Biosimilars: follow-on biologics of innovator biopharmaceutical products

As blockbuster biopharmaceuticals go off patent, biosimilars are increasingly competing with them for a market share. However, the production of biosimilars is rather complex and costly. The approval of biosimilars is also subject to many hurdles. Their introduction to the very expensive biopharmaceuticals market is often associated with marginal price reductions.

The proportion of biopharmaceuticals, i.e. biological pharmaceuticals produced by recombinant DNA technologies, is growing continuously. According to information provided by the Association of Research-based Pharmaceutical Companies (vfa), 109 active biopharmaceutical substances were approved for use in 145 drugs in Germany by mid-2011. In 2009, biosimilars achieved revenues to the tune of 4.7 billion euros, which corresponds to 16 per cent of the entire German drug market.

This lucrative market is highly competitive, especially when the patents of the innovator products are about to expire. For some drugs, including the growth hormone (somatotropin), G-CSF (granulocyte-colony stimulating factor or filgrastim) and erythropoietin (epoetin), 13 biosimilars have already received marketing authorization in the European Union. In addition, many other blockbuster biopharmaceuticals will soon go off patent.

The lower development costs associated with the development of biosimilars along with competitive pressure seems to suggest that extremely high biopharmaceuticals prices are likely to fall, a development that would be highly welcomed by health and care insurance providers and governments. However, real price reductions have been lower than those associated with the introduction of generic drugs into the conventional drug market.

Cell cultures are the basis for the production of biopharmaceuticals and biosimilars.

Different rules apply to biopharmaceuticals and classical generic drugs, which are copies of low-molecular, chemically synthesized drugs. Classical generic drugs can be marketed after a

relatively short and hence cheaper approval procedure. The regulatory authorities usually only require the manufacturers of generic drug products to prove the physical and chemical similarity as well as the bioequivalence – i.e. similar pharmacokinetic and pharmacodynamic properties – of generic drugs and innovator drug products. In the majority of cases, drug manufacturers simply need to compare the effect of the two drugs in a small number of healthy people and demonstrate that their generic formulation is bioequivalent to the brand name product.

Equivalent, but not identical

On the other hand, biopharmaceuticals ("recombinant biologics") are proteins with a complex three-dimensional structure that are synthesized by genetically modified cells, rather than chemically synthesized, before undergoing complex processes of isolation and purification. The bacteria, yeasts and mammalian cells used for the production of biopharmaceuticals do not produce identical active substances, but a microheterogeneous mixture, for example a mixture of different isomers and proteins with variable glycosylation patterns. These mixtures can differ in relation to temperature, nutrient supply, cell density and other production plant-related parameters. Given that it is already a huge challenge for biopharmaceutical producers to reproducibly manufacture biopharmaceuticals, it goes without saying that other manufacturers using different production facilities and cell lines for the production of follow-on biologics find it practically impossible to manufacture biopharmaceuticals that are 100% identical to the brand name drug. And this is why officially approved follow-on versions of innovator biopharmaceutical products are referred to as biosimilars, rather than biogenerics. They are protein-based biologic drugs that are intended to be used as a replacement for existing biologic medicines, with which they are similar, but not 100% identical. Studies need to be carried out to demonstrate that the biosimilars have similar efficacy and safety levels as the reference product.

Bioreactor for the cultivation of mammalian cells used for the production of biopharmaceuticals.

The European Medicines Agency – EMA (formerly known as EMEA) - requires manufacturers to prove the bioequivalence of biosimilars with innovator drugs in several preclinical and clinical studies, in which the biosimilar is compared with the reference, i.e. brand name product, before marketing authorization can be granted. This is why the development of biosimilars is far more complex and costly than the production of generic drugs. It therefore comes as no surprise that only a handful of financially strong companies have so far successfully gone through this procedure. This situation might change given the many innovator drug patents that are due to expire in the near future and the amount it costs to buy them.

Cost reduction and exchangeability

Omnitrope and Valtropin were the first biosimilars to receive marketing authorization for the European market. They cost around 20 to 25 per cent less than the original growth hormone drugs (somatotropin) which are used to treat growth disorders in children. In view of the huge treatment costs, the availability of less expensive drugs might contribute to reducing the financial burden for state health systems.

However, such savings are not just a matter of course. Because the production process of protein therapeutics is different, it is difficult to say whether a new, potentially cheaper biosimilar has the same effect or is equally well tolerated by the patient as the innovator drug. Even the smallest differences, which cannot be detected analytically, could lead to a broad range of adverse reactions in patients, for example as a result of inappropriate immune responses. Concerns have been raised by the Paediatric Endocrinology working group of the German Society for Paedriatric and Adolescent Medicine relating to the treatment of children with the hormone somatotropin.

European regulations take these kinds of issues into account: pharmacists are not allowed to dispense biopharmaceuticals and biosimilars that differ from those on the prescription without the knowledge of a patient's treating physician, and if the physician has not specifically requested it. In Germany, chemically synthesized drugs are treated differently, and so-called "aut idem" rules (exchange rules) apply: if generics are available on the market, the pharmacist is required to dispense the drug that is most economical for the insurance company of a specific patient (for example, if the insurance company has signed a discount contract with a particular producer), unless the treating physician has clearly indicated on the prescription that his or her patient needs a particular brand and must not be given a replacement drug. By deciding not to allow the automatic exchange of biopharmaceuticals and biosimilars, the relevant regulatory authorities have decided in favour of greater security for patients.

It is known that supposedly identical biopharmaceutical formulations developed by different producers and that comply with all the regulatory requirements and have been through numerous clinical trials, nevertheless differ in their efficacy, and different dosages are needed to treat the same disease in different patients in order to achieve the same effect. It is also known that different drugs containing the same active agent have led to adverse reactions of varying extents in different patients. The same is of course true for biosimilars, but not for drugs that are referred to as second brands. Second brands are formulations identical to the innovator drug and produced in the same manufacturing facility, but marketed under different brand names by different distributors. It goes without saying that the aut idem rules can be applied to second-brand biosimilars.

EJ, September 2011

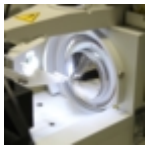
Dossier

05-Oct-2011

Other dossier articles

04.02.2020

Medicine from the blue blood of marine mollusks



30.09.2019

Do gut bacteria have something to do with autism?

17.10.2018

Biologicals are becoming increasingly important to Boehringer Ingelheim

---