biosimilar mABs, how will prescribers and patients be able to accept extrapolation

arguments and how will the comparability and extrapolation data be communicated in the product label? There is a need to educate physicians and patients by a demonstration of biosimilarity and extrapolation of indications. Currently, only 50% of prescribers are aware of biosimilars and an even smaller number of physicians are familiar with the biosimilarity approach and specifically about previously allowed extrapolations for G-CSF. In the absence of efficacy data in extrapolated indications, some expert groups have expressed concerns. For example, the World Marrow Donor Association (WMDA) has published its recommendation not to use biosimilar filgrastims routinely in extrapolated indications in the mobilisation of stem cells, unless the donor is carefully followed and both the recipient and the donor have given the appropriate consent.²⁵

Apart from the accepted extrapolation approach with an anti-TNF inhibition for products such as infliximab, etanercept or adalimumab, there are less clear scenarios, such as the rituximab-mediated depletion of B cells in rheumatoid arthritis and lymphoma, where other potential mechanisms might be implicated in the anti-tumour effect as opposed to the effect of anti-CD20 in autoimmunity. In such cases, separate clinical studies will be required to demonstrate biosimilarity in oncology and autoimmunity indications. Apart from the comprehensive literature review on the mode of action, receptor and ligand-specific assays can help to address extrapolation approach. For example, *in vitro* and *in vivo* (animal and human tissues) evaluation of similarity and linearity in patterns of complement binding and complement-mediated cytotoxicity, Fc-receptor-mediated cytotoxicity and apoptosis could provide an additional argumentation on extrapolation of indications reducing the amount of required clinical data. Finally, PK/PD data from own clinical data as well as PK/PD modelling carried out with both prior and new clinical data could provide with extrapolation evidence.

Evaluation of immunogenicity

With regards to the immunogenicity of complex biosimilars, it is absolutely clear that development of highly sensitive and specific assays is required to underpin appropriate comparability. Immunogenicity has been especially prominent with chimeric mAB products such as infliximab with reports of up to 60% of patients developing unwanted immunogenicity within 12 months of treatment.⁸ Development of anti-mAB antibodies can in some cases result in loss of efficacy and can be associated with safety risks. The interesting dilemma posed for biosimilar developers is that the immunogenicity evaluation of some reference products

was carried in a limited fashion at the time when some of these products were developed and approved. In addition, the emphasis on immunogenicity with some products, such as oncology mABs, was less pronounced due to the relatively short-term horizon and poor prognosis in some oncology indications. Increasingly with advances in the targeted therapy of cancer, some forms of tumours are either curable or require treatment similar to those of chronic diseases. Hence, a comprehensive understanding of immunogenicity is essential in predicting treatment outcomes and planning alternative sequencing options for patients who develop anti-mAB antibodies. Therefore developers are not only required to demonstrate favourable immunogenicity profiles of new biosimilars prior to approval but dependently on regulatory scope of interchangeability attributes (e.g. US vs EU requirements) also to continue monitoring immunogenicity during the post-marketing period. Validated laboratories and kits have been developed to monitor immunogenicity with some mAB and co-marketing of immunogenicity evaluation services or products along with biosimilars, which could immensely benefit biosimilar entry onto the market.

There are no regulatory precedents for interchangeability or switching studies, which were previously conducted by biosimilar companies. As specified above, EMA does not impose interchangeability requirements although EU national authorities do not allow automatic substitution with currently approved biosimilar erythropoietins and filgrastims. The FDA does not provide guidance on how switching studies should be designed. In the absence of interchangeability data, biosimilar entry into developed markets will be limited to *de novo* patients only. The FDA guideline implies that highly similar biosimilar product might qualify for interchangeability. In any case, generating data on the safety of interchangeability could give added value to the product and patient community with, inevitably, some of this commercial value translated into market expansion via inclusion of switchers. In the developing world, interchangeability between numerous domestically available products is cost driven and this has raised serious concerns by some physician and patient groups. It is important to emphasise that many theoretical risks attributed to switching with biosimilars stemming off pure-red cell aplasia (PRCA) events with both reference and biosimilar erythropoietins. However, there was no evidence to suggest that PRCA origin is linked to product switches. In opposite, potential causality could have been attributed to manufacturing changes and/or potential presence of aggregation in the product. Therefore, some other factors might be responsible in immunogenicity-related safety phenomena. For example, in Thailand, 14

erythropoietins had been licensed by 1 January 2009. These products came from a number of countries such as Argentina, China, South Korea, and India. The number of PRCA cases in Thailand has steadily increased over the last few years, prompting the clinical community to step into the evaluation of immunogenicity issues.²⁶ The risk of PRCA development was estimated to be approximately 1 in 2600 patients. Immunogenicity and interchangeability concerns prompted the Nephrology Society of Thailand, the Thai Society of Haematology, the Association of Hospital Pharmacy (Thailand) and the Adverse Product Reaction Monitoring Center of the Food and Drug Administration of Thailand to set up a prospective, immunogenicity surveillance registry of erythropoiesis-stimulating agents with subcutaneous exposure.²⁷ The primary objective of this registry is to estimate the incidence of anti-erythropoietin antibodies and associated PRCA development in patients, and the secondary objective is to evaluate the efficacy of the currently available products for the treatment of erythropoietin-deficiency anaemia in Thailand. The study plans to enrol approximately 5000 patients who are using erythropoietin products with a prospective follow-up of up to 3 years. It remains to be established whether such a study will be able to unravel the causal relationship between switches and PRCA. If PRCA will be linked to some specific products, pharmacovigilance research needs to be fully complemented by adequate pre- and post-approval data on release characteristics, stability, and cold-chain compliance.

With some complex biosimilar products, it is expected that post-marketing pharmacovigilance activities will not be limited solely to the passive surveillance of adverse effects. Prospective registries and/or observational cohort studies equipped with safety and immunogenicity tools are likely to be required within the risk evaluation and management strategy (REMS) instituted in some cases by the FDA and within the risk management plan (RMP) which is mandatory for all new products on the EU market. Case-by-case evaluation of class-specific and product-specific risks will dictate the scope of required pharmacovigilance activities. For example, biosimilar natalizumab, if developed and positioned on EU and US markets, will most probably require the same restricted access as has been established for its reference product due to the risk of a potentially fatal serious adverse effect – progressive multiple encephalopathy (PML). Natalizumab (Tysabri) is currently marketed and distributed by Biogen via a strictly maintained US TOUCH registry aimed at specialists who are well educated in relation to Tysabri risks and well experienced in the treatment of patients with multiple

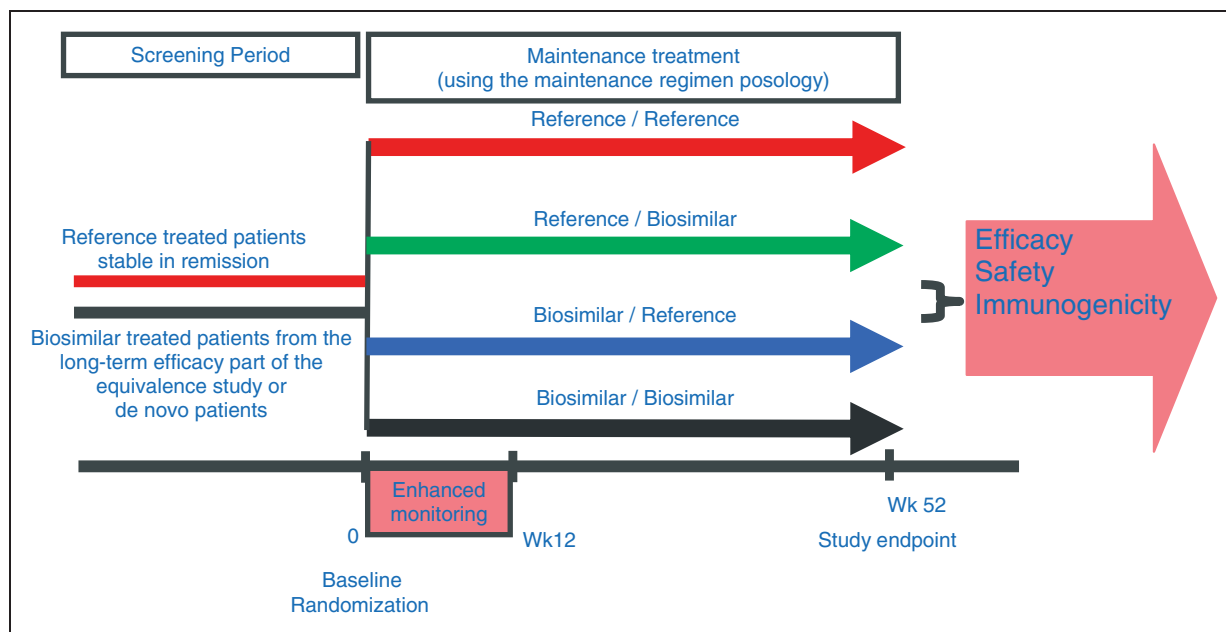


Figure 7. Design of a potential randomized prospectively run switching study with the primary objective of comparing the safety and immunogenicity of reference and biosimilar versions of the product.

sclerosis and severe forms of CD. Biogen, has also developed a validated serology assay which allows stratifying the risk of PML and isolating patient groups with the most favourable risk-benefit ratio. The assay has been included into EU and US product labels. It is expected that similar, if not more complex (with the addition of immunogenicity monitoring), risk minimisation frameworks and risk evaluation measures will be required from the developers of biosimilar natalizumab. At the other end of the spectrum, some better understood classes of biosimilar products such as growth hormones, erythropoietins and filgrastims will require less-extensive pharmacovigilance activities.

Apart from the prospective observational cohort studies, a direct comparison of immunogenicity can be done by means of switching studies. Schematic representation of such a study design is illustrated in Figure 7.

Upon completion of a screening period, patients who are stable and on prior treatment are randomized onto one out of four potential switching combinations. The minimal period required to observe unwanted immunogenicity is approximately 12 months. It has been documented that the highest probability for the emergence of immunogenicity will be in first 3–6 months dependent on dosing regimen. Drawbacks of this study include difficulties with treatment concealment due to different product presentation, although a double dummy execution might be feasible. In

addition, the sample size of such a study as dictated by previously observed rates of immunogenicity might be a limiting factor. Nevertheless, intra-study comparison of immunogenicity rates using principles of descriptive statistics could be of still greater clinical and scientific value than estimating immunogenicity risks using retrospective or uncontrolled observational cohort data. It is likely that such a study will be welcomed by prescribers as direct intra-study proof of interchangeability. Having such a study may also include evaluations of other identified safety risks, when appropriate. According to the Contract Research Organisation (CRO) estimates, the cost of such a study can vary dependently on indications and number of patients recruited but is unlikely to exceed \$10 million for 500 patients (100 patient per arm and taking into account 25% drop-out rate) with autoimmune disease clinical research organisation (CRO) estimate.

It is therefore expected that, at least in the first 5–10 years after the emergence of approved biosimilar mABs, an enhanced post-marketing pharmacovigilance surveillance will be required. Pharmacovigilance legislation in the EU has undergone further changes with new requirements for assessment of the effectiveness of proposed risk management plans and merging post-marketing obligations and commitments (including those for CMC) with the risk management plan. Biosimilar developers should be prepared to undertake various post-marketing studies with those budgeted into product and portfolio planning.

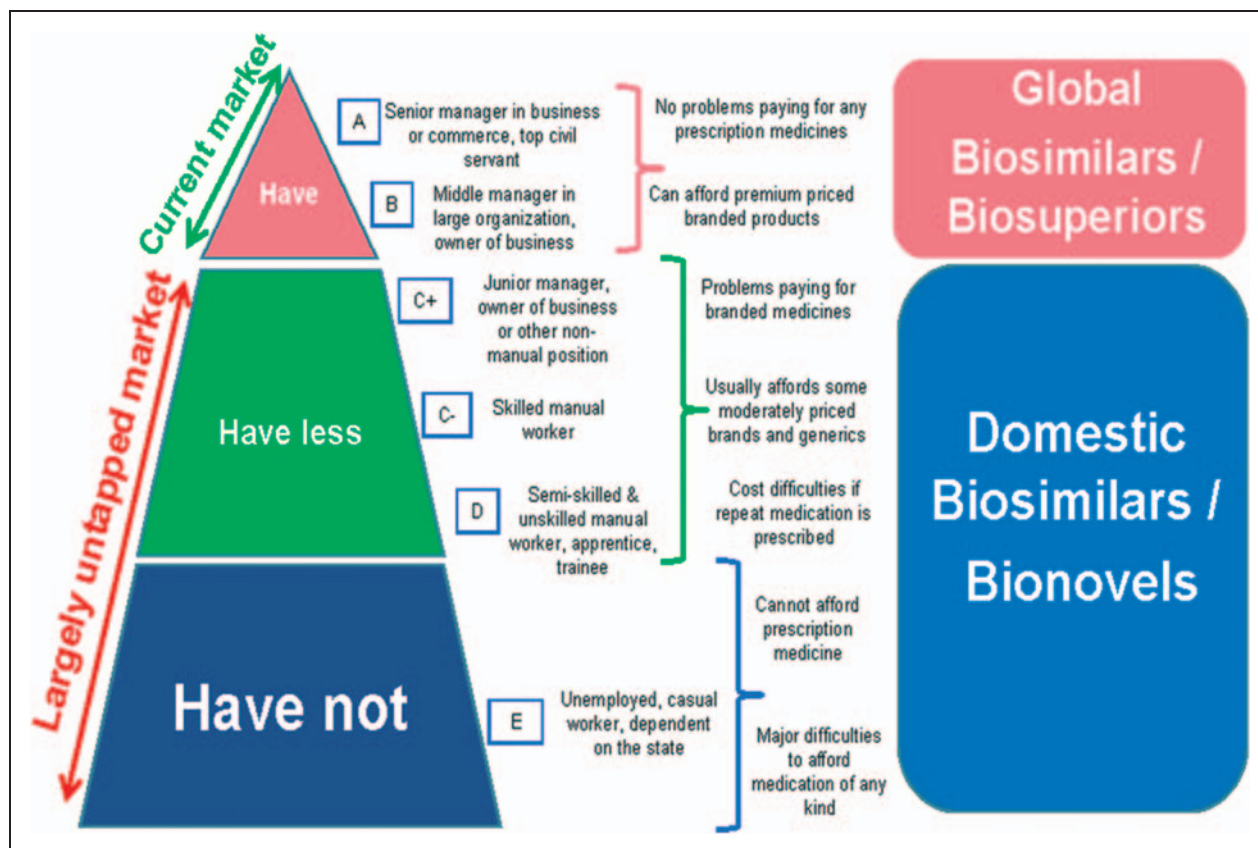


Figure 8. The segmental structure of developing markets.

Considerations for market access

Interchangeability of biosimilars in the EU resides with national law and is outside EMA biosimilar legislation. For most of the EU countries, national law prohibits automatic substitution of biologics. However, in October 2011, a new law was introduced in Germany, permitting the substitution of like-for-like biosimilars.²⁸ The law could actually increase pricing competition in the German market and increase discounts for new biosimilars. With many developed markets having recently emerged from recession, but still facing economic difficulties, governments have begun to implement austerity measures that will see a reduction (in real terms) in healthcare expenditure. Consequently, in a bid to maintain standards of care and patient access to medicines in the face of budgetary pressures, payers can be expected to move toward more cost-effective treatment solutions including greater levels of biosimilar (and generic) usage. In fact, the European Generic Medicines Association (EGA) has orchestrated a push to raise awareness of the cost-saving benefits of biosimilars by highlighting that some €1.6 bn (\$2.2 bn) in cost savings could be made based on six off-patent biologics being made available

in biosimilar form, if they were priced at a 20% discount to the reference brand.²⁹ Regulatory bodies in Europe have introduced a number of pharmacoeconomic-based decisions in order to increase the use of biosimilars. In June 2010, the UK's National Institute for Health and Clinical Excellence (NICE) recommended that somatropin products be interchangeable thus encouraging doctors to prescribe Omnitrope (somatropin; Sandoz). Subsequently, in February 2011, the Scottish health technology assessment agency, the Scottish Medicines Consortium (SMC), recommended that Nivestim (filgrastim; Hospira) be used by the Scottish National Health Service (NHS).³⁰ The move follows SMC approvals for Binocrit (epoetin alfa; Sandoz), Omnitrope (somatropin; Sandoz) and Tevagrastim (filgrastim; Teva). Nivestim's recommendation was based on health economic data for three cycles of treatment for breast cancer, with an estimated cost saving for the Scottish NHS of £10,000 (\$15,453). Despite the application to the SMC being solely based on the use of Nivestim in chemotherapy, the recommendation was extrapolated to cover five additional indications: cytotoxic chemotherapy.

Biologics are high-cost medicinal products and their cost-effectiveness profiles are generally borderline or

Product attributes & positioning	Market access & reimbursement	Sales & promotion	Global supply chain
-Leverage development costs due to regional regulatory differences; -Leverage relationships with global partners; -Global / Regional price differentiation; -Full differentiation on some efficacy attributes (e.g. PROs, QoL, health economics); -Poor education of prescribers / patients about biologics and biosimilars; -Difficulties in accepting extrapolation (e.g. RA, IBD and psoriasis or overall survival data in different cancers); -Immunogenicity & safety will be determined by size and length of studies; -New device format and evaluation for parenteral administration; -Cold chain and pharmacy storage considerations; -Stability data	-Incremental cost-effectiveness benefits due to potential discounting; -Different type of reimbursement dossier; -Cost-minimisation analysis and modelling of outcomes due to limitations of equivalence / NI studies; -Potential benefits due to product attributes; -Educational disease and biosimilar awareness campaigns aimed at prescribers; -Primary market that's benefiting from earlier and expanded use of biologics (new patient positioning); -Secondary and much larger market will consist of switchers following an addition of substitution claim into the label (life-cycle option)	-Leverage relationship and performance of marketing partners; -Biosimilar branding will be possible due to preservation of trademark name; -Benefits from postmarketing data generated with originator; -Promotional activities will need to extend into primary KOL audiences which are dominated by reference companies; -Publication strategy	-Distribution network and long-term stability / superior formulation may allow to outreach new communities; -Leverage relationships with distribution partners; -Plans for back up manufacturing transfer in order to mitigate potential shortages or manufacturing problems

Figure 9. Commercialization of biosimilars.

exceed the reference threshold of £30,000 (€33,000; US\$44,000) per additional quality-adjusted life-year specified by NICE. Currently available in the UK, biosimilar products (Omnitrope, Binocrit, Retacrit and Ratiograstim) are available at a price of around 10–25% less than their reference products. It will be interesting to see whether biosimilar developers will be able to position their products not only in core reimbursable indications but also in those indications in which reference products were previously rejected by health-technology appraisal bodies (e.g. some oncology indications for bevasizumab or cetuximab).

Effectively, biosimilars can bridge to cost-effectiveness dossiers of approved reference products and provide additional value-driven analyses. The relative clinical and cost-effectiveness of biosimilars will be considerably facilitated by actively-controlled studies as opposed to indirect evaluation of comparative efficacy and cost-effectiveness of reference products which are often developed using placebo-controlled studies. In addition, cost savings can be associated not only with price discount but also with better product stability attributes and improved delivery devices, which could translate into further incremental benefits. There are other opportunities that can be explored by biosimilar companies. For instance, biosimilars holding filgrastim and oncology mAb in their portfolio can provide both products at negotiated discount as a part of bundled

oncology service resulting in both products being even more cost-effective than if those would be provided on their own. Clinical trials of biosimilars can include an evaluation of new patient-reported outcomes and those might be utilised in cost-minimization analyses and further increase the budgetary attractiveness of biosimilars.

The key point for the economic consideration of biosimilars is the extent to which the decision uncertainty around cost-effectiveness outcomes is addressed. Importantly, from the emerging market point of view, the emergence of multiple global and domestic biosimilars can satisfy the needs of patients from different classes of society with different reimbursement coverage. It remains to be established whether some poor quality biologics or biosimilar-like versions available in emerging markets provide with true clinical value to patients. Global biosimilar framework will benefit from knowledge on safety and the interchangeability of biologics, allowing for a better understanding of risks and ultimately extending their use in early stages of disease (Figure 8).

Due to lack of reimbursement and poverty in the developing world, biologics constitute a group of products that are beyond the reach of the majority of patients. Lack of access to state-of-the-art treatments results in severe and disabling forms of disease, poor quality of life and premature death. Therefore, access

to discounted domestic biosimilar products provide healthcare solutions for different, underserved patient groups. The task of biosimilar developers is to accumulate a portfolio of products that satisfy the needs of different segments of society and accrue benefits from both premium sales (global biosimilars) and discounted large volume sales (domestic products). However, the clinical value to patients is invariably greater with high-quality global biosimilars developed in accordance with appropriate biosimilar regulatory standards. Further patient- and prescriber-driven research needs to be carried out in order to identify the value with domestic copy products approved often in absence of appropriate regulatory route and even in absence of reference product approved in the concerned territory.

Commercialization of biosimilars will require addressing multiple pre-requisites to achieve successful product differentiation (e.g. through different delivery devices, stability data or extent of clinical data), extensive education of prescribers and the patient community on biosimilarity, and establishing a global supply chain able to cope with distribution problems in the developing world (Figure 9).

In conclusion, the success of the biosimilar business will be determined by a number of factors including the ability to form sustainable development, manufacturing, distribution and commercialization partnerships and alliances. Biosimilar market growth will be a gradual and lengthy process with early entrants reaping the maximum benefits.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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