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# Generic and biosimilar medicinal products in the European Union

The recent revisions of the Community Codes on Medicinal Products have resulted in a number of changes to the procedure for granting marketing authorisation for generic medicinal products, both human and veterinary. The modifications have also resulted in the introduction into the Community Code on Human Medicinal Products of the term "biosimilar", a definition that is perceived in some corners as an acknowledgement of the fact that it is not possible to produce a generic version of a biotechnology product.

## GENERIC MEDICINAL PRODUCTS

The new provisions of the Community Code on Medicinal Products governing marketing authorisation of generic products introduces a system that provides clarification of the approval procedure that such products must follow and the criteria that they must fulfil prior to approval. There are undoubted benefits in the establishment of a simplified system for authorisation of generic products. However, the new system also presents potential future concerns for manufacturers of innovative products given the potentially wide ranging nature of the "global authorisation" discussed below.

It was not solely generic products that benefited from the revision of the Community Codes. The rights of innovative products arising from the grant of marketing authorisation for their products were also clarified. As a result of Article 10(1) of the Community Code on Medicinal Products and Article 13(1) of the Community Code on Veterinary Medicinal Products, repeated in Articles 14(1) and 39 of Regulation 726/2004 (1)<sup>1</sup> (the new Regulation governing centralised authorisation procedures and the functioning of the European Medicines Agency (the EMEA)), it was made clear that innovative products were entitled to eight years data protection and 10 years market protection from generic competition. The net effect of this should be that the data on which the authorisation of a medicinal product or a veterinary medicinal product is based should be protected from use to ground an application for authorisation of a generic product for at least eight years and that an innovative product, whether

authorised in accordance with the centralised procedure or in accordance with the decentralised procedure, should have market protection in the EU for 10 years. However, the Community Code has also introduced the concept of a "global authorisation". An application for generic authorisation of a medicinal or veterinary medicinal product is based on this definition. The term "global authorisation" includes, in addition to the initial authorisation for a reference product, any additional strengths, pharmaceutical forms, administrations routes, presentations, as well as any variations and extensions. The related provisions of the Codes specifically state that all of these marketing authorisations shall be considered to belong to the same global authorisation, in particular for the purpose of applications for authorisation of generic products.

A generic product is defined by the Community Code as a medicinal product with the same qualitative and quantitative composition in active substances and having the same pharmaceutical form as the reference medicinal product. Moreover, its bioequivalence with the reference medicinal product must be demonstrated by appropriate bioavailability studies.

As an initial step in the approval of a generic product, it must be demonstrated that the "reference medicinal product" (or innovative product) on the basis of which an application for generic approval is based has been authorized in the European Union for at least eight years. The authorization for the reference product does not need to be presently in force, although it is self-evident that the authorisation must not have been withdrawn for reasons of public health. Moreover, an applicant for a generic authorisation is not required to demonstrate that the reference product is, or was, authorised in same EU Member State as that in which the application for generic authorization is submitted.

As mentioned above, a fundamental right granted to manufacturers of innovative products is that of protection of its data from generic competition for eight years and market protection from generic competition for 10 years. The approach of the European Commission does, however, raise issues as to how this ten year period is to be calculated.

On 10 April 2006, the European Commission granted the first ever centralised authorisation for a generic version of a veterinary medicinal product. The authorisation resulted in unfortunate consequences for the holder of the marketing authorisation for the reference product on which the approval of the generic product was based. That company saw the ten-year period of protection that Regulation 2309/93 (the original EMEA Regulation), on

<sup>1</sup> Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

which its marketing authorisation was based, led it to expect it was entitled to, reduced to just over eight years by the European Commission Decision.

Metacam the reference product in that case, was initially approved at national level in several EU Member States. However, it was subsequently considered entitled for grant of a Community marketing authorisation via the centralised system as it was a product intended for food-producing animals and its active ingredient, meloxicam, had not been authorised for use in food-producing animals on the date of entry into force of the original EMEA Regulation.

Consequently, on 7 January 1998, the European Commission issued a marketing authorisation, valid throughout the European Union, for Metacam. The original indications for the product that had previously been authorised according to national procedures in several EU Member States also became subject to a centralised authorisation and the related national authorisations were withdrawn.

Following its authorisation in accordance with the centralised procedure, the marketing authorisation holder for the innovative product, Boehringer Ingelheim, would, one presumes, have expected to be entitled to see Metacam, in all its forms, benefit from 10 years' market protection from generic competition. This would mean protection until January 2008.

However, in April 2006, the European Commission granted a marketing authorisation for a generic version of this product to the company Omnipharm for a product called Flexicam. This generic authorisation was evidently within the ten-year protection period. However, the Commission apparently chose not to base its calculation of the protection period to which Metacam was entitled under the EMEA Regulation. Rather, it seems, it chose to base its calculation on a period linked to a previous national authorisation. The net effect of this, and of the authorisation of Flexicam, was to deprive Metacam of part of the 10-year protection period that, as a product authorised in accordance with the centralised procedure, it should one would have thought, have been entitled to expect.

The approach adopted by the European Commission in this case seems essentially to suggest that, on one hand the Institution has the power to grant centralised authorisation for a generic of a nationally approved product, and on the other hand, it has the power to derogate from the provisions of the EMEA Regulation granting a defined protection period to a product that it had, itself, previously authorised. The question arises as to whether there is a valid legal basis for such an approach. The EMEA's own guidance raises questions about this. In its recently published Guidance for users of the centralised procedure for Generics/Hybrid Applications, published on 24 October 2006, the EMEA provides that automatic access to the Centralised Authorisation Procedure is given to applicants for generic approval based on reference products previously authorised under the Centralised Authorisation Procedure. Moreover, optional access can be granted when the reference medicinal product was authorised under the national/ Mutual Recognition (MRP)/ Decentralised Procedure. However, to be entitled to participate in such a procedure, the generic manufacturer must provide sufficient evidence that the generic product brings a significant therapeutic, scientific or technical innovation or a community authorisation is justified on grounds of the interest of patients at Community level.

An additional concern raised by the revised provisions relates to the protection of data related to "evolving"

reference protects as a result of the "global authorisation" of generic products according to the newly revised Community Codes. If the global authorisation covers both the reference product and any subsequent variations and extensions to the product, what protection is available to data generate to support the subsequent application for authorisation?

## BIOSIMILARS

One of the new aspects of the revised Community Code on Medicinal Products is the introduction of the category of products referred to as "biosimilars". The Code does not provide a specific definition of biosimilars. It does, however, make clear that biosimilars are not generics. As a result, they can not be authorised in accordance with the procedures for authorisation of generic products for which the Code provides. Owing to, in particular, differences between biosimilars and their reference products relating to raw materials or differences in manufacturing processes the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided.

Following introduction of the denomination "biosimilar", the EMEA, in late 2004 and early 2005, issued guidelines concerning authorization for marketing of biosimilar products. These include a general guideline document, guidelines concerning clinical and non-clinical issues relating to the comparability of biotechnology-derived proteins as active substance, and guidelines concerning quality issues relating to the comparability of biotechnology-derived proteins as active substance. These guidelines reflect the view expressed in the Community Code that, due to the complexity of biological/biotechnology-derived products, traditional "generic" approvals would be scientifically inappropriate for these products. Instead, the "similar biological medicinal products" approach, based on a comparability exercise, must be followed.

Marketing authorisation of biosimilar products is granted by the European Commission according to the Centralised Authorisation Procedure. Prior to any decision of the European Commission concerning authorization of medicinal products, including biosimilars, according to the Centralised Authorization Procedure, the Committee for Medicinal Products for Human Use (CHMP) of the EMEA must give its opinion on the application for authorization. The CHMP opinion relates essentially to whether the data and information accompanying the application are sufficient for the type of authorization sought. Although the opinion of the CHMP is not legally binding (only the European Commission has the power to make a binding decision), the European Commission is required by law to provide a detailed explanation should it choose not to follow a CHMP opinion. The Commission's decision normally follows 2-3 months after a CHMP opinion. In late January 2006, the CHMP announced its first positive opinion on an application for authorization of "a similar biological medicinal product". On 12 April 2006, the European Commission granted a centralised European marketing authorization for the product Omnitrope (somatotropin). This was the first authorization of a biosimilar under the new EU legislation. The Omnitrope application referenced data and information contained in the marketing authorization (MA) file for Pfizer's hGH, Genotropin.

Just two weeks after its first biosimilar approval, the Commission adopted a decision approving a second biosimilar for Valtropin (somatotropin recombinant), a joint

project from Biopartners and LG Life Science Ltd. (South Korea). Valtropin is similar to Humatrope (somatotropin), the reference medicinal product produced by Eli Lilly and originally authorized in the EU in 1990.

Following authorization of Valtropin, Biopartners announced that it had submitted an application seeking authorization of a biosimilar version of interferon alfa called Alpheon. The reference product was Roferon-A from Hoffman-LaRoche. However, on 28 June 2006, the CHMP issued a negative opinion on the application concluding that major concerns regarding the comparability of the biosimilar and its reference products existed. It added that "There were also concerns that BioPartners did not have enough data on the stability of the API and of the final drug product. In addition, the process used for making the drug had not been adequately validated".

Just a few weeks after its EU approval, Omnitrope was launched in Germany and Austria, priced at 20 percent below Genotropin. Sandoz was required to invest heavily in promoting Omnitrope, among other reasons due to the need to break down initial physician opposition to prescribing biosimilars. Biopartners is expected to need to

offer Valtropin at a similar discount if it is to compete with Omnitrope. Omnitrope will have an advantage of several months' sale on the German and Austrian markets, but Valtropin might be able to reap the benefit of Omnitrope's promotional efforts.

The EU pharmaceutical industry is facing increasing competition, not solely from traditional competitors, such as the US and Japan, but also from emerging industries in countries such as China. The revisions to the Community Codes both provide tools and highlight concerns that this represents.

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