



Understanding Biosimilars

A new generation of pharmaceuticals

ratiopharm
▶ direct

Introduction

Biosimilars are a fast emerging segment of the biopharmaceutical Industry. These compounds will have the most impact on the biologic market over the next ten years. But what is a 'biosimilar' or 'similar biological medicinal product'. The term refers to a second-entry version of a biologic medicine whose product patent protection has expired. In the following sections there is an overview of ratiopharm and the development, production and registration of biosimilars.

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About ratiopharm



ratiopharm is one of the leading international manufacturers of generics. The firm produces high-quality patent-free drugs and offers them at a low price. ratiopharm has thereby been making a significant contribution to reducing health service costs and has thus been contributing to an improvement in the medical care of large sections of the population. The family firm, headquartered in Ulm, has branches in 24 countries; ratiopharm products are available in 38 countries round the world. With a total turnover of 1.7 billion euros in 2006, the firm is one of the largest international producers of generic pharmaceuticals. In Germany, ratiopharm, with its 750 different products and around 170 million packs sold every year, is the most used and most prescribed pharmaceuticals brand.

The family firm has a history going back more than 125 years. It was founded by Adolf Merckle in 1881 in Aussig. After 1945, his son rebuilt the firm as Merckle GmbH in Blaubeuren. In 1973, Adolf Merckle's son founded ratiopharm GmbH, Europe's first generic pharmaceuticals firm. In 2005, Dr Philipp Daniel Merckle, from the fourth generation of the Merckle dynasty, assumed general responsibility for the ratiopharm Group.



The firm's know-how lies in developing, producing and marketing chemically synthesised, patent-free active ingredients.

The firm was quick to recognise the significance of biotechnologically produced drugs and decided, at the end of the 90s, to develop and produce such drugs in-house, which is a much more costly and time-consuming process than manufacturing standard generics.



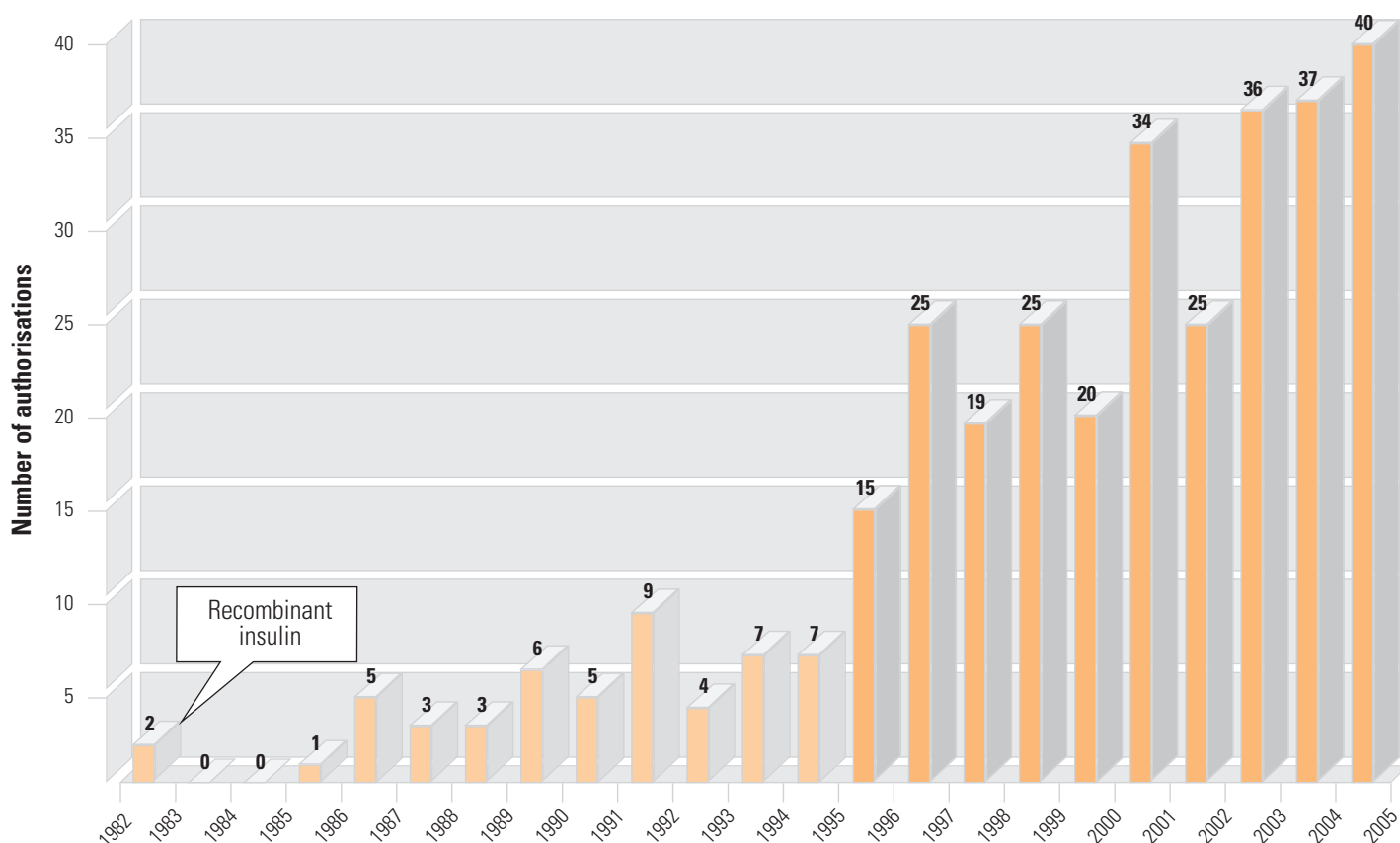
"The manufacture of follow-up products for patent-free biotechnological drugs, referred to as 'biosimilars', is one of the most interesting growth fields in the world," says Dr Philipp Daniel Merckle, with great conviction. "Biosimilars can also reduce annual healthcare costs by up to 600 million euro. ratiopharm has therefore decided to include biotechnological active ingredients as well in its product range."

The group entered this new commercial field by founding a subsidiary, BioGeneriX AG, in 2000. BioGeneriX undertakes the biopharmaceutical and clinical development of suitable biotechnological active ingredient candidates. Merckle Biotec GmbH is the subsidiary responsible for the manufacture of biopharmaceutical active ingredients and biopharmaceutical final products within the ratiopharm Group. ratiopharm has invested 40 million euros in Merckle Biotec GmbH, and, in March 2006, a multi-purpose facility for the production of biotechnological active ingredients in Ulm became operational. In order to introduce biotech products onto the market, ratiopharm direct GmbH was founded in 2005. ratiopharm direct concentrates on the European hospital business and, within this sector, primarily on the areas of oncology and nephrology. This means that the ratiopharm Group had completed all of the groundwork necessary to launch biotechnological follow-up products on the market. More than 100 years of experience in the production of drugs, linked with know-how as an internationally leading generics provider, are proving an ideal combination in the development and marketing of biotechnology products.

Biotechnological drugs

In 1982, human insulin, which was manufactured from cells modified using genetic technology, was the first biotechnological drug brought onto the market. This was soon followed by a human growth hormone, interferons for the treatment of hepatitis, cancer and multiple sclerosis, a protein for the production of white blood cells after chemotherapy, the hormone erythropoietin (EPO) – which regulates red blood cell production – for dialysis patients, and many more. Many diseases could not be treated at all until biological drugs became available. The medical and commercial significance of these biotech products is continuing to grow, as Figure 1 also shows.

Figure 1 – New authorisations of biotechnological active ingredients and vaccines per year



Source (accessed 28/08/2007): <http://www.bio.org/ataglance/bio/200210apr.asp>

In 2006, there were 122 drugs manufactured using genetic technology on the market in Germany, and more than 200 worldwide. The global turnover in relation to biopharmaceuticals was estimated in 2006 to be approx. 55 billion US dollars and could rise to more than 70 billion US dollars by 2010. However, biopharmaceuticals, due to their high development and manufacturing costs, are amongst the most expensive of any drugs. The expiry of patent protection for many first generation biopharmaceuticals is now opening up the field for cost-reducing follow-up products. In the view of many experts, significant cost savings can be achieved across healthcare budgets, which could also result in these innovative therapies being made available to larger sections of the patient population.

The history of biotechnology



Man has been employing biotechnological processes since the dawn of civilisation. 6,000–8,000 years ago, the Sumerians had mastered the brewing of beer, which is based on the metabolic output of micro-organisms. The processes for producing vinegar, yoghurt and cheese provide typical examples of age-old biotechnological applications.



In the meantime, biotechnology has found applications in all sorts of spheres and, depending on how it is used, is classified into what are referred to as green, red, blue, white and grey biotechnologies. Green biotechnology is used in agriculture, while red is used in medicine and pharmaceutical technology. Blue biotechnology helps products to be obtained from the sea. In white biotechnology, cells are used as synthesis factories, e.g. to produce certain antibiotics. Finally, grey biotechnology is used in waste processing.



Red biotechnology, which is the type of biotechnology relevant to medicine, has a 25-year history. Its main area of application is the manufacture of recombinant active ingredients used to treat serious diseases. The first active ingredient of this type was a human protein, insulin, used to treat diabetes, which was obtained from the bacterium *Escherichia coli*. In 1982, a drug marketing authorisation was issued in respect of this recombinant insulin by the American health authority, the FDA.

The manufacture of biotechnological drugs



The manufacture of biopharmaceutical proteins is based on the universal genetic code. This is because any section of DNA – irrespective of the organism in which it is found – codes for the same amino acid sequence, i.e. the same protein, in any other cell. In order to obtain active proteins, human DNA is thus introduced into easily cultivable cells (e.g. bacteria, yeast, or even mammalian cells). The recombinant cells are then multiplied, and they produce the desired human protein, which is then isolated and purified.

Recombinant cells are produced in accordance with a specific working process. Initially, the gene for the desired protein is isolated from human DNA. The gene is then incorporated into a genetic carrier and, in this form, is transferred into the cells in which the synthesis of the active ingredient is to take place. Cells that have taken up the DNA with the human gene are identified with the help of markers. They are then isolated and selectively multiplied. Using this method, one can obtain pure cell cultures with the same hereditary information, in which each individual cell synthesises the desired 'foreign' protein. Many such 'pure cultures' are compared with each other, with regard to the quantity of the protein produced. A master cell bank is



Production of the master cell bank



Production of the cells

established from the culture with the best yield, and this cell bank can be stored in a deep-frozen state for a long time. Working cell banks are produced from the master cell bank. Cells can be taken from these at any time and can be newly cultivated. These are then used for large-scale production in bioreactors – this process is also referred to as fermentation.

During fermentation, the desired protein is produced. For this process, the choice of cells is key, both in terms of yield and in terms of any biochemical modifications, e.g. glycosylation (adding saccharides to the protein), which can be important for the product's efficacy. Whilst bacterial host cells generally allow high yields to be obtained, mammalian cells are required for the glycosylation of proteins. Mammalian cells, however, are much harder to cultivate, and often produce relatively low yields. Typical mammalian cells used are CHO (Chinese hamster ovary) and BHK (baby hamster kidney) cells.

After the cultivation, the active protein is isolated from the cell culture using centrifuging and filtration and is purified using chromatography. The purification process involves three stages: initial preparation, refinement and final purification. The result is a stable, storable active ingredient, free of residual impurities. The final stage is the pharmaceutical formulation of the ingredient into a usable drug.



Cell fermentation



Purifying the protein

Biosimilars

Whilst low-molecular substances, e.g. acetyl salicylic acid, are generally small molecules, biotechnological active ingredients are generally 100 to 1000 times larger. Small molecules possess simple chemical structures, whereas biotechnological active ingredients form complex, 3-dimensional structures and can display a certain degree of variability, as is the case everywhere in nature, as they are formed in biological systems. This variability could express itself, for instance, in the formation of the tertiary structure, or in the glycolysation of proteins, and this could affect the efficacy of the product. Biological variability is determined in part by the conditions under which the production process takes place. Due to this variable micro-structure on the part of biotech active ingredients, one refers not to exactly identical generics, but to 'biosimilars', i.e. similar molecules. In order for a biosimilar product to be authorised, the variability must be kept within specific bounds. The bounds of this variability may be no wider than have been accepted by the authorities in respect of the reference product.

To fulfil these conditions, bioequivalence studies – as carried out with standard generics – are far from sufficient. Rather, a time-consuming, comprehensive pre-clinical and clinical study programme has to be implemented.

Biosimilars are thus follow-on products from biotech drugs, whose efficacy, safety and quality has been demonstrated in comparison with the model preparation and which are produced and sold on the market once the patent in question has expired.

In contrast to classic generics, the development and production of biosimilars takes a lot more time and expense and requires suitable high-tech know-how. As is clear from Figure 2, the total costs of developing a biosimilar, at up to 100 million euros, are 50 to 100 times the costs of developing a standard generic. The project duration, at six to nine years, is two to three times as long.

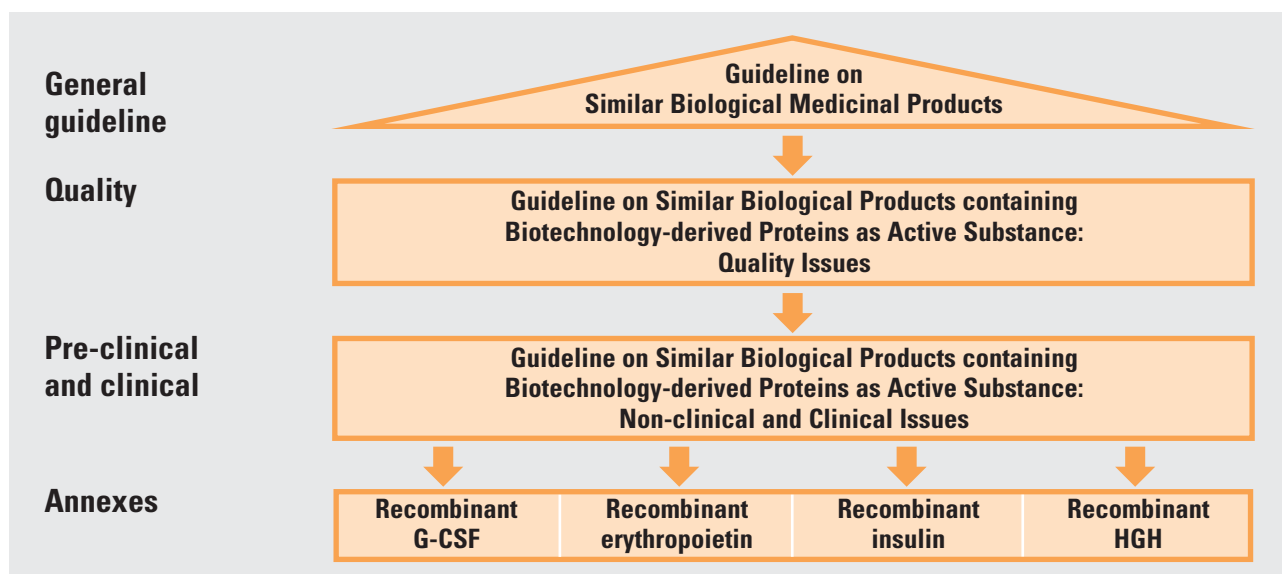
Figure 2 – Biosimilar development lead-time and costs

| Generic | | Biosimilar | |
|------------------------|----------------------|------------------------|------------------------|
| Development costs: | ~ € 1–1.5 m | Development costs: | ~ € 50–100 m |
| Development lead-time: | ~ 3 years | Development lead-time: | ~ 6–9 years |
| Clinical studies: | bioequivalence study | Clinical studies: | Phases I and III, (IV) |

The authorisation of biosimilars

Biosimilars, in contrast to chemical substances, can be authorised only through the central procedures administered by the EMEA, the European Medicines Agency, which is based in London. In order for the efficacy, safety and quality of biosimilars to be demonstrated, the EMEA has set up a system of hierarchically structured, mandatory guidelines (Figure 3). The basic guideline defines the concept of biosimilars and stipulates general requirements with regard to authorisation. The conditions for demonstrating the quality of biosimilars are set out in a second guideline. This guideline contains criteria that must be observed in the production of biosimilars, plus rules concerning the analytical methods that are used to demonstrate the physical/chemical properties, biological activity, degree of purity and possible contaminants. The third EMEA guideline provides information about the necessary pre-clinical and clinical studies. The pre-clinical investigations include studies concerning the binding of the active protein to its receptors, animal studies into the pharmacodynamic effects and toxicological studies. In the clinical study programme, the distribution and metabolism of the active ingredient in the blood and in various bodily tissues must be demonstrated, in each case in comparison to the reference product. Likewise, the relationship between dosage and effect must be demonstrated. Finally, Phase III studies have to be carried out, in addition to the Phase I studies. These are generally conducted as randomised studies, in which the drug is compared to the reference preparation, and these require a large group of patients. Depending on the indication, the number of patents can, on occasion, reach several hundred or thousands. Within the framework provided by the general guidelines, there are further, product-specific guidelines. The product-specific guidelines that have been drawn up so far are those for recombinant G-CSF (filgrastim), recombinant erythropoietin, recombinant insulin and recombinant human growth hormone (HGH). Further product-specific guidelines are in the pipeline.

Figure 3 – The hierarchical structure of the EMEA-guidelines



If, therefore, a biosimilar is developed and authorised by the EMEA in accordance with these guidelines, this means that it has been demonstrated that the product corresponds to the reference product in terms of effect, safety and quality.

The safety of biotechnological drugs

Drawing a sample



Biotechnological drugs, by their nature, have an immunogenic potential, since any protein administered to the body from the outside can trigger an allergic immune reaction. Experience to date with biotech active substances shows, however, that their immunogenicity does not take effect in most patients. Nonetheless, the EMEA is currently producing a further guideline (“Guideline on Immunogenicity Assessment of Therapeutic Proteins”) in order that this aspect is also taken account of in the authorisation process in a suitably standardised way. Furthermore, every manufacturer of biotechnological active ingredients is obliged to establish an in-house pharmacovigilance system. In this system, all adverse effects recorded by the company are documented. All serious adverse effects of biotechnological drugs have to be notified electronically to the EMEA, which is responsible for the development and maintenance of a European pharmacovigilance database, called EudraVigilance. To ascertain and assess the risk of biotech products, the tool of standard pharmacovigilance is generally insufficient. For new biotech products and for biosimilars, the authorities stipulate that a separate risk-management plan be drawn up.

For the manufacturers of biosimilars – and not least for doctors and patients – the EMEA requirements in relation to authorisation provide the highest possible degree of safety: the strict, standardised criteria guarantee the quality, efficacy and safety of biosimilars.

The characteristics of biosimilars

Biosimilars are

- biotechnological high-tech products
- products requiring extensive know-how
- products that are time-consuming and costly to produce
- products for which clinical Phase I and Phase III studies are required
- products that can be authorised only through central EMEA procedures
- products whose efficacy, safety and quality has been demonstrated in comparison to the reference product
- products that are marketed only once the patent in question has expired
- products that contribute to cost savings in healthcare

Websites

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