FROM THE ANALYST'S COUCH

Biosimilar competition: lessons from Europe

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Since 2005, the European Union has had a regulatory pathway through which biosimilars are approved centrally by the European Medicines Agency (EMA), as with pioneer biologics. So far, biosimilars have been approved in four separate classes: somatropins, erythropoiesis-stimulating agents (ESAs), granulocyte colony-stimulating factors (G-CSFs) and, most recently, monoclonal antibodies that are specific for tumour necrosis factor (TNF). In 2009, the US Food and Drug Administration (FDA) was given the authority to introduce a pathway for the approval of biosimilars, and draft guidance has been released; however, the pathway is not yet finalized and its potential impact on the uptake and price of biosimilars in the United States remains unclear.

Here, with the aim of understanding more about the likely future uptake of biosimilars in Europe and the United States, we analyse experiences in Europe with biosimilar products referenced to the ESA Eprex (epoetin alfa) and the G-CSF Neupogen (filgrastim) in five countries — Germany, the United Kingdom, Sweden, France and Italy — using audit data from IMS (FIG. 1). These biologics have been major products globally and so could provide a useful indication of the development of the markets for other major products for which patent protection is anticipated to expire in the next decade.

Analysis of market experience

Characteristics of the biosimilar products analysed. Erythropoietin (EPO) is a naturally occurring glycoprotein that controls erythropoiesis (red blood cell production) to treat anaemia in patients undergoing dialysis and in patients with cancer, and G-CSF is a hormone that stimulates the production of white blood cells as a treatment for neutropenia. Recombinant products are available for these natural substances in both original (Eprex and Neupogen) and longer-lasting forms (Aranesp and Neulasta), but the biosimilars approved so far are referenced only to Eprex and Neupogen. There are currently five biosimilar products approved in Europe that reference Eprex (the first of which was approved in 2007) and six biosimilar products that reference Neupogen (the first of which was approved in 2008). Entry occurred at a faster rate in the case of biosimilars referencing Neupogen. By the end of 2011, the five countries had between three and five filgrastim biosimilars available. By contrast, except for Germany (where all five ▸

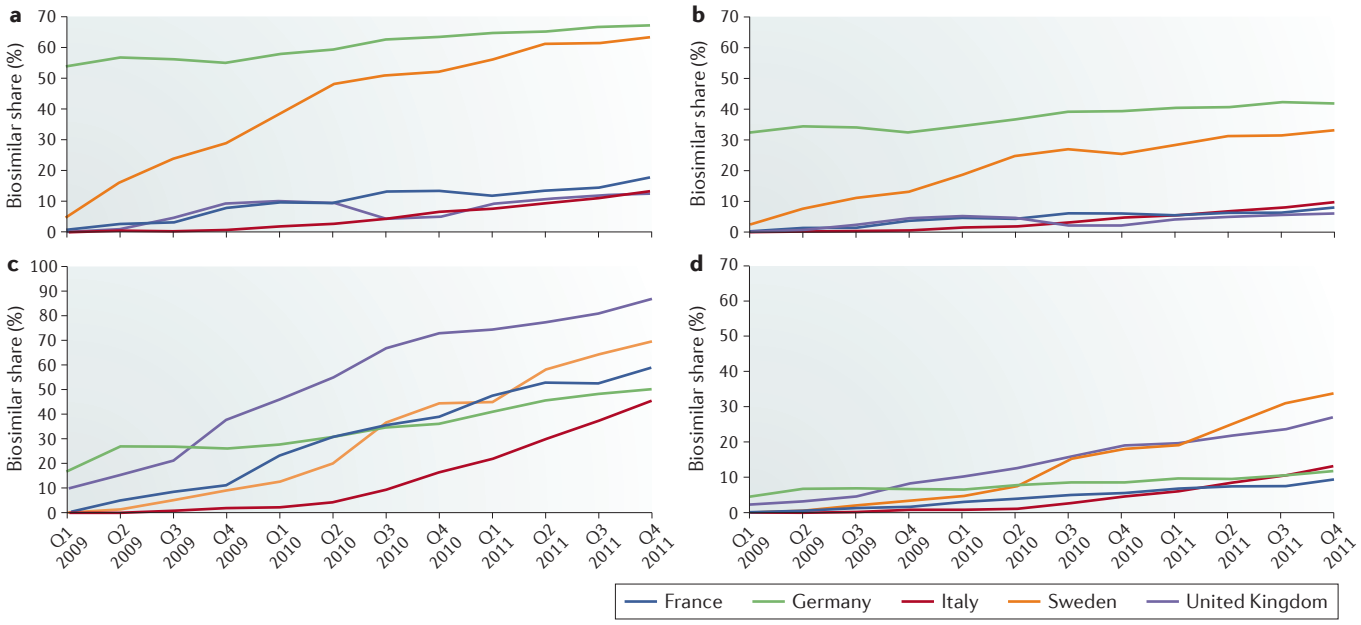

Figure 1 | **Market share for biosimilars in Europe (2009–2011).** Panel **a** shows the biosimilar share of the epoetin (Eprex) market segment, and panel **b** shows the expanded erythropoiesis-stimulating agent (ESA) market segment (also including darbopoetin alfa (Aranesp)), calculated based on daily doses. The biosimilar products are Retacrit and Binocrit in France; Epoetin Alfa Hexal, Silapo, Abseamed, Retacrit and Binocrit in Germany; Abseamed, Retacrit and Binocrit in Italy; Retacrit and Binocrit in Sweden; and Retacrit and Binocrit in the United Kingdom. Panel **c** shows the biosimilar share of the filgrastim (Neupogen) market segment, and panel **d** shows the expanded granulocyte colony-stimulating factor (G-GCSF) market segment (also including pegfilgrastim (Neulasta)), calculated based on daily doses. The biosimilar products are Zarzio, Tevagrastim, Ratiograstim and Nivestim in France; Filgrastim-Hexal, Ratiograstim, Biograstim and Nivestim in Germany; Zarzio, Tevagrastim, Ratiograstim and Nivestim in Italy; Ratiograstim and Nivestim in Sweden; and Zarzio, Ratiograstim, Nivestim, Filgrastim Teva, Tevagrastim and Filgrastim Sandoz in the United Kingdom. Source: IMS MIDAS.

biosimilars referencing Eprex were available by early 2009), the other countries had only one to three epoetin biosimilars on the market over the 2009–2011 sample period (Supplementary information S1 (box); section 1).

Characteristics of the countries analysed. Of all the countries analysed, Germany has provided the most favourable incentives for biosimilars. In addition to a reference pricing system in place for biosimilars, Germany has specific targets or quotas for physician and sickness funds for biosimilars that vary by region (Supplementary information S1 (box); section 1). Of the other countries included in our sample, Sweden and the United Kingdom have a history of encouraging generic competition for small-molecule drugs through physician and reimbursement incentives. By contrast, France and Italy have centralized price regulation and budgetary controls, with relatively low rates of generic competition historically. However, these are large markets for biological products, so they also could be attractive markets for biosimilar producers. In contrast to the FDA, the EMA does not evaluate interchangeability, and questions of substitutability at the pharmacy level are left to member states. At this point, none of the member states allows substitution for biosimilar products.

Market experiences for biosimilars. FIGURE 1a shows the market share in units (defined daily doses; DDDs) for the biosimilars referenced to Eprex in the five European countries. The basic data source is IMS quarterly data over the 2009–2011 period with standard units converted to DDDs using information from the WHO (World Health Organization) on the DDD for each product (Supplementary information S1 (box); section 2). Biosimilars referenced to Eprex in Germany and Sweden have a market share in excess of over 60% by the fourth quarter in 2011 (FIG. 1a), whereas the other three countries have epoetin biosimilar shares of less than 20%. Shares in terms of US dollars exhibit similar outcomes across these countries (Supplementary information S1 (box); section 3).

Biosimilars referenced to Neupogen in the G-CSF market exhibit a very different pattern. In particular, there is a more rapid and extensive market penetration for biosimilars than in the case of Eprex. This is shown in FIG. 1c. Biosimilars attained shares of between 45% (Italy) and 87% (the United Kingdom) by the end of 2011. This greater acceptance of filgrastim biosimilars in the G-CSF market appears to reflect both medical considerations and reimbursement policies (Supplementary information S1 (box); section 3).

A preliminary analysis of pricing behaviour indicates that biosimilar discounts are typically less than 25%. This is generally consistent with published surveys and reimbursement information for selected European countries (Supplementary information S1 (box); section 3.) Our analysis of the pricing of biosimilars is qualified by the fact that some markets have substantial rebates to providers for both the reference product and biosimilar counterparts that are not captured in IMS data audits of invoices.

In FIG. 1b and FIG. 1d, we consider the biosimilar share of the market segment comprising both the first- and second-generation recombinant products in the overall ESA market (Eprex and Aranesp) and for the G-CSF market (Neupogen and Neulasta). The second-generation products require substantially fewer infusions over a course of treatment with potential benefits to patients and lower costs of administration. In both categories, they were introduced prior to biosimilar entry. As shown in FIG. 1b and FIG. 1d, there are substantially smaller shares in terms of this broader market segment when compared to FIG. 1a and FIG. 1c. This reflects the fact that the second-generation products have the largest overall share in most countries. In the case of the G-CSFs in particular, Neulasta had shares between 50% and 80% of this market across the five countries in the fourth quarter of 2011 (Supplementary information S1 (box); section 3).

Lessons from the European experience

One major finding is that the competitive performance of the biosimilars we analysed in Europe is mixed both across countries and products. Although the European Union has a common regulatory system for approving biosimilars, differences in reimbursement practices and incentives as well as variations in medical practices have resulted in different outcomes across countries. It is difficult to generalize across different health-care systems, but Germany and Sweden arguably provide the closest cases to the United States. Both countries have relatively high prices for innovative drug products, a history of generic utilization and a decentralized approach to drug utilization and reimbursement. This suggests that biosimilars could achieve significant shares relative to their referenced products in the United States after a transition period. At the same time, biosimilar price discounts are likely to be modest compared to generics, reflecting much greater costs of development, fewer competitors and the absence of interchangeability for the foreseeable future.

A second major finding is that cost savings from the introduction of biosimilars in the European countries analysed have been tempered by the fact that competition has been limited to the first-generation reference products in the ESA and G-CSF classes, whereas the longer-lasting second-generation versions have generally maintained leading shares in these categories. Dynamic competition through the market entry of next-generation biologics is an important consideration in analysing the market impact of biosimilars and their potential savings to the health-care system. Many of the more complex monoclonal antibody biologics, which recently experienced their first EU biosimilar approval (for the TNF antagonist infliximab), also have next-generation products under development or regulatory submission (Supplementary information S1 (box); section 4) .

Even if biosimilars gain a substantial share of sales from their referenced products, their share of overall patient treatments may be limited in the face of incremental quality advances if physicians and patients opt for next-generation products. Furthermore, many of the new firms entering the biological space appear to be focused on 'biobetters' rather than biosimilars in the recognition of these dynamic developments. It remains to be seen how competition will evolve for the more complex biological products with patent expirations as well as biosimilars and biobetters on the horizon in the case of the European and US markets.

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