New EU approach to medicines for children reviewed by Hogan & Hartson

It has been estimated that more than 50% of medicines used to treat children in Europe have not been tested for use in this population, neither have they been authorized for use in the care of young people. On January 26, new European Union legislation on medicines for children entered into force.

The Pediatric Medicines Regulation aims to balance the ethical issues raised by conducting trials on children with concerns arising from treatment with products that have not been tested on them and the effects, both positive and negative, of which have not been assessed, say Elisabethann Wright and Susan Clements of international law firm Hogan & Hartson, who review the new legislation and its implications.

The Regulation aims to increase the development of medicines intended to treat children, encourage research into drugs for this population and to improve the quality and quantity of information available in this area.

The new legislation applies regardless of whether the drug in question is intended for pediatric use

All pharmaceutical companies seeking to sell their medicines in the EU have an interest in this legislation, whether or not the products are intended to treat children. Indeed, applicants for marketing authorizations for new medicines and line extensions at EU and EU member state level must comply with its stringent requirements. The requirements apply irrespective of whether or not the medicinal product for which authorization is sought is intended to be administered in children. However, they do not apply to generic products, biosimilars, hybrids, products containing substances acknowledged to have well-established medicinal use and herbal and homeopathic medicines.

The Regulation is also of particular interest to pharmaceutical companies seeking to develop off-patent medicinal products for use in children. Indeed, it provides for a new type of approval called a Pediatric Use Marketing Authorization. The Regulation imposes an extensive system of requirements on companies and provides for penalties for non-compliance. However, it also offers rewards and other incentives.

Requirements

The Regulation introduces the requirement that applications for marketing authorizations for new medicinal products include either the results of studies in the pediatric population that have been carried out in accordance with an agreed Pediatric Investigation Plan (PIP), or proof of having obtained a waiver or deferral from this obligation. This obligation also applies to applications for extension of an existing authorization for products that are currently covered by either, a supplementary protection certificate (SPC) or, by a patent that will be eligible for an SPC, to cover a new indication, new pharmaceutical form or new route of administration.

The obligation applies irrespective of whether or not the medicinal product for which authorization is sought is intended to be administered to children. It applies equally to both centrally authorized and nationally approved products.

The Regulation provides for the establishment at EU level of an expert Pediatric Committee (PDCO) within the European Medicines Agency (EMEA). It will be made up of five experts from the Committee for Human Medicinal Products (CHMP), representatives of the 22 EU member states that are not previously represented by members of the CHMP, three health professionals appointed by the European Commission, and three representatives of patients' associations, also appointed by the European Commission. It is with this Committee that an undertaking applying for either a marketing authorization for a new medicinal product, or a variation or extensions for existing patent protected medicinal products must agree a PIP. The purpose of a PIP is to generate data determining the conditions under which the medicinal product may be used to treat children. The requirement to agree a PIP does not extend to generic products, biosimilars, hybrids, products containing substances acknowledged to have well-established medicinal use and herbal and homeopathic medicines.

Waivers and Deferrals

An undertaking may seek either a waiver of a deferral from the Committee from the obligation to provide pediatric studies. A waiver may be granted where evidence is provided that the medicinal product, or class of products, is likely to be ineffective or unsafe in part or all of the pediatric population, where the disease or condition for which the product or class is intended occurs only in adults, or where a specific product does not represent a significant therapeutic benefit over existing treatments.

A request to have initiation or completion of some or all of the measures included in the program deferred may accompany submission of a PIP. A request for a deferral must be justified on scientific or technical grounds or on grounds related to public health.

In order to increase the availability of information and to avoid unnecessarily repeating studies, details on these clinical trials will be included in the EU database of cli-

nical trials (EudraCT). Guidance will be drawn up on the nature of the information to be included and on which information will be made public.

The Commission or the national regulatory authority must ensure that the marketing authorization application complies with the agreed PIP. Provision is made in the Regulation to permit the CHMP, the competent authority, or the undertaking to ask the Committee's opinion on compliance of the marketing approval application with the PIP. The CHMP or a competent authority may also ask the Committee's opinion on the quality, safety and efficacy of the product for its use in children.

Where a marketing authorisation includes an indication for pediatric use the label must display a symbol to reflect this. The European Commission will select the symbol to be used by January 26, 2008.

Appropriate steps to ensure the maintenance of supply of products approved for pediatric use have been addressed in the Regulation. Where, following expiry of data protection and market protection periods for which the Regulation provides, the marketing authorization holder intends to withdraw the product from the market, it must comply with certain specific requirements. The undertaking must inform the EMEA of its intention to withdraw the product no less than six months before it is removed from the market. It must also transfer the marketing authorization or allow a third party which has declared its intention to continue to place the product on the market to use the pharmaceutical, preclinical and clinical documentation contained in the file of the medicinal product.

Rewards

There are a range of rewards for undertakings for compliance with the PIP. This includes undertakings that have products for which pediatric development is already in progress when the Regulation enters into force. However, these will benefit only if "significant" studies contained in an agreed PIP are completed after entry into force of the Regulation on January 26. The European Commission will draw up guidelines on how to assess whether or not studies are significant.

For newer medicines benefits include:

- six months extension of the SPC to which the product is entitled;

- two years extension of market exclusivity for orphan medicines. The reward is for conducting studies in the pediatric population and is therefore granted even when a pediatric indication is not authorized provided that the results of the studies conducted are reflected in the SPC and, where appropriate, the package leaflet; and

- optional access to the centralized EU level procedure for marketing authorization applications that include one or more pediatric indications on the basis of studies conducted in accordance with the agreed PIP.

For older medicines, a new type of approval, a Pediatric Use Marketing Authorization (PUMA) will be available. This type of authorization, for which eight years' data protection and 10 years' market protection are provided, will apply solely to products for which the patent has expired and which are not protected by an SPC. It covers therapeutic indications developed exclusively for use in the pediatric population in accordance with an agreed PIP. Optional access to the centralized EU level procedure is available for PUMAs. The medicinal product granted a PUMA can use the existing brand name for the corresponding product authorized in adults.

Penalties

The Regulation envisages penalties at EU and national level for non-compliance with its provisions. Each member state is required to determine effective, proportionate and persuasive penalties and to inform the European Commission of these penalties by October 26. At the request of the EMEA, the Commission may also impose financial penalties for breaches of the provisions of the Regulation in relation to products authorized according to the centralized procedure. It will make public the names of those penalized for infringement of the Regulation or of its implementing measures and the amounts of, and reasons for, the financial penalties imposed

Next steps

The legislation is a regulation, thus directly applicable, which means that it takes immediate effect in all the member states. However, it provides that some of its provisions will enter into force later on. Indeed, the dates by which the obligations to agree a PIP enter into force have been staggered. For medicinal products that have not yet been authorized by January 26, the obligation enters into force on July 26. Although the PIP request should, in principle, be submitted no later than the completion of the relevant human pharmacokinetic studies in adults, if a product is already developed beyond such studies (after Phase I), this legal deadline for submission of the PIP is not applicable.

For previously authorized products protected either by an SPC or else by a patent that will be eligible for one, and for which variation or extension of an existing authorization is sought, the obligation enters into force on January 26, 2009. In the meantime, companies may approach the Pediatric Committee, to agree a PIP.

The Regulation should lead to increased assurance concerning the quality, safety and efficacy of medicinal products prescribed for pediatric use. However, obligations are strict. It remains to be seen whether the industry will consider the benefits for which the Regulation provides adequate to compensate for the additional studies undertaken and the costs involved.