Generics & global EU approvals: cause for concern?

The revisions to the EU's Community code on medicinal products which came into effect last year include changes to provisions concerning the authorisation of generic medicinal products. These modifications have been welcomed in some quarters. However, their application may raise issues of interpretation. Of particular interest will be the term "global marketing authorisation". It may well be left to the courts to interpret their application, says Elisabethann Wright, counsel at the law firm Hogan & Hartson in Brussels.

The changes to the Community code concerning generic products owe much to the case law of the European Court of Justice of the last decade. The court was asked on a number of occasions to determine the relative rights of holders of marketing authorisations for reference products and those of their generic competitors. This it did with some alacrity. Unfortunately for the innovative industry, the general conclusion was that these interpretations were not to its benefit.

Among the conclusions of the court was, for example, its decision in the *Generics*[1] case, where it concluded that an authorisation of a product as "essentially similar" to a reference product covered all therapeutic indications, dosage forms, doses and dosage schedules already authorised for that product. Other decisions of the court, such as those in *Approved Prescription Services*[2], in which a liquid and a capsule were deemed to be essentially similar, and *AstraZeneca*[3], where a similar conclusion was drawn by the court as regards tablets and capsules that had previously been withdrawn from the national market, contributed to the evolution of the European understanding of the term "essential similarity".

Following the adoption of changes to the community code, it now defines in substantial detail the elements of an authorisation of a reference product that would appear to fall within a subsequent authorisation of a generic product. How these elements will be applied in practice is still a matter of debate.

The second paragraph of Article 6(1) of the revised code introduces the "global marketing authorisation". Falling within this definition, in addition to the initial authorisation for a reference product, are any additional strengths, pharmaceutical forms, administration routes and presentations, as well as any variations and extensions. The provision particularly states that all of these marketing authorisations belong to the same global authorisation, in particular for generic approval applications.

The definition of a "generic medicinal product" in Article 10(2)(b) of the revised Community code covers a wide variety of elements. It is not limited to medicinal products with the same qualitative and quantitative composition in active substances, the same pharmaceutical form and demonstrable bioequivalence. It also covers the different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance unless these differ significantly in properties with regard to safety and/or efficacy. The various immediate-release oral pharmaceutical forms are also considered to be the same pharmaceutical form.

Article 10(1) of the code says that an applicant for marketing authorisation is not required to provide the results of preclinical tests and clinical trials if it can show that the product is a generic of a reference product that is, or has been, authorised in a member state or in the Community for not less than eight years.

There are at least two important consequences of this provision. The first is that it is unnecessary for the reference product to be on the market when the generic application is submitted. Evidently, a product that has been withdrawn from the market for reasons of public health would not fall within this exception. However, the absence of any indication of the length of time during which the product can be absent from the market and still remain a potential reference product is unclear. Guidance from the commission in this area would be important and welcome.

The second consequence of this provision is that the reference product does not need to have been placed on the market in the EU member state in which a generic application is made. It needs simply to have been authorised, either under the centralised procedure or by any member state's competent authority. How some member states are likely to react when faced with an application for a generic product based on a reference product previously authorised in another member state could prove interesting.

The apparently very broad application of the term "global authorisation" could have an impact in two particular areas. The first relates to applications for approval of a product for therapeutic uses other than that for which it was originally authorised. The question arises as to which would be the most appropriate application route for such a product. If it fell within any of the categories identified in the new EMEA regulation as either bound by, or entitled to, authorisation under the centralised procedure, it should be approved under that procedure.

However, if the product fell within any of the definitions in the global authorisation, would it be perceived as simply an extension of an existing product authorisation or, if the marketing authorisation holders differed, as a generic of the reference product? In either circumstance, should the second authorisation benefit from the eight years of data exclusivity and 10 years of market exclusivity allowed under the EMEA regulation for authorisations granted in accordance with the procedure for which it provides?

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Irrespective of the authorisation entitlement of such a product, problems of interpretation may arise concerning the position of subsequent generic applications. These would concern in particular the "global authorisation" to which a subsequent generic product should be entitled. Should this global authorisation include the original reference product plus any subsequent centralised authorisations of that product for a different therapeutic application? If interpretation of the term "global authorisation" is considered to include such subsequent authorisations, what approach should be adopted if a generic application is submitted before any data and market protection extensions to which the second authorisation is entitled have expired? These are issues that need to be addressed.

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[1] case C-368/96; [2] case C-36/03; [3] case C-223/01