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Children: Seen and Treated

The quality and quantity of research into medicines intended to treat children is an oft-neglected concern. In a clarion call for change, Elisabethann Wright and Susan Clements at Hogan and Hartson investigate the new paediatric medicines regulation, which demands quality, safety and efficacy from medicinal products

Elisabethann Wright has been practicing European law for almost 20 years. She focuses on EU law relating to life sciences, with particular emphasis on pharmaceutical law, food law and the environment. She is also engaged in European public law and European court litigation. Elisabethann has extensive experience in litigation before the European Court of Justice, the European Court of First Instance and the European Free Trade Agreement (EFTA) Court. She was also a Référendaire at the European Court of Justice for many years. Elisabethann's practice includes advising on the challengability of decisions of EU institutions and the validity of EU legislation. She also advises on EU law relating to government contracts.

Susan Clements' practice focuses on life sciences. Susan has extensive experience in EU law and has advised on regulatory matters, competition law and litigation. Her work includes advising on all aspects of EU law relating to medicinal products and medical devices, including approval, marketing and post-marketing obligations. Her work has also included managing compliance audits, representing clients before the European Commission, co-ordinating filings in multiple jurisdictions and advising on litigation before the European Court of First Instance and the European Court of Justice.

It has been estimated that more than 50 per cent of medicines used to treat children in Europe have not been tested for use in this target group, neither have they been authorised for use in the care of children. On 26th January 2007, new EU legislation on medicines for children entered into force. The paediatric medicine regulation aims to balance the ethical issues raised by conducting trials on children with concerns arising from the treatment of children with products which have not been tested on them and the effects of which have not been assessed. The regulation plans to increase the development of medicines that are intended to treat children; to encourage research into medicines for use in treating children; and to improve the quality and quantity of information available in this area. It imposes an extensive system of requirements on companies and provides penalties for non-compliance. However, it also offers rewards and other incentives.

REQUIREMENTS

The regulation introduces the requirement that applications for marketing authorisation for new medicinal products include either the results of studies in the paediatric population that have been carried out in accordance with an agreed Paediatric Investigation Plan (PIP), or proof of having obtained a waiver or deferral from this obligation.

This requirement also applies to applications for the extension of an existing authorisation 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 a new route of administration.

The obligation applies irrespective of whether or not the medicinal product for which authorisation is sought is intended to be administered to children, and has effects equally on both centrally authorised and nationally authorised products.

The regulation provides for the establishment at EU level of an expert Paediatric Committee (PDCO). This Committee is to be established within the European Medicines Agency (EMEA) by 26th July 2007. 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 application for either a marketing authorisation 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 obligation to agree a PIP enters into force over a number of staggered dates. For medicinal products that have not yet been authorised by 26th January 2007, date of entry under the regulation comes into force on 26th July 2008. 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 (that is beyond Phase I), this legal deadline for submission of the PIP is not applicable.

For previously authorised products protected either by a supplementary protection certificate (SPC) or by a patent that will be eligible of an SPC, and for which variation or extension of an existing authorisation is sought, the obligation enters into force on 26th January 2009. The requirement to agree a PIP does not extend to generic products, biosimilars, hybrids, products containing substances acknowledged to have well established medicinal use, herbal medicines and homeopathic medicines.

WAIVERS AND DEFERRALS

Either a waiver or a deferral may be sought from the Committee to avoid the obligation to provide paediatric 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 paediatric population, where the disease or condition for which the product or class is intended occurs only in the adult population, or where a specific medicinal 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 programme 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 clinical trials (EudraCT). Guidance will be drawn up on the nature of the data to be included and on which information will be made public.

The European Commission or the national regulatory authority must ensure that the marketing authorisation 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 authorisation 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 paediatric use, the label must display a symbol to reflect this. The European Commission will select the symbol to be used by 26th January 2008.

Appropriate steps to maintain the supply of products approved for paediatric use have been addressed in the regulation. Where the marketing authorisation holder intends to withdraw the product from the market following expiry of the data protection and market protection periods for which the regulation provides, 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 authorisation, 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 ensuring compliance with the PIP. This includes undertakings that have products for which paediatric 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 26 January 2007. 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 paediatric population, and is therefore granted even when a paediatric indication is not authorised, provided that the results of the studies conducted are reflected in the SpC and, where appropriate, the package leaflet
- Optional access to the centralised EU level procedure for marketing authorisation applications that include one or more paediatric indications on the basis of studies conducted in accordance with the agreed PIP

For older medicines, a new type of marketing authorisation – a Paediatric Use Marketing Authorisation (PUMA) – will be available from 26th July 2007. This type of authorisation, 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 paediatric population in accordance with an agreed PIP. Optional access to the centralised EU level procedure is available for PUMAs. The medicinal product granted a PUMA can use the existing brand name for the corresponding product authorised 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 26th October 2007. At the request of the EMEA, the European Commission may also impose financial penalties for breaches of the provisions of the regulation in relation to products authorised according to the centralised procedure. The Commission shall make public the names of those penalised for infringement of the regulation or of its implementing measures and the amounts of, and reasons for, the financial penalties imposed.

CONCLUSION

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

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References

1. **Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12th December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004, OJ L 378/1, 27th December 2006**