European Medicines Agency

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Report from the Paediatric Committee on its first anniversary

The European Medicines Agency's Paediatric Committee (PDCO) celebrates its first anniversary in July 2008, after a year of operation in which the Committee successfully implemented its responsibilities stemming from the European Union (EU) Paediatric Regulation[1].

At the heart of the PDCO's role is its commitment to promote the health of children in Europe by reducing the use of unlicensed and off-label medicines in the paediatric population. Working in cooperation with Member States and EU partners, and in conjunction with learned societies and industry, the PDCO has made good progress on achieving its objectives to facilitate the development and availability of medicines for use in the paediatric population and to improve the information available on the use of medicines for children. These objectives are being met without subjecting the paediatric population to unnecessary clinical trials and without delaying the authorisation of medicines for adults.

The PDCO held its first meeting on 4 July 2007. It is composed of five members of the Agency's Committee for Medicinal Products for Human Use (CHMP) with their alternates, appointed by the CHMP itself, and one member and one alternate appointed by each Member State (except Member States already represented through the members appointed by the CHMP). A process is currently underway at the European Commission to appoint three members and alternates representing healthcare professionals and three members and alternates representing patients' associations.

The PDCO elected Dr Daniel Brasseur (Belgium) as Chair and Professor Gérard Pons (France) as Vice-chair. It has held 13 monthly meetings since the start of its activity in July 2007. The Committee is supported in its activities by the EMEA secretariat, mainly by the paediatric section of the Scientific Advice and Orphan Drugs Sector.

Paediatric investigation plans and waivers – The Committee's core activities
In its first year of operation, the PDCO performed strongly in its core activities relating to the assessment and agreement of paediatric investigation plans (PIPs)[2] and waivers[3].

From August 2007 to July 2008, the PDCO received 233 validated applications – of which 49 were requests for a full waiver for all conditions and all subsets of the paediatric population – covering approximately 420 indications.

[1] Regulation (EC) No 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use, as amended by Regulation (EC) No 1902/2006.
[2] A paediatric investigation plan is a development plan aimed at ensuring that the necessary data are obtained, through studies in children, when it is safe to do so, to support the authorisation of the medicine for children. The plan should be submitted by pharmaceutical companies to the Paediatric Committee, which is responsible for agreement or refusal of the plan.
[3] A request for a waiver is submitted by an applicant in cases where there is evidence showing that the medicine concerned is likely to be ineffective or unsafe in the paediatric population, or that the disease or condition targeted occurs only in the adult population, or that the specific medicine does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

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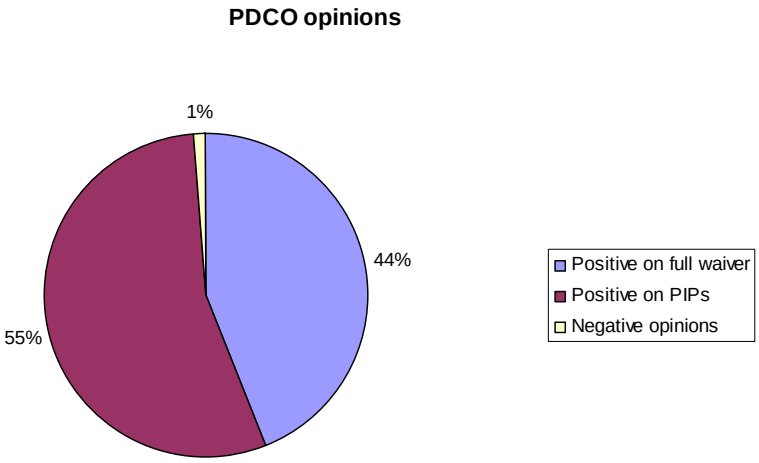
On average, each application for a PIP or a full waiver covers two indications, both of which require a separate scientific evaluation. The assessment of each indication may cover several age groups, which also require a separate evaluation.

As a result of the assessment of these applications, the PDCO adopted 71 opinions, one of them negative. 31 opinions were adopted for full waivers and 39 for PIPs. An opinion on a PIP may also contain deferrals[4] and/or waivers for the obligation to gather clinical trials data in certain age groups of chilres.

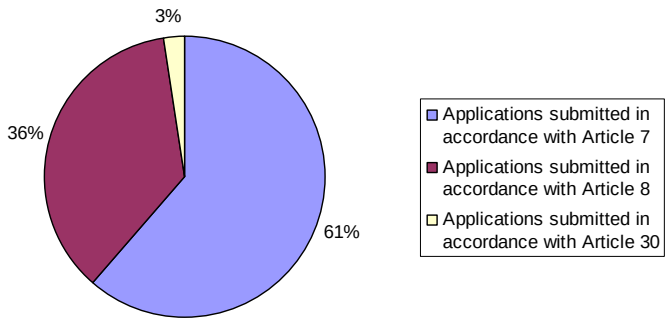


PDCO opinions on PIPs and waivers are transformed into EMEA decisions. The EMEA adopted decisions on 30 of the 71 opinions on PIPs and waivers. Of these, 15 were for full waivers and 15 for PIPs.

The majority of applications (61%) were for medicines that are not yet authorised. A further 36% of applications were for medicines that are already authorised and still under patent, and for which a variation or extension of the marketing authorisation for a new indication, new route of administration or new pharmaceutical form is sought. Finally, applications for an off-patent product developed specifically for children with an age-appropriate formulation accounted for 3% of applications.

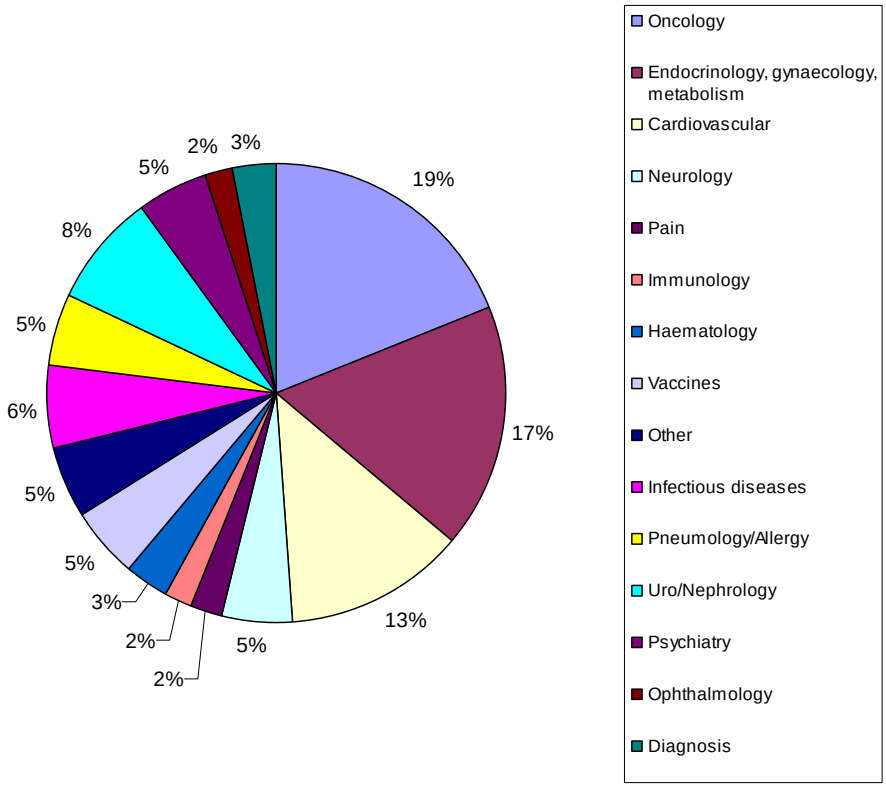
[4] A deferral of a Paediatric investigation plan (PIP) may be requested and shall be granted when it is appropriate to conduct studies in adults prior to initiating studies in the paediatric population, or when studies in the paediatric population would take longer to conduct than studies in adults.

Validated PIP/waiver applications

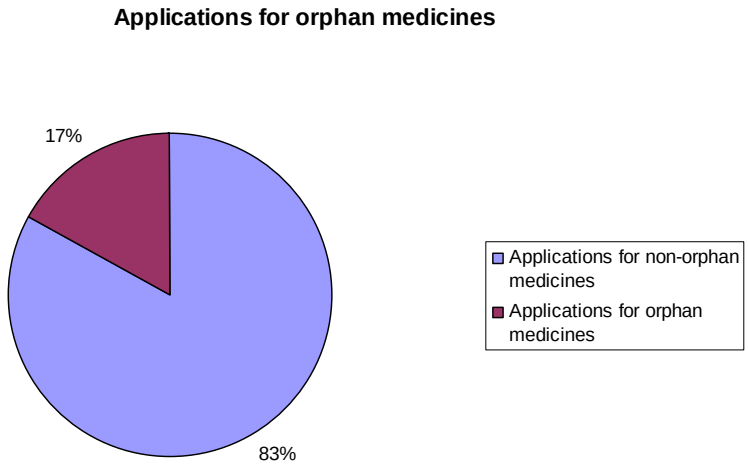


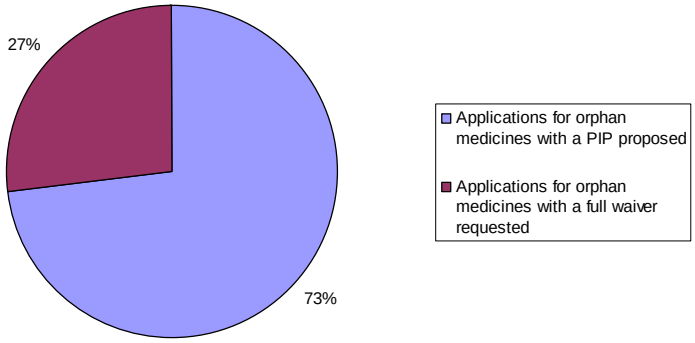
The most-represented therapeutic areas were oncology (19%), followed closely by endocrinology, gynaecology and metabolism (17%) and cardiovascular disorders (13%).

Applications by therapeutic area



The development of better medicines for children will also have an impact on the field of rare diseases. Orphan medicines, which are intended for the diagnosis, treatment or prevention of rare diseases, represented 17% of the PDCO applications. For 73 % of these, an application for a PIP was submitted, and for 23 % waivers were requested.





Guidance and procedures – The Committee's regulatory work

In compliance with the implementation of the Paediatric Regulation, the PDCO put in place a number of scientific and operational procedures. These included:

- A guidance document on the content and format of data to be collected by Member States on all existing uses of medicines in the paediatric population. The data collected by the Member States in accordance with this guidance should be communicated by national competent authorities to the Agency by January 2009. The PDCO will establish an inventory of paediatric needs based on the information obtained from the survey.

- A list of class waivers for conditions that do not affect children and for which the requirement to submit a PIP can therefore be waived. The list includes, for example, different types of cancer (lung cancer, basal cell carcinoma, breast and ovarian cancer, multiple myeloma), neurodegenerative conditions (Alzheimer's disease, Parkinson's disease) and other conditions that occur only in the adult population (age-related macular degeneration, menopausal disorders, etc.). The list of waivers will be regularly updated in light of the advance of knowledge and science in the paediatric field.

- A proposal, adopted by the EMEA Management Board, for an implementing strategy for the European network of paediatric research. The EU-wide network will bring together existing national and European networks, investigators and centres with specific expertise in the performance of studies in the paediatric population. The objectives of the network will be to coordinate studies relating to paediatric medicines, to build up the necessary scientific and administrative competences at European level, and to avoid unnecessary duplication of studies and testing in the paediatric population.

- Priority list for studies into off-patent medicines (medicines not covered by a patent in Europe) in the context of the call from the European Commission for funding through the EU's Seventh Framework Programme. The PDCO is currently revising the first list in advance of the next call.

- A recommendation to the European Commission on a symbol for use on medicines authorised for use in children. The PDCO concluded that there was no symbol for which the benefits outweighed the risks of medication error. The Commission followed the Committee's recommendation and did not select a symbol.

- Contribution, together with the EU Member States and the European Commission, to draft guidance on the information concerning paediatric clinical trials to be entered into the EU Database on Clinical Trials (EudraCT) and on the information to be made public by the EMEA.

- Contribution, in conjunction with the EMEA secretariat, to the European Commission guideline on 'Ethical Considerations on clinical trials in paediatric populations' .

Cooperation with other EMEA committees
In collaboration with the EMEA's scientific committees and working parties, the PDCO is taking major steps in its long-term commitment to improve the availability of medicines for the paediatric population. The PDCO actively contributes to address paediatric aspects of medicine development in guidelines. For example, the PDCO endorsed a concept paper, jointly prepared with the Committee for Medicinal Products for Human Use (CHMP) and the Committee on Herbal Medicinal Products (HMPC), on paediatric formulation to address the different approaches needed by the different subsets of the paediatric population (from pre-term newborn to adolescents) in the context of the development of a medicine.

Cooperation with Member States
The Member States contributed to the work of the PDCO to a great extent, both through the work of their representatives in the Committee and through the support given by their medicines regulatory authorities.

In accordance with the Paediatric Regulation, all available results from paediatric studies and trials had to be submitted by marketing-authorisation holders to the national competent authorities or to the EMEA by 26 January 2008. Further paediatric studies should be submitted on an ongoing basis within six months of their completion. In this context, the EMEA is working towards implementing a strategy for the exchange of paediatric information with Member States. In view of the high workload anticipated for the review of all these data, the PDCO will contribute to the prioritisation of the studies for assessment.

To further increase the cooperation, the PDCO and the EMEA secretariat organised training on the implementation of the new paediatric legislation for assessors and for 'paediatric contact points' within the national competent authorities.

Cooperation with learned societies
The PDCO made great efforts to develop close interactions with academic experts, to ensure that PDCO opinions on PIPs or waivers reflect the state-of-the-art knowledge in the various fields of

paediatrics. Topics discussed included formulations, toxicology, specific aspects of clinical development in various therapeutic areas (e.g. cardiovascular, ophthalmology, bone diseases, epilepsy and seizures), modelling and simulation in clinical trials, and post-authorisation activities.

It is planned that learned societies will be increasingly involved in the PDCO's work, via the provision of external experts, input on the development of guidelines, the identification of scientific questions to be answered, and input on standard elements for PIPs (such as the type of studies to be carried out, endpoints, duration and comparators) in various therapeutic areas. The PDCO will become the scientific advisory body for the European network of paediatric research, which will involve specialists' networks in particular.

Learned societies will also play a major role in implementing the concept of 'proactive pharmacovigilance' in the paediatric population. An example of this approach to the safety of medicines is the inclusion in the ENCePP[5] project of paediatric pharmacovigilance centres, in order to ensure the availability of appropriate expertise in paediatric pharmacovigilance, and with a view to investigating new sources and methods for intensive monitoring of paediatric use of medicines.

Cooperation with the FDA

The EMEA maintains regular contacts with the United States Food and Drug Administration (FDA) under the 'Principles of Interaction between EMEA and FDA Office of Pediatric Therapeutics'. The objectives of this interaction are to facilitate regular exchange of information on scientific and ethical issues and other information on paediatric development programmes in Europe and the US, in order to avoid exposing children to unnecessary trials and to facilitate the submission of global paediatric development plans by applicants based on scientific grounds that are compatible for both authorities.

During monthly teleconferences, the EMEA and the FDA discuss product-specific paediatric development (PIPs/written requests/deferrals) and waivers from the obligation to perform such paediatric development.

Between August 2007 and July 2008 the FDA and the EMEA discussed 72 products, of which 22 were in-depth or expanded scientific discussions.

Paediatric Regulation - A new approach for industry

The compliance of the pharmaceutical industry with the Paediatric Regulation, mainly concerning the submission of PIPs and waivers, has led to a shift in the approach of pharmaceutical companies to research and development and in the allocation of resources. The new legal framework has also created new opportunities for dialogue and interaction between industry and regulators.

The Paediatric Regulation provides for the EMEA to offer scientific advice to applicants developing paediatric medicines. EMEA/CHMP paediatric scientific advice can be requested, free of charge, prior to the submission of a paediatric investigation plan or at a later stage, and follows the same procedure as the scientific advice for other medicines. Advice is given on the design and conduct of trials necessary to demonstrate the quality, safety and efficacy of a medicine in the paediatric population. To date, the EMEA has received 60 requests for scientific advice in the field of paediatrics, of which 35 relate only to paediatric development.

[5] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance.

Looking ahead

As of 26 July 2008, pharmaceutical companies, who submit an application for a marketing authorisation for a medicine, will have to provide the results of studies in children conducted in accordance with an approved PIP, or an EMEA decision on a waiver or on a deferral.

In its second year of activity, the PDCO, based on the experience gained, will continue with its role of reviewing applications for PIPs and waivers. The high level of applications is expected to be maintained. The Committee will also see an intensification of its work in relation to the verification of compliance with agreed PIPs and the review of modifications to agreed PIPs.

In parallel, the PDCO will continue to work on implementing the Paediatric Regulation provisions the further implementation of the Paediatric Regulation provisions for the establishment of the paediatric research network and the development of an inventory of therapeutic needs on paediatric population.

The PDCO will further strengthen its collaboration with its various partners and will establish links with patients/parents' organisations once the representatives of patients' organisations join the Committee.