

BIOSIMILAR WARFARE: THE ARRIVAL OF GENERIC BIOPHARMA- CEUTICALS – THE OMNITROPE DECISION

ISABEL TEARE

Partner, Linklaters, London

Introduction

Biopharmaceuticals are reported to make up some 10 per cent of the pharmaceuticals market, with many new products in the pipeline. On 12 April 2006 the first biosimilar medicine, Omnitrope, was approved by the European regulatory authorities. The same product had previously been approved in Australia, but elsewhere had been bogged down in regulatory uncertainty for years. Omnitrope was quickly followed by a second EU biosimilar approval, for Valtropin. The United States regulator has also approved Omnitrope after long delays and court proceedings.

These biosimilar approvals may be the first of many, at least in Europe, presenting a major new threat to the innovative pharmaceutical and biotechnology industry. This article looks at how the European regulators have leapt into action, with the United States hesitantly following and considers what the future may bring.

What is a biosimilar?

The active ingredients in most medicines tend to be of the ‘small molecule’ variety. The molecules making up the chemical may indeed be small, or they may be quite large and complex. They may involve difficult manufacturing steps. But, ignoring impurities, you either have it or you don’t. A generic producer can therefore manufacture an exact copy of the original medicine, including defined amounts of the active ingredient and the various inactive ingredients (the excipients).

Biopharmaceuticals are different. Typically, these are copies or modified versions of large, biological molecules naturally found in the body. They may include proteins, sugars, DNA or RNA. Compared to ‘small molecule’ active ingredients, they are

extremely large and complex. Some of the larger ‘small molecules’ can be over 1,000 in molecular weight (Pfizer’s statin, Lipitor, has a molecular weight of about 1200.) But the smallest biopharmaceuticals are much larger than this. Insulin, a relatively small protein, has a molecular weight of about 6,000. Indeed, its small size made it easier to characterise in the early days of biotechnology, leading to its early use as a biopharmaceutical. The larger biopharmaceuticals can be many multiples of this. Erythropoietin has a molecular weight of about 34,000. Wyeth and Amgen’s antibody fusion protein, Enbrel, has a molecular weight of about 150,000. Human growth hormone, which will be discussed further below, is at the smaller end of the biopharmaceutical scale, with a molecular weight of about 22,000.

Biopharmaceuticals are typically manufactured using biological processes, for example using living cells to produce proteins from inserted DNA. They tend to be more heterogeneous than the small chemical compounds used in non-biological medicines and are sensitive to manufacturing process variations and differences in the living cells or organisms used. This can have a major impact on the clinical properties of the products and potentially on patient safety. A small change could result in a completely different immune response, for example. They also tend to be less stable than ‘small molecules’, often requiring specific storage conditions.

A biosimilar (also referred to as a biogeneric, a generic biologic, or a follow-on biological or protein) is a generic version of a biopharmaceutical product. Making an exact replica of a biopharmaceutical would be almost impossible. But the product must be close enough to the originator product to justify cross-referral. Companies producing biopharmaceuticals have to demonstrate to regulators that the ‘biological factories’ that they use and the manufacturing conditions are sufficiently consistent to produce a highly reliable product. Manufacturing a copy product will involve establishing a new biological process. Many variations are possible. For example, a particular protein might be made using bacterial cells, yeast cells or even cultured human cells. Depending on how a protein is made, it may or may not have long, branched sugar molecules attached to it in particular places (glycosylation). Each will have its own advantages and disadvantages, and will present particular difficulties to be overcome in perfecting the manufacturing process.

Biopharmaceuticals started to come onto the market in the early 1980s. In 1982, Eli Lilly launched a recombinant human insulin, replacing the previously used preparation derived from the pancreases of pigs and cattle. By 2000, some 77 biopharmaceutical products were available.¹ Until recently, many have benefited from patent protection, and many others still do. However, now that the first patents in this area are

¹ G. Ashton, ‘Growing pains for biopharmaceuticals’, *Nat. Biotech* 19, 307-311 (2001).

expiring (20 years from the mid-1980s, or 25 years for those with maximum extended protection), generic manufacturers are seeking to enter the market.

Because of their complexity and difficulty of manufacture, as well as offering potentially powerful new treatments, biopharmaceuticals tend to be expensive. This presents a potentially exciting opportunity for copyists. Although only sophisticated companies will have the expertise and capital necessary to address this market, those that do so successfully may achieve healthy profits. This is against a background of intense pressure on margins in the rest of the generics market due to the proliferation of entrants.

How were biosimilars dealt with in the past?

Regulators have become accustomed to dealing with generic medicines. They are familiar with cross-referring to data relating to the originator product, once the applicable period of data exclusivity has expired, in order to satisfy themselves as to the safety and efficacy of the generic medicine. Legislation has been introduced in the United States, Europe and several other countries to allow regulators to cross-refer to the non-clinical and clinical data filed by a producer of an innovated product when considering a generic version. Legislation provides for a period of data exclusivity, during which time no such cross-referral can take place. However, once this period has elapsed, generic products can be relatively quickly approved. (Whether the products can be put on the market is another matter. Patent or other intellectual property rights may operate to prevent sale until they expire.)

Biopharmaceuticals cannot be dealt with so simply. While a generic manufacturer may identify an approved product as a reference, the copy product will not be identical for the reasons discussed above. For a long time regulators floundered over this. This is illustrated by the Omnitrope story (see below). Very little actually happened, and until very recently no biosimilar products were approved for sale in the United States or Europe.

What has changed in Europe?

In March 2004, the EU completed a major overhaul of the legislation on the approval of medicines. The existing Directive² governing how Member States were to deal with the approval of medicines was extensively amended,³ and the Regulation⁴ establishing the central approval procedure was replaced.⁵

Under the old regime, the key to use of the abridged procedure is the meaning of the term ‘essential similarity’

used in Article 10(1) of Directive 2001/83/EC (in its unamended form). The term was considered by the European Court of Justice in the *Generics (UK) Limited* case.⁶ A medicinal product was to be regarded as ‘essentially similar’ to the original medicinal product where it had the same qualitative and quantitative composition in terms of active substances, had the same pharmaceutical form and was bioequivalent, unless it was apparent in the light of scientific knowledge that it differed significantly from the original product as regards safety or efficacy.⁷

This definition was the subject of much controversy, and a new, broader definition was introduced when the Directive was revised in 2004:⁸

... ‘generic medicinal product’ shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. In such cases, additional information providing proof of the safety and/or efficacy of the various salts, esters or derivatives of an authorised active substance must be supplied by the applicant. The various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form. Bioavailability studies need not be required of the applicant if he can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate detailed guidelines.

Despite the expansion of ‘generic medicinal product’ to include ‘different salts, esters, ethers, isomers ...’ and so on of an active substance, even the new definition will not encompass biosimilars. This is because of the differences in the exact molecular make-up of similar biopharmaceuticals. The old regime had no specific regulatory provision for issuing marketing authorisations for them. Indeed, when that legislation came into force, the science was arguably not sufficiently advanced to warrant such a distinction. As the science progressed it became apparent that the rules on generics would not be sufficient to deal with biosimilars, and EU legislators sought to fill the vacuum by introducing a new

2) Directive 2001/83/EC.

3) By amending Directive 2004/27/EC.

4) Council Regulation (EEC) No. 2309/93.

5) Regulation (EC) No. 726/2004.

6) Case C-368/96, judgment of 3 December 1998.

7) The Advocate General, Antonio Tizzano, reiterated this test in his Opinion (C-112/02) on the *Kohlpharma* case, published on 11 September 2003.

8) Amended Directive Article 10(2)(b).

Article 10(4) into the amended directive:

Where a biological medicinal product which is similar to a reference biological product does not meet the conditions of the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided. The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Appendix I [which sets out analytical, pharmacotoxicological and clinical standards and protocols for testing] and the related detailed guidelines. The results of other tests and trials from the reference medicinal product's dossier shall not be provided.

This is all very well, but still leaves uncertainty as to what will be required to get a biosimilar approved and onto the market. Much will depend upon the complexity of the product, and the potential severity of its side effects. In any event most biosimilar products must be authorised via the central European route (that is, by application to the European Medicines Agency, the EMEA). This is because the annex to Regulation 726/2004 requires the central route to be used where a product is developed using a biotechnological process, namely: recombinant DNA technology, controlled expression of genes, coding for biologically active proteins from a cell culture and hybridoma and monoclonal antibody methods.

The Omnitrope story

Human growth hormone is a natural molecule produced by the body. Various conditions caused by a deficiency of the hormone, or some other metabolic or genetic problem, have for many years been treated with human growth hormone from outside the body. Initially the hormone was extracted from deceased people. However, as biotechnology progressed, methods of manufacture using recombinant DNA and cell cultures took over. Several manufacturers developed their own products and methods of production, many of which were patented. These manufacturers obtained marketing approvals based on their own pre-clinical and clinical research programmes.

In Europe

Sandoz's Omnitrope is different. It is the first recombinant human growth hormone to be the subject of a biosimilar approval process. In 2001 Sandoz GmbH (part of the Novartis group) applied for European approval using the 'well-established medicinal use' route. This application preceded

the overhaul of the European regulatory system described above. It was therefore not at all clear that a biosimilar product could be regarded as 'essentially similar' to a reference biopharmaceutical and so use the generic approval route. At the time, Article 10 of Directive 2001/83 provided for an alternative route to obtain approval:

The applicant [for a marketing authorisation] shall not be required to provide the results of toxicological and pharmacological tests or the results of clinical trials if he can demonstrate:

...

(ii) ... that the constituent or constituents of the medicinal product have a well established medicinal use, with recognized efficacy and an acceptable level of safety, by means of a detailed scientific bibliography ...

and it was this which Sandoz relied upon, filing a detailed scientific bibliography as well as data from its own studies designed to show comparability.

In June 2003 the EMEA's scientific committee (the Committee for Proprietary Medicinal Products, as it then was, now the Committee for Medicinal Products for Human Use) recommended approval of Omnitrope. However, in late 2003, the European Commission refused to grant a marketing authorisation. At the time, the Commission said that Sandoz should not have relied on 'well established medicinal use' when it would be filing a mixture of published materials and its own clinical data. It said that an approval pathway for biosimilar products was available using the 'essential similarity' route. (This does not sit easily with a later statement from the Commission that biosimilar products 'cannot be regarded and regulated as generics' because they are 'complex biological molecules claimed to be similar – but not identical – to already authorised biotechnology medicines'.)⁹ Sandoz began legal proceedings against the Commission in January 2004, asking the European Court of First Instance to annul the Commission's decision.¹⁰ This action referred to the earlier *Scotia* case which had been criticised for taking an inappropriately rigid approach to the application of an earlier form of the generics legislation.¹¹ (The action does not appear to have been pursued, presumably in the light of the changes in the law and the different approach to biosimilars that ensued.)

In July 2004 Sandoz applied again. Although by this time the new legislation had been passed (see 'What has changed in Europe?' above), most of it had yet to be implemented. In particular, the provisions relating to the approval of biosimilars introduced into Article 10 of the directive were not due to be implemented until October 2005, and the application of these provisions by the EMEA would not take

9) Commission Press Release, 20 April 2006.

10) Case T-15/04.

11) Case C-440/93, judgment of 5 October 1995.

effect until November 2005. The EMEA nevertheless relied on the ‘*similar biological medicinal product*’ legal basis in Article 10(4) of the directive as amended. The reference medicinal product cited for Omnitrope was Pfizer’s Genotropin, which was originally authorised in the EU in 1988. The application dossier contained a fully quality Module 3 and reduced non-clinical and clinical Modules 4 and 5, in addition to the required elements of the comparability exercise. A second positive scientific opinion was given by the EMEA in January 2006, and the product finally received approval on 12 April 2006. Sales commenced shortly afterwards.

In the United States

Sandoz also sought approval of Omnitrope in the United States, commencing its application in July 2003. In August 2004, it emerged that although the United States regulator (the Food and Drug Administration, or FDA) had completed its review, it had been unable to reach a final decision on approval. Sandoz had used the route relating to standard generics laid down in the Hatch-Waxman Act.¹² Pfizer, which produces the branded human growth hormone Genotropin, had strongly opposed the approval of Omnitrope in this way. The FDA’s failure to reach a decision, attributed to both scientific and legal uncertainty, faced a challenge by Sandoz in the courts. On 10 April 2006, the District Court for the District of Columbia granted summary judgment to Sandoz, requiring the FDA to issue a decision on the product’s approval, although no deadline was set.

The FDA had held workshops to discuss the scientific and technical issues surrounding follow-on proteins in 2004 and 2005. A background White Paper and draft guidance were to follow but have not so far been seen. The FDA was also under pressure from legislators Senator Hatch and Representative Waxman (whose names appear on the Hatch-Waxman Act) at least to deal with certain products (insulin and human growth hormone). Finally, on 30 May 2006 the FDA approved Omnitrope. The FDA was careful to state that this did not create a new pathway for all biosimilars. Most biopharmaceuticals are approved in the United States under the Public Health Service Act, rather than as drugs under the Food, Drug and Cosmetic Act. The Public Health Service Act does not include an abbreviated approval pathway. The FDA also emphasised the special characteristics of human growth hormone, which make it possible to compare one product with another. Important here were human growth hormone’s long history of use and extensive description in the literature, as well as its relative simplicity (being a protein without attached sugar molecules). It seems that a change in US law will be necessary to permit the approval of other biosimilars.

In Australia

Interestingly, Omnitrope received approval in Australia in September 2004 and has been on the Australian market since November 2005.

Followed by Valtropin

The approval of Omnitrope in Europe was swiftly followed by a second biosimilar approval. This was for Biopartners’ product, Valtropin, also a recombinant human growth hormone. In a press release dated 4 May 2006, Biopartners referred to Valtropin as ‘the first product in our broad and advanced pipeline to gain authorisation’, adding that ‘Biopartners is currently developing a sustained release version of Valtropin that is currently in Phase III clinical trials’. Biopartners states that its mission is ‘to develop biosimilars and innovative formulations of ‘first generation’ biopharmaceuticals’ and adds that it is ‘developing a comprehensive range of biopharmaceutical products ... across many therapeutic areas’. Valtropin was developed in collaboration with LG Life Sciences. This second authorisation, and the comments that accompanied it, indicate that this is only the start of a wave of biosimilar products.

EMA guidance

As noted above, Article 10(4) of the amended directive does not set out with any particularity what is required to obtain a biosimilar approval. However, since the implementation of the revised pharmaceuticals legislation, the EMA has issued a series of guidance documents on biosimilars. Preparation of these guidelines began before the ink was dry on the pages of the revised legislation.

The *Guideline on similar biological medicinal products*¹³ was discussed by the CPMP in June 2004 and released for consultation in November 2004, before coming into effect on 30 October 2005. It outlines the basic principles in the biosimilar process and sets out to provide a ‘user’s guide’. Important principles include: (i) the use of a single reference product, as authorised in the EU, throughout the comparability programme; and (ii) the pharmaceutical form, strength and route of administration should be the same as those of the reference product, or any differences must be supported by additional data. The guideline refers to vaccines and allergens. Since these are currently regarded as unlikely to be thoroughly characterised at a molecular level, they must be dealt with on a case-by-case basis.

Several of the supporting guidelines came into effect on 1 June 2006. These include the following.

12) Drug Price Competition and Patent Term Restoration Act of 1984.

13) CHMP/437/04.

*Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues.*¹⁴ This sets out what the EMEA will require for a biosimilar application to succeed. The application dossier must include a full quality dossier. Comparable clinical efficacy and safety also have to be demonstrated.

*Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues.*¹⁵ This addresses the requirements to demonstrate quality. Note that the same reference product must be cited for quality as for safety and efficacy.

*Annex – guidance on similar medicinal products containing recombinant granulocyte-colony stimulating factor.*¹⁶ This and the following two annexes provide product-class specific guidance and ‘presents the current view of the CHMP on the application of the main guideline for medicinal demonstration of comparability of two rG-CSF-containing products’.

*Annex – guidance on similar medicinal products containing somatropin.*¹⁷

*Annex – guidance on similar medicinal products containing recombinant human soluble insulin.*¹⁸

And coming into effect on 1 July:

*Annex – guidance on similar medicinal products containing recombinant erythropoietins.*¹⁹

The following further guidelines are currently being finalised.

*Concept paper on guideline on comparability of biotechnology-derived medicinal products after a change in the manufacturing process – Non-clinical and clinical issues.*²⁰ This draft guideline replaces one²¹ which addressed two situations: first, where the manufacturing process for an authorised product was to be changed, and second, where a biosimilar product is proposed for authorisation. Since the second situation is now addressed by the new guidelines on biosimilars, this guideline will deal with the second situation only.

*Concept paper on guideline on immunogenicity assessment of therapeutic proteins.*²² The deadline for comments is 1 June 2006.

*Concept paper on similar biological medicinal products containing recombinant alpha-interferon.*²³ This paper is open for comments until 1 August 2006.

Clearly, the EMEA and Commission contemplate a significant number of biosimilar applications coming through and have prepared or are preparing detailed guidance for a variety of biopharmaceuticals.

Implications and conclusions

After a long period of uncertainty, the first biosimilar products are on the march in Europe, the United States and Australia. The 2004 overhaul of the European medicines legislation has provided European regulators with both the impetus and the opportunity to get to grips with this question. As well as granting two product approvals, the EMEA has issued a series of guidance documents, showing that it is gearing up for a series of further biosimilar product reviews. The FDA, normally in the vanguard of regulatory developments, approved a product but only after intense pressure from several directions. It indicated that this was a special case, and that a change in the law is necessary before it can implement a general system of review of biosimilars for the United States market. As governments around the world seek ways to bear down on the rising costs of healthcare, however, it would seem that approval of these products in the United States and other countries is only a matter of time.

While the skills and technology needed to produce biosimilars are far greater than those required for ordinary generic products, a number of companies have identified themselves as being up to the challenge. Innovator companies now need to consider what strategies are available to protect their positions. Many products will still benefit from patent cover, data exclusivity or both. Supplementary periods of patent protection will be available for many products, through legislation that offers extended patent cover to make up for time lost in the regulatory approval process. But as these periods of protection draw to a close, innovator companies need to consider improvements to their products, particularly if these can attract patent protection. Pegylation of protein molecules, in order to extend their life in the body, is an example of a technology which can sometimes attract further protection. Other areas where protection might be achieved are innovations in manufacturing processes or modes of administration. But one thing seems certain: biosimilars will eventually invade the market as generics have done.

© Linklaters 2006

14) EMEA/CHMP/BMWP/42832/2005.

15) EMEA/CHMP/BMWP/49348/2005.

16) EMEA/CHMP/BMWP/31329/2005.

17) EMEA/CHMP/BMWP/94528/2005.

18) EMEA/CHMP/BMWP/32775/2005.

19) EMEA/CHMP/BMWP/94526/2005.

20) EMEA/CHMP/BMWP/9437/2006/corr.

21) CPMP/3097/02.

22) EMEA/CHMP/BMWP/246511/2005.

23) CHMP/BMWP/7241/2006.