FROM THE ANALYST'S COUCH

Biosimilars: initial excitement gives way to reality

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Innovative drug developers are facing an unprecedented number of challenges in maintaining revenue growth. Fewer novel drugs are being approved, a large number of blockbusters are facing patent expiry, and public and private payers across the major drug markets are implementing cost-containment policies in response to sky-rocketing healthcare costs, which is affecting drug margins.

This increasing focus on cost containment is boosting the sales growth of generics. In the US, payers are under increasing pressure to utilize cost-containment policies, such as tiered formularies, which provide incentives to use generics because they reduce patient co-pay for generic drugs. In Europe, factors such as generic substitution are also helping to drive uptake. The reward for generics companies who gain market share is significant: Datamonitor estimates that US$157 billion (around 40%) of 2005 brand sales will be exposed to generic competition by 2015.

Biologics accounted for just under one-fifth of total drug sales in 2004, and their high cost and strong forecast sales growth (FIG. 1) make them a prime focus for both cost containment and generic competition. As protein drugs are produced by cells in culture or whole organisms, which are inherently more variable than chemical synthesis methods, establishing bioequivalence of a protein produced by another manufacturer requires a rigorous assessment of quality, safety and efficacy[1]. In light of these issues of establishing bioequivalence, generic biologics are termed 'biosimilars'.

Currently, the two mature biologics sectors are recombinant protein therapeutics (rDNA proteins) and monoclonal antibodies (mAbs), which are set to generate >90% of total biotech sales from 2004–2010. Given that the innovator's cell line plays a key role in determining the mAb's characteristics, the proprietary nature of the cell line makes it difficult to recreate a genuine biosimilar[2,3]. Therefore, rDNA proteins are the leading focus for generics companies.

Wave of approvals unlikely

Many first-generation rDNA proteins are now off-patent, leaving them open to generic competition. The approval of Sandoz's growth hormone somatropin (Omnitrope) in the European Union in April 2006 (REF. 4) and the US in May 2006 (REF. 5) triggered speculation that there would be a wave of biosimilar approvals. However, the European approval process for biosimilars is relatively new, and there is no regulatory approval pathway for biosimilars of innovator therapeutics that were approved as Biologic License Applications (BLAs) in the US. In fact, in the US, Omnitrope was approved via the Abbreviated New Drug Application (ANDA) process, using the Section 505(b)(2) pathway of the Hatch–Waxman Act. Despite this, subsequent approvals using this pathway in the US are likely to be dealt with on a case-by-case basis, and successful approval will depend on how complex and well-understood the protein is. Another factor impeding wide-scale biosimilar launches in the US is that the majority of biologics were approved as BLAs, which lack the Section 505(b)(2) provision. It is likely that new legislation will be required before the FDA can approve biosimilars of BLA proteins, and the agency has said that there has been little progress on this issue in Congress so far. Therefore, in the short-term, well-characterized biologics approved as New Drug Applications (NDAs) — insulins and growth hormones — are the most likely products to face biosimilar competition.

With the issuing of draft guidelines outlining abbreviated approval requirements for biosimilars in 2005, Europe has a more advanced regulatory framework[6,7]. However, as for the US, approval is assessed on a case-by-case basis, and is based on how well the product is characterized, the degree of molecular complexity and the state of the art for the relevant analytical and manufacturing process. Furthermore, post-marketing studies are required for biosimilars. Nevertheless, the majority of biosimilar sales in the short- to medium-term are expected to be generated in Europe until the FDA establishes a regulatory framework for biosimilar versions of biologics approved as BLAs.

New marketing approach needed

There is a higher barrier to entry for the biosimilar market than for small-molecule generics. Entering the biosimilar market carries higher costs, greater risks, and greater time and expertise in relation to the clinical development of these products (FIG. 2). Furthermore, the marketing and launch of biosimilars requires a different strategy than small-molecule generics. Marketing and patient support are more important for biosimilars, favouring companies with significant financial resources and who have had experience in marketing branded products. The generics market has historically used prices to secure market share, so it is important for biosimilar developers to understand and act on these factors. Early-stage success in the biosimilars market, however, is more dependent on the speed to market and successful marketing strategies. As the biosimilars market matures, companies with low-cost manufacturing capabilities (for example, companies in China and India) will increase market share over the longer term. The development of 'super-biosimilars' (second-generation versions of biosimilars) will also help to drive longer term market growth.

As a result of different marketing strategies and market characteristics, classes of rDNA proteins will achieve varying levels of success. Factors such as the level of competition, ease of product development and characterization, and the level of patient support required all affect market potential. This is already having an impact on the numbers of biosimilar products in development for different rDNA protein classes (FIG. 3). For example, there are a number of human growth hormones in development, in part because of their relatively straightforward characterization. On the other hand, strong brand loyalty, together with the need for physician detailing and marketing, makes the insulin market less attractive to biosimilar developers. ▸

BIOSIMILARS | MARKET INDICATORS

- Global sales of biologic products (by 56 of the leading pharmaceutical and biotechnology companies) are growing rapidly, and are forecast to almost double from US$56 billion in 2004 to $105 billion by 2010 (FIG. 1). Therefore, this market represents a significant target for generics companies, but there are higher barriers to entering the biosimilars market than the small-molecule generics market (FIG. 2). Key factors set to affect the biosimilars market over the short- to medium-term include regulatory issues, marketing strategies and the class of rDNA protein being targeted (FIG. 3). Over the longer term, the emergence of biosimilars from low-cost manufacturing sites plus the next generation of so-called 'super-biosimilars' is also set to drive market growth.

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FURTHER INFORMATION

European Medicines Evaluation Agency: Guidelines on biosimilar medicinal products: http://www.emea.eu.int/htms/human/biosimilar/biosimilarfin.htm

Food and Drug Administration: Information on Omnitrope: http://www.fda.gov/cder/drug/infopage/somatropin/default.htm

FURTHER READING

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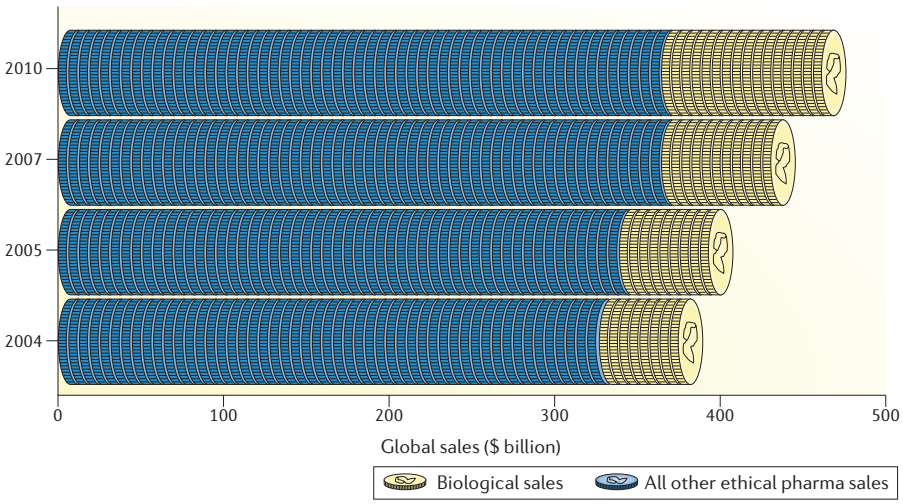

Figure 1 | **Global sales of biologic products.** Sales from 56 of the leading pharma and biotech companies are growing rapidly, and are forecast to almost double from $56 billion in 2004, to $105 billion by 2010. Note: sales figures from 2005 onwards are forecasts. Data from company reports and Datamonitor forecasts.

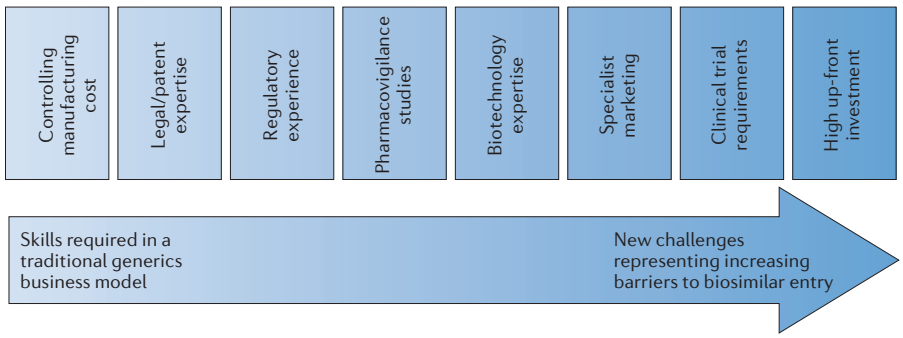

Figure 2 | **Skills and barriers required to develop biosimilars.** The biosimilars market presents fundamentally higher barriers to entry than the small-molecule generics market.

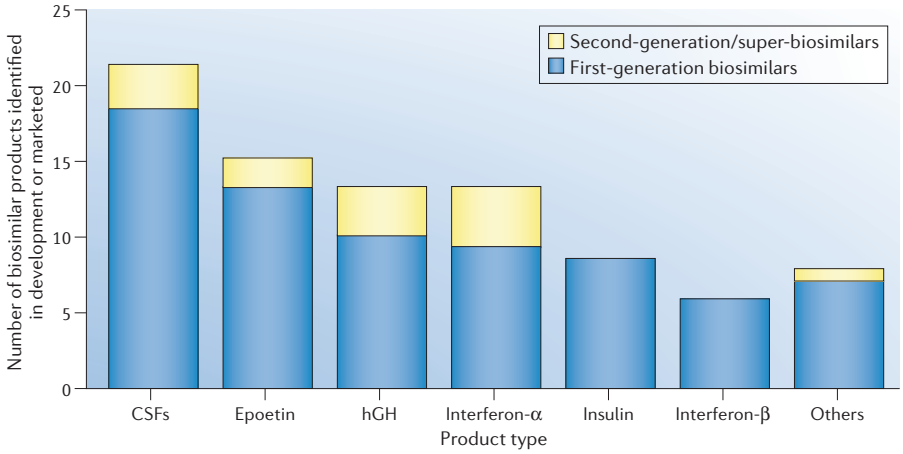

Figure 3 | **Biosimilar suitability depends on drug class.** The market potential of biosimilars is affected by issues such as existing competition, ease of product development and characterization, and required level of patient support. As a result, there are varying numbers of biosimilars in development for the main classes of recombinant protein therapeutics. CSF, colony-stimulating factor; hGH, human growth hormone.