

# Bringing a drug to market in the EU using the new decentralised procedure



Anthony Warnock-Smith

**Medicinal products are highly regulated in the European Union (EU) and are subject to a separate, complicated system of approvals that governs how, when, where, and in what form such products will be allowed to be sold within the borders of the EU. Anthony Warnock-Smith examines the use of the new decentralised procedure when bringing a new drug to market in the EU.**

The regulation of medicinal products is governed in the EU by Directive 2001/83/EC relating to medicinal products (the "Directive"). Also known as the Consolidated Directive, it brings many years of separate legislation together into one, detailed document. It was last updated in 2005, when a number of far-reaching, fundamental, and sometimes controversial changes were made, including the introduction of a new decentralised procedure for the authorisation of medicinal products.

Although the Directive contains many complexities, the fundamental premise of it is simple: no medicinal product may be placed on the market in the EU unless the relevant competent authority grants a marketing authorisation. As a result, one of the most important considerations a pharmaceutical company has to make when bringing a drug to market in the EU is which marketing authorisation to apply for. Previously, there were only two possible routes to authorisation, but changes to the legislation in 2005 mean that applicants can now have three possible choices.

Prior to the introduction of a uniform, EU-wide system, each Member State had responsibility for granting and regulating medicinal products within its borders. Updates and amendments to EU legislation governing medicinal products over the years have resulted in the harmonisation of the approvals system to help facilitate the free circulation of authorised medicinal products throughout the EU. However, as is illustrated by the following, in many ways the approvals system remains somewhat disjointed.

Depending on a product's eligibility, each of the authorisation routes offers various advantages and disadvantages, as further detailed below.

## ... the centralised procedure

The centralised procedure is compulsory for products developed by means of certain biotechnological processes, orphan drugs and new active substances for the treatment of Aids, cancer, neurodegenerative disorders, diabetes, and from 1 May 2008, autoimmune diseases and other immune disfunctions and viral diseases. In addition, it is open to medicinal products containing a new active substance never before authorised in the EU, medicinal products that can be proven to have a significant therapeutic, scientific or technical innovation, or where the authorisation would be in the interests of human or animal health.

Products authorised pursuant to the centralised procedure are granted marketing authorisations that cover all EU Member States and the EEA. A further distinguishing feature of this route includes the requirement for the marketing holder to secure also a single EU-wide

trademark for the product. However, the convenience of the centralised procedure is also accompanied by fees that are significantly higher than the national procedure.

## ... national marketing authorisations

With the exception of products granted a marketing authorisation under the centralised procedure as set out above, all products are granted marketing authorisations on a country-by-country basis by the competent authorities in each Member State. Such marketing authorisations permit the holder to market the product in question in the Member State concerned, subject to any restrictions or requirements that accompany the authorisation.

## ... the mutual recognition procedure

Medicines legislation also foresees the possibility that most pharmaceutical companies will wish to market their products in more than one EU country, and provides two mechanisms to applicants that avoid the need to submit full marketing authorisation applications in each country.

The first of these, the mutual recognition procedure, enables pharmaceutical companies who already hold a marketing authorisation in one EU Member State to ask additional Member States to recognise the marketing authorisation that has already been granted. The procedure involves the preparation of an assessment report by the original Member State that is forwarded to the additional Member States for its consideration. Assuming the other Member States agree with the report, a marketing authorisation will then be issued for the product in the Member States concerned. However, the Mutual Recognition procedure often sees disagreements between Member States that can hold up the procedure and lead to delays. For such occasions, there is a detailed disputes procedure that must be followed.

## ... the decentralised procedure

The second of these, the decentralised procedure, which was introduced during the changes to the legislation in 2005, aims to avoid some of the potential disputes between Member States and the resulting delays to authorisation by engaging each of the Member States to which the applicant wishes to apply at the time the first marketing authorisation is made. Consequently, this procedure is open only to products that have not yet been granted a marketing authorisation in the EU. Under the decentralised procedure, the applicant chooses one Member State to be its reference Member State. The chosen reference Member State then prepares a draft assessment report that is submitted to the other Member States for their

.....  
*continued . . .*

simultaneous consideration and approval. In allowing the other Member States access to the application at this early stage, it is hoped that any potential issues and concerns of the Member States can be dealt with quickly and efficiently and without the politics that sometimes weigh down the mutual recognition procedure. However, disputes will be inevitable in some cases and on these occasions, the decentralised procedure follows a course of action that is similar to that of the mutual recognition disputes procedures.

There are several key advantages of the decentralised procedure. Foremost amongst these is a strong commercial advantage: because the applicant receives identical marketing authorisations for its medicinal product in all chosen Member States at the same time, it is possible to launch a new product on the market in several different EU countries simultaneously, thus reducing the associated launch costs and potentially creating a strong brand and presence for the product in the EU from day one. In addition, the fact that identical marketing authorisations will be issued for the medicinal product concurrently should lead in theory to a significant reduction in the regulatory hurdles the applicant must go through in the first instance to obtain the marketing authorisations, and this is coupled with a potential reduction in the future administrative burden of the marketing authorisation holder with regard to the variations, extensions and renewals of the marketing authorisations in each Member State.

Exactly how successful the procedure is in controlling Member State disputes and reducing the administrative burden of applicants remains to be seen. However, where the centralised procedure is not

a possible nor viable route for companies wishing to obtain approval for and market a new medicinal product in the EU, the decentralised procedure represents an attractive, and in any event more affordable pathway for companies looking to bring their medicinal products to market in the EU.

Following the introduction of the decentralised procedure in 2005 the former Mutual Recognition Facilitation Group was reorganised into the Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMD(h)). Its purpose is the examination of questions relating to marketing authorisations of medicinal products in two or more Member States under the mutual recognition procedure or the new decentralised procedure. Its report at the end of its first full year of operation shows that in 2006 there were 596 mutual recognition procedure applications and 450 new decentralised procedure applications. In that same year 105 of the mutual recognition procedure applications were referred to the CMD(h) and 22 to the Committee for Medicinal Products for Human Use (CHMP) for arbitration. Under the decentralised procedure, in marked contrast, only one was referred to the CMD(h) and none to the CHMP. That extreme and stark difference between the two procedures is probably a pure statistical effect given the newness of the decentralised procedure but it may be some indication of the additional certainty levels which the new system may afford. Next year we will have a much more complete picture. \*

*Anthony Warnock-Smith is a Partner and Head of the Life Sciences group at the London office of international law firm Morgan Lewis.*

## An analyst's view: the Paediatric Regulation

“When you talk about the Paediatric Regulation and especially with reference to clinical trials, there are a lot of things that I think are still ambiguous or at least not clearly defined,” says V Sriram, an analyst with Frost & Sullivan. In an interview with *EURALex*, Mr Sriram accepted that “in principle” the entire Regulation has been very well received by the pharmaceutical industry, but added that it still contained areas of relative obscurity.

He mentioned uncertainties surrounding the size of the required study and difficulties in specifying the appropriate population for such trials, including larger trials or smaller studies focusing of pharmacokinetics. “I don’t think the guidelines are very well laid out for recruiting the population for these trials,” Mr Sriram added.

And he also believes that questions remain as to the method of comprehensively implementing the European Medicines Agency (EMA) legislation in the area of paediatric medicines. Other complex issues include confusion over the role of ethics and informed consent. “How do you actually get informed consent from a paediatric population?” the analyst posed. Mr Sriram conceded that minors may in fact be bypassed over the issues, with eventual consent being obtained from the legal guardian or parent, however, he suggested that this could still potentially lead to legal complications in the future.

Among other sectors, the current focus of the legislation will be on cancer and infectious diseases. And before the trial can go ahead, a paediatric investigation plan (PIP) must be submitted to the EMA for review. This could hurt products that are actually at the developmental stage because the kind of screening processes and the initial phase of drug discovery that is focused on the adult population, compared with that aimed at the paediatric population, might not always concur, Mr Sriram suggested.

This means that the investment that has already gone into developing a formulation or a dosage for an adult population has to be replicated on a mandatory basis for a paediatric setting. And Mr Sriram pointed out that this is not restricted to financial investment, but also the time and effort in compiling the necessary documentation. It is this combined effort that will be required to satisfy regulatory authorities with regard to the quality, safety and efficacy of paediatric medicines that may impact on companies’ plans to initiate the discovery and development of new products, he suggested.

“A lot of effort has to be put into submitting dossiers for paediatric versions of medicines, for which the adult versions are already doing very well in the market,” Mr Sriram stressed. It is this obligation for companies that is “definitely” set to slow down the rate of innovation in the European R&D scene, at a time when the industry is already concerned that it lags behind the US, whilst India and China are expanding at a blistering pace.

At the same time, Mr Sriram believes that pharmaceutical and biotechnology companies will be happy with the six-month extension to the supplementary protection certificate (SPC). When the period of protection has ended on a paediatric product and the marketing authorisation holder intends to discontinue it, the company should actually transfer the marketing authorisation, or allow a third party, which has expressed an interest, to declare its intention to continue to place the medicinal product in question on the market, he pointed out.

Mr Sriram conceded that once the patent expires the product is indeed open to generic competition, but surmised that this was “not a rapid spill-over effect in all the cases”. \*