

SUMMARY OF REGULATION ON MEDICINES FOR PAEDIATRIC USE

AIMS AND OBJECTIVES OF THE REGULATION

The overall aim of the Regulation is to improve the health of children in the European Union.

The objectives include:

- increasing the development of medicines for use in children,
- ensuring that medicines used to treat children are:
 - subject to high quality research,
 - appropriately authorised for use in children,
- improving the information available on the use of medicines in children.
- achieving the above objectives without subjecting children to unnecessary clinical trials or delaying the authorisation of medicines in the adult population.

These will be achieved through the application of a number of new regulatory provisions, structures and procedures.

KEY PROVISIONS

Requirements and incentives

All applications for marketing authorisation (MA) for new medicines, including orphan medicines, must contain the results of all studies and information required in a previously agreed paediatric investigation plan (PIP). The PIP will contain a full proposal of all the studies (and their timings) necessary to support the paediatric use of an individual product and will cover all of the paediatric age groups and all necessary age-appropriate formulations. This is the default position of the Regulation. In some cases it will be possible to defer the start of some or all of the studies in relation to the development of the product in adults. In this case the paediatric data will be provided after the initial MA has been granted. In other cases the requirement may be waived for part or all of the paediatric population, for example where there is no paediatric therapeutic need or where paediatric use of the product is not appropriate. But, unless a deferral or a waiver has been granted, paediatric data must be provided in **all** applications for the authorisation of new medicinal products. This applies from 26 July 2008. The requirement also applies to applications to add a new indication, new pharmaceutical form or new route of administration for medicines still covered by patent protection. In these cases, the requirement applies from 26 January 2009.

The Regulation also includes incentives for companies to develop medicines for use in children. This is to stimulate paediatric development for products not bound by the requirements described above, as well as to reward the industry for conducting the obligatory investigation programmes. When an agreed paediatric plan is completed and all the information has been submitted to the regulatory authorities, the medicinal product will be granted an extra 6 months patent protection (through an extension of the duration of its Supplementary Protection Certificate [SPC]), provided that the medicinal product is authorised in all Member States and relevant information from the paediatric studies (whether negative or positive) has been incorporated into the summary of product characteristics. This extension will be granted whether or not the data support a paediatric indication. The incentive only applies if the product has an

active SPC; there is no financial incentive in cases where there is no SPC or where the SPC has expired, and there is no mechanism to extend the duration of the period of the patent itself. For orphan medicinal products the incentive takes the form of an extra two years market exclusivity in addition to the ten years market exclusivity that is granted on authorisation of an orphan medicine. The financial incentives do not apply retrospectively. So they do not apply if the contents of an agreed paediatric investigation plan were completed before entry into force of the Regulation, unless the plan contains “significant studies” which were completed after the Regulation’s entry into force.

The requirements and the financial incentives are independent of each other. Thus a Marketing Authorisation Holder may be required to provide a completed PIP for a product but may be ineligible for the incentive (for example, because the SPC has expired before the PIP is completed). Conversely, a marketing authorisation holder may not be obliged to submit a completed plan, but may do so in order to benefit from the financial incentives.

The Regulation also establishes a new type of marketing authorisation, called the paediatric use marketing authorisation (PUMA), intended to stimulate the development of off-patent products for use in the paediatric population. Only medicines that are intended solely for use in children will be eligible for a PUMA. Although they are relatively weak it is hoped that the incentives associated with a PUMA will encourage the development of new paediatric formulations for these older products. Applications for PUMAs, which must contain the results from an agreed PIP, can refer to third party data for the same active substance, are able to use the centralised procedure for authorisation, and if authorised, will benefit from ten years market protection.

Paediatric Investigation Plan (PIP)

The PIP is a research and development programme aimed at ensuring that the necessary data are generated to determine the conditions in which a medicinal product may be authorised for the paediatric population. It is necessary to draw up such a plan whenever there is an intention to apply for either a marketing authorisation for a new medicine, or for a new indication, pharmaceutical form or route of administration of an existing authorised medicine which is covered by patent protection, or when applying for a PUMA. The plan must specify the timing and the measures proposed to assess the quality, safety and efficacy of the medicinal product in all relevant subsets of the paediatric population, as defined in ICH E11¹. In addition, it must describe any measures to adapt the formulation of the medicinal product which make its use more acceptable, easier, safer or more effective for the different subsets of the paediatric population. The PIP must be submitted to the Paediatric Committee no later than upon completion of the pharmacokinetic studies in adults. This time point was chosen to ensure that the paediatric development of the product is considered at a very early stage of the overall product development rather than as an afterthought. It is accepted that in many cases the initial submission will be preliminary as it will be too early in the development process to have a complete and detailed plan. The Regulation, therefore, allows the Committee to request further information or initial modifications to the plan. It also allows for modifications of the plan at a later stage as the product development progresses. The plan must, however, be agreed by the Paediatric

¹ Note for guidance on clinical investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99) <http://www.emea.eu.int/pdfs/human/ich/271199en.pdf>

Committee, both in order to fulfil the requirements for a valid application for marketing authorisation and to fulfil the criteria to qualify for the financial incentives provided by the Regulation. If the Paediatric Committee refuses to agree a plan, the applicant can request the Committee to re-examine its opinion. If following re-examination the Committee remains negative and the applicant disagrees with the opinion, the applicant has recourse to the European Courts of Justice. The Paediatric Committee also has to agree to any requests for deferrals to the timing of the studies in the plan or waivers from the requirement to develop the product for use in all or part of the paediatric population.

Paediatric Committee

Membership

The Regulation establishes a new scientific committee of the EMEA, the Paediatric Committee (PDCO). It must be set up within six months of entry into force of the Regulation. The Committee membership includes five members of the Committee on Human Medicinal Products (CHMP) plus their alternates. The CHMP is the main scientific committee of the EMEA and is responsible, amongst other things, for giving opinions on applications for centralised marketing authorisations for medicinal products and on scientific advice on medicines development. These five members will provide an important link between the two committees. Member States which are not represented on PDCO by a CHMP member will appoint a member and an alternate. In addition, the European Commission will appoint three members plus alternates to represent health professionals and three members plus alternates to represent patient associations. The European Commission will appoint these six members and alternates following a public call for expressions of interest and after consulting the European Parliament. The EMEA, the Agency and the Commission are expected to cooperate to ensure that the final composition of the Committee, including members and alternates, covers those scientific areas relevant to paediatric medicines. The members, who are appointed for a renewable period of three years, may be accompanied by other relevant experts at the Committee meetings. The members, alternates and experts must not have any financial or other interests in the pharmaceutical industry that could affect their impartiality.

Tasks

The Paediatric Committee has a number of important responsibilities and its effective functioning will be pivotal to the success of the Regulation. Its most important task is to assess the content of paediatric investigation plans for individual medicinal products and to produce opinions on them. In addition, the Committee gives opinions on applications for deferrals and waivers. In this regard, the Committee may itself impose a waiver if it considers that the product may be unsafe or ineffective in the paediatric population or that the product will not provide any significant therapeutic benefit. The Committee will also, on request, give an opinion on the compliance of an application for marketing authorisation with an agreed PIP or on the safety, quality and efficacy of a medicinal product for paediatric use.

Other specific tasks include establishing an inventory of specific needs for paediatric medicinal products and giving scientific input in the development of any documents related to achieving the Regulation's objectives.

The Committee also has an advisory role to the EMEA and to the Commission. This includes giving advice on the new symbol which is to appear on the labels of all

medicines with an authorised paediatric use, on the establishment of the European paediatric clinical trials network, on communication issues relating to conducting research in the paediatric population and on any question relating to the paediatric use of medicines.

The Committee is expected to meet monthly for three to four days.

Paediatric Use Symbol

All products that have an authorised paediatric indication will be required to display a new designated symbol on the package label to ensure that they are readily identifiable. This applies irrespective of when the indication was granted. The meaning of this symbol, which will be selected by the European Commission on the basis of a recommendation from the Paediatric Committee, will be explained in the patient information leaflet. Companies whose products were authorised for paediatric use before the publication of the symbol will have two years following publication to change their package labels.

Paediatric study programme

Funding for research into the paediatric use of off-patent medicines or active substances will be provided through the Community research programmes. The exact amount of funding is not specified in the Regulation. This will be established by the European Commission following consultation with the European Parliament and the Member States as well as the scientific community, industry and other stake holders. To obtain Community funding under the rules governing the framework programme, the applicants must bid successfully in response to a call for research proposals. The study must take place in more than one Member State of the European Union or with a qualifying associated, candidate or third country. An inventory of therapeutic needs for the paediatric population will be compiled by the Paediatric Committee and will help to identify research priorities. It is anticipated that the first calls for proposals will be issued by the European Commission in early 2007.

Paediatric Research network

The Regulation also requires the EMEA to develop a European network for paediatric clinical trials. This network will bring together existing national and European networks as well as individual investigators and centres with specific expertise in the conduct of studies in the paediatric population. The objectives of the European network include coordinating studies relating to paediatric medicinal products, building up the necessary scientific and administrative competences at European level, and avoiding unnecessary duplication of studies and testing in the paediatric population. There is no specific funding provided through the Regulation for this European network, although some funds will be made available from the EMEA budget. Constituent individual networks, centres and investigators will still need to obtain funding for their infrastructure and research activities from other sources, such as national governments, the pharmaceutical industry or the Community framework programmes. Some Member States, anticipating the increased amount of research which the Regulation will stimulate, have already taken steps to create national networks for paediatric clinical trials. This includes the UK, where the Medicines for Children Research Network (MRCN)² was formally launched in December 2006.

² <http://mcrn.org.uk/>

ACHIEVING THE OBJECTIVES

Increasing the development of medicines for use in children

The regulatory requirements and financial incentives established by the Regulation should go a long way to increasing the development of medicines for paediatric use. As described above, for all new medicines data must be generated covering all the relevant subsets of the paediatric population and age-appropriate formulations, unless the product has been granted a waiver. This also applies to new indications, new pharmaceutical forms and new routes of administration for medicines still covered by patent protection. Furthermore, unless the product has been granted a deferral these data must be submitted at the time of the application for marketing authorisation.

The creation of the paediatric use marketing authorisation (PUMA), which has its own associated incentives, should stimulate the development of off-patent medicines for paediatric use. This will also be helped by the provision of Community funding for studies relating to medicines or active substances not covered by patent protection.

Ensuring that medicines used to treat children are subject to high quality research and appropriately authorised for use in children

A number of measures contained within the Regulation are aimed at ensuring that the research conducted in children is of high quality. For example, the European Medicines Agency (EMA) and its scientific committees will provide free advice to applicants on the design and conduct of the studies in a paediatric investigation plan and on the design and conduct of paediatric pharmacovigilance and risk management systems. In support of the latter, the EMA/CHMP has already finalised guidance on the conduct of pharmacovigilance in the paediatric population. Further guidance will be developed on the conduct of paediatric clinical trials in different therapeutic areas and in specific paediatric populations. In addition, the European Commission is developing a document on ethical considerations for clinical trials performed in children, which was released for a four month consultation period in October 2006³.

The European network established by the Regulation aims to facilitate the coordination of studies relating to paediatric medicines as well as helping to increase the expertise necessary to conduct high quality research, for example by providing training and developing guidance on best practice.

The application process for marketing authorisations can appear complex, especially for smaller companies which may not have much experience in this area. The EMA, as well as national authorities, will give free regulatory advice on submitting applications for marketing authorisations in paediatric indications. Such applications are also eligible for the centralised procedure which, in a single process, enables a company to obtain a marketing authorisation that applies throughout the European Union.

The Regulation contains a provision to discourage the discontinuation from the market of authorised paediatric medicines. If a company intends to discontinue a paediatric medicine that has benefited from the financial incentives of the Regulation,

³ Ethical considerations for clinical trials performed in children - Recommendations of the Ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use (http://ec.europa.eu/enterprise/pharmaceuticals/paediatrics/docs/paeds_ethics_consultation20060929.pdf)

the company must either transfer the marketing authorisation to a third party or allow a third party to use the scientific documentation relating to the medicine in order to support an application for marketing authorisation.

Increasing the information available

The Regulation contains a number of measures which are intended to increase transparency as well as the amount of information publicly available on the paediatric use of medicines. The responsibilities for transparency are divided between the EMEA and the European Commission. The EMEA has the responsibility of publishing the names and qualifications of the members of the Paediatric Committee; the list of waivers; all opinions of the Paediatric Committee, after the deletion of commercially confidential information; a register of all medicines with paediatric indications authorised following completion of a PIP and the deadlines for placing the products on the market; the names of any marketing authorisation holder intending to discontinue a paediatric medicine from the market; and the inventory of paediatric therapeutic needs compiled by the Paediatric Committee. The European Commission is responsible for selecting and publishing the new symbol that must be placed on the label of every medicine with an authorised paediatric use; for publishing an inventory of all national incentives and rewards for paediatric medicines development offered by the Member States; the names of all those infringing the terms and provisions of the Regulation; the names of the companies and products that have benefited from the Regulation and the names of companies that have failed to comply with any of the obligations of the Regulation. The Commission is also charged with writing a general report on the experience acquired as a result of the application of the Regulation. This will include a detailed inventory of all medicinal products authorised for paediatric use since its entry into force. The Commission must also present an analysis of the economic impact of the rewards and incentives, together with an analysis of the estimated public health impact.

There are three principal measures that will increase the information publicly available on the paediatric use of medicines. The Regulation establishes a paediatric clinical trials database which will contain information on all clinical trials conducted according to a paediatric investigation plan, including trials conducted solely in countries outside the EU. This will be based on the clinical trials database which was established by the Clinical Trials Directive⁴. Parts of this paediatric database, including the trial results, will be publicly accessible. In addition, companies must submit to the regulatory authorities the data from all paediatric trials completed before the entry into force of the Regulation. The regulatory authorities have the power to update the relevant summaries of product characteristics and patient information leaflets with this information, if appropriate. Finally, when the data from paediatric investigation plans have been submitted, the relevant summaries of product characteristics and patient information leaflets must reflect the results of the studies whether they are positive or negative.

Avoiding unnecessary trials

⁴ Directive 2001/20/EC OF the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (*Official Journal L 121, 1/5/2001 p. 34 - 44*). http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf

The Regulation contains a number of measures aimed at avoiding unnecessary trials in the paediatric population. This is particularly important in view of the heightened ethical concerns about involving children in clinical trials. The Regulation specifies that whenever carrying out its tasks, the Paediatric Committee must consider whether or not any proposed studies can be expected to be of significant therapeutic benefit to and/or fulfil a therapeutic need of the paediatric population. A principal provision in this respect is the power of the Paediatric Committee to impose a waiver from the requirement to provide data from a paediatric investigation plan, for example if it considers that the product is likely to be ineffective or unsafe in part or all of the paediatric population or that the product does not represent a significant therapeutic benefit over existing treatments. If such a waiver is imposed, the product cannot benefit from the financial incentives of the Regulation, and it is therefore unlikely that a commercial sponsor would proceed with development of the product in children.

Public availability of parts of the paediatric clinical trials database is also important in this respect. Access to details of trials in progress and the results of completed trials will help investigators, applicants and others to judge whether the proposed trial will contribute to the evidence base for the product. In addition, the free scientific advice on the content of a paediatric investigation plan provided by the EMEA and national authorities should help to avoid errors in design and methodology which may render the trial uninterpretable.