A Decade of Biosimilars: Have Expectations Been Met?

Since the European Union approved the first biosimilar, Sandoz's biosimilar recombinant human growth hormone somatropin, in 2006,[1,2] with marketing commencing in 2007,[3] a total of 35 biosimilars have been approved in the EU.[4]Five biosimilars have been approved in the United States.[5] Such products have potential to improve drug access for patients while cutting healthcare costs. Yet how much of this potential has been realised?

The biologics sector is an attractive one. Six of the top eight drugs by revenue in 2016 were biologics,[6] and the market share of biotech products is forecast to increase from 24% in 2015 to 29% in 2022. EvaluatePharma estimates that biotech product sales totaled $220 billion in 2017, compared with $453 billion for conventional pharmaceuticals. The company predicts that, in 2022, 50% of the value of the top 100 products will come from biologics.[7]

With increasing numbers of patent expiries, the global biosimilars and follow-on biologics market is expected to grow at a compound annual growth rate (CAGR) of 38.8% in the first half of the period from 2017–2027, and 11.3% in the second half of the forecast period, according to Visiongain.[8] Estimated at $5.31bn in 2016, the biosimilars market is predicted by Visiongain to reach $41.07bn by 2027.

Potential for Cost Savings

While discounts on biosimilars cannot match those of small molecule chemical generics due to the level of investment required for their development, regulatory approval and manufacturing, they are still expected to generate significant savings owing to the high unit costs of their originators. A small molecule generic typically takes two to three years and $2–5 million to develop, while biosimilars take up to five years and $40–300 million to develop, according to CVS.[9]

A May 2017 report from QuintilesIMS,[10,11] 'The Impact of Biosimilar Competition in Europe', shows a consistent average price reduction in therapy areas where biosimilars have been introduced. Increased biosimilar competition affects not only the price for the directly comparable product, but for the whole product class. Other observations in the report include: the entrance of just one biosimilar into the market can be sufficient to lower prices across the class; in some therapeutic classes, lowering the price of the reference product can limit the market penetration of the biosimilar; there is a first-to-market advantage in biosimilar markets; and overall, biosimilar competition contributes to increased patient access of the whole market. Pricing discounts as high as 45% and 72% (Norway) have been seen for biosimilars in Europe.[12,13]

Experience to date is limited in the US, but CVS Health Corp (a major US pharmacy benefit manager) has predicted biosimilar price discounts of 20–30%.[14] In June 2017, the Galen Institute estimated that biosimilars could reduce spending on biologics in the United States by $44 billion over the next decade, based on a RAND Corporation study.[15,16] The Galen Institute notes a Congressional Budget Office prediction that biosimilars could yield savings of $25 billion for patients and taxpayers over 10 years. When the first approved biosimilar in the US, Sandoz's filgrastim-sndz (now filgrastim-bflm), was launched in 2015, its list price was 15% lower than that of the originator biologic; sales of the originator then decreased from approximately $1 billion in 2015 to $765 million in 2016.[17]

According to the Association for Accessible Medicines (formerly GPhA) CEO, Chip Davis, biosimilars have been deemed the top growth driver for the pharmaceutical industry in 2017.[18] Stakeholder education to build confidence in these products remains a primary goal for the industry. In addition, the complexity of the legal landscape and the payer system, especially in the US, will remain key challenges. In a move that favours biosimilar manufacturers, the US Supreme Court ruled on June 12, 2017, that biosimilar companies will not have to give originator manufacturers an additional 180 days' notice after US Food and Drug Administration (FDA) approval before launching their newly approved biosimilars.

Switching and Interchangeability

On the strength of accumulating real-world evidence, any biosimilars are now deemed 'medically switchable' in the eyes of regulators, academic medical societies and clinicians. Interchangeability is a more sensitive issue. The EMA currently makes no specific recommendation on the interchangeability of the biosimilars it approves, leaving that decision to EU member states. However, several national regulatory authorities, including the Dutch Medicines Evaluation Board (MEB), the Finnish Medicines Agency (Fimea), the Irish Health Products Regulatory Authority, Healthcare Improvement Scotland, and Germany's Paul Ehrlich Institute, have taken national positions endorsing the interchangeability of biosimilars under the prescriber's supervision.[19]

The US FDA, in contrast, invites biosimilar applicants to specifically apply for an interchangeability designation – a step up from approval as a biosimilar – and has recently defined the criteria by which it will judge such applications.[20,21] The draft guidance recommends that sponsors aiming to have a biosimilar approved as interchangeable with a reference product should carry out one or more switching studies, designed to show that patients can alternate between the two products safely and without diminished efficacy.

FDA definition of interchangeability:
"Interchangeable products are both biosimilar to an FDA-approved reference product, and can be expected to produce the same clinical result as the reference product in any given patient. An interchangeable product may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product. In addition, for a biological product that is administered more than once to an individual, the risk in terms of safety or efficacy of alternating or switching between the biological product and the reference product will not be greater than the risk of using the reference product without alternating or switching."[22]

Real-world Evidence for the Safety and Efficacy of Biosimilars

The most compelling evidence for the clinical performance of biosimilars comes from Europe, which has led the way in this field. In 2017, the EMA announced that, over the last 10 years, the EU monitoring system for safety concerns has not identified any relevant difference in the nature, severity or frequency of adverse effects between biosimilars and their reference medicines.[23]

In 2016, marking the 10th anniversary of the launch of the first biosimilar in Europe in 2006, Medicines for Europe stated that:[24]

- Across Europe, nearly 90% of doctors know what biosimilar medicines are and nearly 60% have already prescribed them
- EMA-approved biosimilars have generated more than 400 million patient days of positive clinical experience, "accompanied by massively increased access to modern biological medicines"
- Between 2006 and 2014, biosimilar medicines increased patient access by 44% overall within the EU-5 countries.

Numerous real-world studies support the safety and efficacy of licensed biosimilars compared with originators. Key examples published in 2016 and 2017 are listed in Table 1.

Evolving Opinions

In light of this accumulating real-world evidence, several leading academic medical societies now support biosimilar use. The positions taken by a selection of US and European organisations are summarised below:

- **American Society for Clinical Oncology (ASCO):** Included biosimilar versions of filgrastim in its guidelines for use of white blood cell growth factors, published in 2015[37]
- **US National Comprehensive Cancer Network (NCCN):** Has suggested that biosimilars should be prescribed as an alternative to the originator product[38]
- **European League Against Rheumatism (EULAR):** Has stated that "the advent of biosimilars provides potential for reduction of pressure on healthcare budgets"[39]
- **American College of Rheumatologists (ACR):** In response to the FDA approval of biosimilar infliximab, ACR stated that the organisation "welcomes the introduction of biosimilars to the US healthcare system and is hopeful that the decrease in cost resulting from the availability of safe and effective biosimilars in the US will increase our patients' access to life-changing therapies and improve their overall health"[40]
- **European Crohn's and Colitis Organisation (ECCO):** Following publication of the results of NOR-SWITCH, ECCO issued a statement that "switching from the originator to a biosimilar in patients with IBD is acceptable"[41]
- **American College of Physicians (ACP):** Stated that "unresolved policy issues need to be addressed to ensure maximum utilisation of biosimilars by patients and physicians" as one of its recommendations on ways to stem the escalating cost of US prescription drugs[42, 43]
- **European Society for Medical Oncology (ESMO):** Advocated biosimilars as 'must-have weaponry' in financially sustaining healthcare systems on a global scale[44]

Prescriber surveys in the US and Europe also reflect the growing confidence in biosimilars. A 2016 survey of members of the European Crohn's and Colitis Organization (ECCO) found that 44.4% of 118

- A real-world prospective study in 1400 patients with chemotherapy-induced febrile neutropenia confirmed the clinical similarity of biosimilar filgrastim to the originator Neupogen®[25]
- A Johns Hopkins Bloomberg School of Public Health systematic review of 19 studies reported that TNF-α inhibitor biosimilars for the treatment of rheumatoid arthritis and other autoimmune diseases appear to be as effective and safe as their branded equivalents[26,27]
- The NOR-SWITCH Study, a non-commercial switching study sponsored by the Norwegian government, was a Phase III randomised trial of 482 patients at 40 sites who were on stable treatment with originator infliximab (Remicade®) for at least six months. Participants were randomised to either continue Remicade® or switched to the biosimilar, and followed up for 52 weeks.[28] Switching to biosimilar infliximab was found to be safe and non-inferior to continued treatment with Remicade® across multiple indications
- The triple-switch EGALITY study was a randomised, double-blind trial involving 531 patients with moderate to severe plaque psoriasis that compared biosimilar etanercept with the originator product, Enbrel.®[29,30,31] Patients underwent three switches back and forth between the originator and biosimilar, with no clinically meaningful differences in safety and efficacy
- At the annual European League Against Rheumatism (EULAR) congress, data were presented on patients transitioned from originator etanercept (n=254) and infliximab (n=396) to their biosimilar counterparts.[32] In both cases, there were no treatment-emergent safety or immunogenicity issues, and efficacy was sustained for up to two years
- Delegates at the annual European Crohn's and Colitis Organisation (ECCO) congress heard that 10 real-world studies involving nearly 600 patients with inflammatory bowel disease all showed comparable efficacy and safety following a switch to biosimilar infliximab from the originator[33]
- A meta-analysis of results from 11 published real-world studies including 829 patients showed that biosimilar infliximab has "excellent clinical efficacy and safety" in patients with Crohn's Disease or ulcerative colitis[34]
- One-year outcomes from the Danish DANBIO registry reported sustained efficacy and safety after 802 patients with inflammatory arthritis were switched within routine care from Remicade® to biosimilar infliximab (CT-P13, Remsima®) without a prescriber-led decision in each case[35]
- A study in patients with breast cancer receiving neoadjuvant myelosuppressive chemotherapy (n=218) showed that switching back and forth between originator filgrastim (Neupogen) and biosimilar filgrastim (Zarxio) (5 µg/kg/day) over six cycles of treatment was no less effective or well tolerated than receiving either Neupogen or Zarxio throughout all six cycles[36]

Table 1: Examples of real-world biosimilar studies published in 2016–17

respondents considered biosimilars to be interchangeable with the originator product, up from 6% in 2013.[45] Only 19.5% of respondents said they had little or no confidence in the use of biosimilars, down from 63% in 2013. In addition, a 2016 survey by Industry Standard Research found that two-thirds of biopharma companies with a biologics offering currently market, or plan to market, biosimilars, including companies with no internal manufacturing capabilities.[46] This figure is up from 46% the previous year.

Barriers to Biosimilar Uptake

Innovator companies have employed a variety of multipronged strategies to counter biosimilar competition. These include development of 'biobetter' and/or follow-on biologic medicines, gaining regulatory approval for additional indications and new formulations, patent extensions and litigation, reducing prices and launching new patient assistance programmes.[47] Among these, patent extensions and litigation can be particularly effective in helping delay the introduction of biosimilars. However, most such strategies are unlikely to have a significant long-term impact on the approval, launch and uptake of biosimilars.

Although much progress has been made to date, education is still needed to quell physician and patient doubts about biosimilars.

In conclusion, the biosimilar sector has seen significant progress over the past decade, with the EMA leading the way in establishing regulatory pathways.[48] The regulatory environment for biosimilars continues to evolve, based on advances in technology and analytical methods, and the availability of new targets for biosimilar development. The second half of 2017 is likely to see an expansion of product classes of biosimilars in both the EU and US, with additional guidance from regulatory agencies as to what is needed to obtain approval of biosimilars in these classes.[49]

Expectations have probably been met in Europe, including glimmers of large discounts such as those in the Scandinavia region, though in some EU countries and other ICH regions, like the US, are still trying to play catch-up with regard to cost savings – for both payers and patients. Looking ahead, resolution of the uncertainty around interchangeability and the patent log-jam will further advance the biosimilar market, helping to deliver on the promise of improved cost-effectiveness and patient access to this powerful category of therapies.

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