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## Paediatric investigation plans for pain: painfully slow!

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► **To cite this version:**

Elin H. Davies, Cecile M. Ollivier, Agnes Saint Raymond. Paediatric investigation plans for pain: painfully slow!. *European Journal of Clinical Pharmacology*, 2010, 66 (11), pp.1091-1097. 10.1007/s00228-010-0886-2 . hal-00619925

**HAL Id: hal-00619925**

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Submitted on 7 Sep 2011

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1 Title page

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3 **Paediatric Investigation Plans for Pain: painfully slow!**

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37 **behalf of the EMA or of its scientific committees.**  
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**Abstract**

*Purpose:* To examine the early impact of the Paediatric Regulation, which entered into force in Europe on 27 January 2007, on the development of pharmaceutical drugs in the therapeutic field of pain submitted to the Paediatric Committee (PDCO) and to the European Medicines Agency (EMA).

*Methods:* Paediatric Investigations Plans (PIPs) submitted with a Decision (outcome) reached between September 2007 and March 2010 were included in the analysis.

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*Results:* From seventeen Paediatric Investigation Plans submitted, fourteen have resulted in EMA Decision, three were withdrawn by the applicants, eight were granted a full waiver from development, and one resulted in a negative opinion. Decisions as issued included 15 clinical trials, with at least 1282 children to be recruited into studies across five different products. Neonates were included in four of the products.

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*Conclusions:* The small number of submissions indicates a lack of new drugs being developed for the management of pain. Ethical concerns that too many vulnerable children will be recruited into clinical trials must be balanced against limiting the number of off-label prescribing and obtaining age-appropriate information on paediatric use. Now is an opportune time for clinicians, academics, learned societies and industry to collaborate for the benefit of children in pain.

**Key words**

Paediatric, Pain, Clinical trials, Paediatric Regulation, Paediatric Committee (PDCO), Paediatric Investigation Plan (PIP)

**Introduction**

A new piece of legislation (Regulation (EC) No 1901/2006 as amended) namely the 'Paediatric Regulation' governing the development and authorisation of medicines for use in children aged 0 to 17 years was introduced in the European Union in January 2007.

The Paediatric Regulation [6] also brings in many new tasks and responsibilities for the European Medicines Agency (EMA), chief of which is the creation and operation of a Paediatric Committee (PDCO) within the Agency to provide objective scientific opinions on any development plan for medicines for use in children.

Since the Paediatric Regulation entered into force in January 2007, the regulatory environment for paediatric medicines has dramatically changed. The Regulation requires pharmaceutical companies to consider the needs of the paediatric population during the development of their medicinal product.

The objective of the Paediatric Regulation is to improve the health of children in Europe by:

- facilitating the development and availability of medicines for children aged 0 to 17 years,
- ensuring that medicines for use in children are of high quality, ethically researched, and authorised appropriately,
- improving the availability of information on the use of medicines for children,

without:

- subjecting children to unnecessary trials,
- or delaying the authorisation of medicines for use in adults.

The paediatric regulation requires companies to submit a Paediatric Investigation Plan (PIPs; for further description of EMA terms see table 2) for their product, which is evaluated by the PDCO in 60 to 120 days. There is a possible clock stop at D60 to allow companies to respond to requests for modification of the plan. PDCO opinions on PIPs and waivers are transformed into binding European Medicines Agency decisions [7]. The PIP is submitted for review by the PDCO no later than the completion of the relevant human pharmacokinetic studies in adults. A waiver can be granted for a specific product, an indication or a class of products based on of the following three grounds:

- (i) That the specific medicinal product or class of medicinal products is likely to be ineffective or unsafe in part or all of the paediatric population,
- (ii) That the disease or condition for which the specific medicinal product or class is intended occurs only in adult populations or
- (iii) That the specific medicinal product does not represent a significant therapeutic benefit over existing treatments.

For products already authorised, including active substances protected by a supplementary protection certificate, or by a patent eligible for a supplementary protection certificate, Article 8 of the Regulation applies. In these circumstances, companies have the obligation to submit the results of an agreed PIP covering all existing and

1 new indications, new route of administration or new formulation, unless a waiver has been granted by the  
2 PDCO.

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5 For medicinal products not yet authorised Article 7 of the Regulation applies, and companies have the obligation  
6 to submit results of an agreed PIP, unless a waiver has been granted by the PDCO. Deferrals for the completion  
7 of trials (not for the submission of PIPs) can also be granted by the PDCO, to protect the safety of children until  
8 additional safety data in adults is available.  
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11 For off-patent products already available on the market for adults only, without information and/or a formulation  
12 appropriate for children of all ages Article 30 can apply, where companies submit a PIP on a voluntary basis  
13 leading to a Paediatric Use Marketing Authorisation (PUMA). The PIP must be agreed and covers paediatric  
14 indication and formulation. An overview of Article 7, 8 and 30 can be seen in Table 1.  
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17 Ethical concerns that too many vulnerable children are recruited into clinical trials must be balanced against  
18 limiting the number of off-label prescribing and obtaining age-appropriate information on paediatric use. Within  
19 the context of a clinical trial safety monitoring can be done rigorously, and any safety concerns noted early on,  
20 minimised or prevented.  
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23 The PDCO is not responsible for marketing-authorisation applications for medicinal products for paediatric use.  
24 This remains fully within the remit of the Committee for Medicinal Products for Human Use (CHMP) [1].  
25 However, the CHMP or any other competent authority may request the PDCO to prepare an opinion on the  
26 quality, safety and efficacy of a medicinal product for use in the paediatric population if these data have been  
27 generated in accordance with an agreed paediatric investigation plan.  
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30 A review of all the PIPs submitted with a Decision reached between September 2007 and March 2010 was  
31 conducted to examine the impact of the Regulation in the therapeutic field of Pain, not only in terms of numbers  
32 of PIPs received but also in relation to the number and types of clinical trials to be conducted, and the number of  
33 children to be recruited.  
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**Method**

Utilising the EMA Paediatric Database, all the Paediatric Investigation Plans (PIPs) received by the EMA between September 2007 and March 2010 were searched to identify those in the therapeutic field of pain.

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The EMA Paediatric Database includes all PIPs and/or waivers submitted to the PDCO and EMA since June 2007 along with all procedural steps leading to the PDCO Opinion and European Medicines Agency decision (outcome).

It also records scientific data, while streamlining work procedures by producing pre-filled documents and interacting directly with a secure e-mail system to send messages and documents to external addressees (including applicants).

Key word 'pain' was used in search fields 'condition/ indication' and therapeutic area as the main parameter to identify the PIPs of interest.

The Pain PIPs identified were then categorised according to type of product (Table 2): Article 8 for products already authorised, Article 7 for medicinal products not yet authorised and for off-patent products already available on the market for adults only Article 30.

Key word 'diabetes', 'Human Immunodeficiency Virus (HIV)' and 'infectious diseases' were used in search fields 'condition/ indication' and therapeutic area as the main parameters to identify PIPs to be compared in terms of numbers of pharmaceutical drugs that have been submitted with the therapeutic area of pain.

**Results**

Seventeen submissions were made to the Paediatric Committee (PDCO) for assessment. Three were withdrawn by the applicants during the procedure; the reasons for withdrawal were not communicated to the European Medicines Agency and PDCO.

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Twelve submissions were for Article 7 and from a known class, with only one of the submissions being a product with a new mechanism of action. The thirteenth submission was for Article 8 and the fourteenth submission was a Paediatric Use Marketing Authorisation request, which was also a well known product widely used for other indications.

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Seven out of the twelve Article 7 submissions were for fixed dose combinations, one of which included development in the adolescent age group while the other was an application for a full waiver. The PDCO did not consider that they offered significant therapeutic benefit to children as fixed combination. Although the effect of the substances on their own was known, the effect of the combination was unknown and would have required studies. However the PDCO was of the opinion that fixed combinations were not appropriate in this case as they do not allow flexibility in the dosing according to age and weight. Therefore waivers for paediatric development were granted for all age groups for these fixed combinations.

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One eighth product was also a request for a Waiver in all age groups, based on the ground that the medicinal product did not represent a significant therapeutic benefit over existing available products. This submission was for an old product well known and widely used, but with a new formulation for intravenous use. In this instance, the PDCO did not agree that the product lacked the potential to meet the current needs; however they had significant concerns about the content of the formulation for this product and about the lack of clinical data for prescribing in the neonatal age group. Discussions with the company regarding these concerns led to the development of a clinical trial designed to specifically investigate these key safety concerns.

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One of the Article 7 submission resulted in a negative opinion; the grounds for refusal cannot be communicated for legal reasons.

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Finally out of the last three PIPs submissions under Article 7 were for the same active substance but included both acute and chronic pain indications, with immediate and prolonged release formulations. The initial application included a request for a partial waiver for the 0-23 months age group. Following extensive discussion with the applicant, the PDCO agreed on PIPs for all the paediatric age groups, in both indications but utilising modelling and simulation of pharmacokinetics in children less than 2 years.

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The last PIP under Article 7 was for acute pain. The initial submission included a request for a partial waiver for the 0-23 months age group. Following discussion with the applicant, the PDCO agreed on PIPs for children from 6 years to less than 18 years and a partial waiver in children from birth to less than 6 years of age. The partial waiver was granted based on the ground that the product does not represent significant benefit over existing treatments.

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The Article 8 PIP submission was refused by the PDCO. The PDCO had concerns that the proposed measures and timelines were not appropriate to generate necessary data in determining the conditions in which the

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1 medicinal product may be used to treat the paediatric population or subsets thereof, nor in adapting a paediatric  
2 formulation. The PDCO also considered that the product would not bring significant therapeutic benefit. A  
3 product-specific waiver was granted on PDCO own motion on the grounds that the specific medicinal product is  
4 likely to be ineffective or unsafe in all the paediatric population.  
5

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7 Another product submitted a request for a Waiver for children older than 2 years due to expected lack of efficacy  
8 in this age group and lack of significant therapeutic benefit. The PDCO was in agreement with the data presented  
9 by the applicant and therefore a Partial Waiver for children over 2 years of age was granted.  
10

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12 Overall, Opinions as issued by the PDCO following discussion with the applicant resulted in the agreement of 13  
13 clinical trials, with a total of at least 1282 children to be recruited across five different products. The number of  
14 studies per product ranged from one to six.

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17 For two of the products, the PDCO agreed to studies across the full paediatric age range (from birth to 18 years),  
18 starting with the older children (6 – 17 years) and proceeding in a staggered stepwise manner to the younger  
19 children (2-5 years followed by the less than 2 years age group). This staggered approach was adopted to  
20 maximise the safety of the children.  
21

22  
23 Following extensive discussion between the PDCO and the company, efficacy did not need to be demonstrated  
24 in a blinded fashion in two clinical trials, on the grounds that data would be generated in other studies with the  
25 same compound, all be it in a different pain model.  
26

27 Evaluation by the PDCO takes account where possible the guidance on Clinical Investigation of Medicinal  
28 Products for Treatment of Nociceptive Pain (Committee for Proprietary Medicinal Products (CPMP) [10] and  
29 the Guideline on Clinical Medicinal Products intended for the Treatment of Neuropathic Pain [11]  
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32 Four studies for one product were placebo controlled, as there was no pharmacological alternative currently used  
33 or available in clinical practice. However, the study protocols included clear guidance for 'rescue treatment'.  
34 Five other studies across three different products were active-controlled, however only two were blinded due to  
35 complexities in achieving this. Four of the studies were for pharmacokinetics only, and one of the studies was a  
36 modelling and simulation of pharmacokinetics.  
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39 Neonates were included in four agreed PIPs. Only one applicant had included neonates in their original PIP  
40 submission, and their inclusion in the other three PIPs was only after evaluation by PDCO, and subsequent  
41 discussions with the companies. Preterm neonates were included in two agreed PIPs, again following PDCO  
42 evaluation, with the primary aim of identify pharmacokinetics data in three PIPs. Population-pharmacokinetics,  
43 micro assay and sparse sampling were agreed in all four PIPs, limiting the individual burden for each infant. This  
44 is an important step forward given the lack of current available data for many drugs in the neonatal age group,  
45 while causing minimal pain and distress.  
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49 Three out of the five proposed PIPs were non-opioids intended for mild to moderate pain. One PIP was  
50 specifically for Procedural pain and the last PIP was for acute pain. Only the new product had the potential to  
51 work as Step III analgesia, as defined by the World Health Organization three-step analgesic ladder [2].  
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### Formulations

The development of intravenous and age-appropriate oral formulation, in immediate and prolonged release forms, has the potential to be of significant therapeutic benefit to the paediatric population.

Eleven of the fourteen submissions included formulations for oral use, two of the fourteen included intravenous formulation, one submission was for inhalation use and the last submission was for nasal spray. Age-appropriate formulations were not adequately addressed in seven of the original submissions. Following review by the PDCO two of the applicants agreed to develop age-appropriate formulation. This would indicate that the legislation has been able to positively influence the development of age-appropriate formulations where it otherwise may not have been developed.

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## Discussion

Effective management of childhood pain is a high priority. There is now conclusive evidence that paediatric patients of all ages, including the extremely premature neonates [3], are capable of experiencing pain as a result of tissue injuries, medical illnesses, therapeutic and diagnostic procedures, trauma and surgery. A range of medications is available to treat a variety of pain types [4] but not all are suitable for all age subsets. There is increasing knowledge in the understanding of developmental neurobiology, developmental pharmacology and of the psychological needs of children in pain, however a gap remains.

The paediatric population (birth to 18 years) in the European Union is close to 100 million, and up to 10% of these will undergo some type of surgical procedures every year, not to mention other painful conditions. Paediatric patients experience pain in different clinical situations following trauma, during hospital stay and in pathological conditions treated by physicians outside the hospital, such as headache and acute abdominal pain which are common during childhood. An epidemiological survey of 9,000 school children found that one third of seven year old children and half of 15 year olds had headaches. In a survey done in school children in Germany (n=749) [5] 83% of children and adolescents reported experiencing pain during the preceding 3 months. Many of these children, in all age groups will require analgesia.

Prior to the implementation of the Regulation the Paediatric Working Party a temporary working party of the Committee on Medicinal Products for Human Use (CHMP) —conducted an exercise between 2001 and 2007 to establish 'Paediatric Needs' [8]. The lists of paediatric needs as adopted by the Working Party serves as a basis for the inventory of needs that is to be established and published by the Paediatric Committee in accordance with the Paediatric Regulation. This list is intended to guide the Committee when assessing PIPs.

Another list, the 'Priority List of off-patent medicines' [9] has been set up to direct research on off-patent medicines for which there is a high need in the paediatric population. With the availability of funding, provided through the European Union Framework Programmes, the aim is that more of these medicines will be developed for children and submitted for a Paediatric Use Marketing Authorisation. Conditions with higher therapeutic needs were initially identified as early as 2002-2003, mostly based on the severity of the disease; the paediatric groups affected (with special priority for the neonatal population); the non-availability of treatment alternatives; and the high prevalence of the disease in the paediatric population. For each condition, published therapeutic reviews of medicines used in children were analysed to identify off-label products of therapeutic interest and priorities for research. The list comprises a number of medicines relating to various therapeutic areas and is regularly updated.

Analgesia in the paediatric population was identified as an area with high therapeutic needs in the 'Priority List' and in the 'Paediatric Needs'.

Pain management has one of the highest needs compared to other therapeutic areas, especially when considering the high incidence and prevalence of pain in the paediatric population across all conditions. When comparing the number of PIP submissions in pain to other therapeutic fields in the same time period however we note that the numbers of products being developed are small. In the same period, twenty-one PIPs were submitted in the therapeutic area of Diabetes (Twelve still under review), and twelve submitted for Human Immunodeficiency

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1 Virus. (Nine still under review). The prevalence and incidence of these indications compared to pain (five still  
2 under review) are comparatively much less, but are noted to be very active areas in terms of drug development.  
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5 Development in Pain is low in comparison to the high incidence and despite the high therapeutic need identified  
6 in the priority list.  
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**Conclusion**

There is an apparent lack of innovative drugs being developed for pain, compared to some other therapeutic areas, however this may not be a paediatric only problem. Despite the Paediatric Regulation industry remain at liberty to study in any therapeutic area of their choice. This is an opportune time for clinicians, academia, learned societies and industry to collaborate for the discovery of new products, the generation of new data and the development of new formulations to ultimately benefit the needs of children and neonates in pain. The Paediatric Regulation serves to enforce industry to consider the needs of children in the development plans of their products, while the PDCO serves to ensure that only studies that offer significant value are agreed upon for the final Decisions.

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**Acknowledgements**

The authors would like to thank the Paediatric Committee and the paediatric team at the European Medicines Agency who contribute every day to make better medicines for children. We are very grateful for the cooperation of the children and parents who take part in the clinical research and hope that children will soon benefit from the Paediatric Regulation. It would not be possible without their help and cooperation.

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**Conflict of interest**

The authors declare that they have no conflict of interest.

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**Table 1** A short description of EMA terms including weblinks (updated from Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency (Eur J Clin Pharmacol (2010) 66:39–48)

Term	Description
Centralised Procedure	A Community registration procedure created by Council Regulation (EEC) No. 2309/93 and amended by Regulation 726/2004 for the authorization of medicinal products, for which there is a single application, a single evaluation and a single authorisation allowing direct access to the single market of the European Community. The opinion of the CHMP is transmitted to the European Commission to be transformed in a further 67 days into a single marketing authorisation applicable to the whole European Union. This procedure is compulsory for medicinal products derived from biotechnology, and in 4 specific therapeutic areas (products against HIV, cancer, neurodegenerative diseases and diabetes), and available at the request of companies for other innovative new products. Applications are submitted directly to the EMEA. <a href="http://ec.europa.eu/enterprise/pharmaceuticals/procedure/cproc_en.htm">http://ec.europa.eu/enterprise/pharmaceuticals/procedure/cproc_en.htm</a> <a href="http://www.ema.europa.eu/index/authorisation.htm">http://www.ema.europa.eu/index/authorisation.htm</a>
Class waiver	The Agency already adopted decisions on class waivers in October 2009 for conditions that do not occur in children, or for products likely to be unsafe or ineffective in children. The list of waivers is regularly updated in light of the advance in knowledge and science in the paediatric field. <a href="http://www.ema.europa.eu/htms/human/paediatrics/classwaivers.htm">http://www.ema.europa.eu/htms/human/paediatrics/classwaivers.htm</a>
CHMP	The <b>Committee for Medicinal Products for Human Use</b> (CHMP) is responsible for preparing the Agency's opinions on all questions concerning medicinal products for human use, in accordance with Regulation (EC) No 726/2004. <a href="http://www.ema.europa.eu/htms/general/contacts/CHMP/CHMP.html">http://www.ema.europa.eu/htms/general/contacts/CHMP/CHMP.html</a>
CHMP Opinion	CHMP's scientific conclusions on issues related to medicinal products, e.g. whether the data submitted allow to conclude that there is an overall positive benefit/risk of a new product in a proposed indication and whether the product should be placed on the market.
Compliance	A compliance check is performed to verify that all the measures agreed in a PIP and reflected in the Agency's decision have been conducted in accordance with the decision, including the agreed timelines. Compliance is one of several prerequisites for obtaining the rewards and incentives provided for in Articles 36 to 38 of the Paediatric Regulation.
EMA	The <b>European Medicines Agency</b> (EMA) created by Council Regulation (EEC) No. 2309/93 of 22 July 1993, and renamed by Council Regulation 726/2004 of 31 March 2004, is based in Canary Wharf, London. The Agency is responsible for coordinating the existing scientific resources put at its disposal by the competent authorities of the Member States for the evaluation and supervision of medicinal products. <a href="http://www.ema.europa.eu">http://www.ema.europa.eu</a>
European Commission	<b>Commission of the European Communities:</b> The "civil service" of the European Union It is the executive organ of the Community. It proposes Community policy and legislation, implements the decisions taken by the Council of Ministers, and supervises the day-to-day running of Commission policies.
Follow-up SA	Any application for SA following the initial application on the same area/condition. For example, the initial advice can be on the pharmacokinetics and the exploratory phase II trial, and later the pivotal Phase III trial could be the subject of a follow-up advice.
Informed Consent applications	According to Article 10c of Directive 2001/83/EC as amended, following the granting of a marketing authorisation, the authorisation holder may allow use to be made of the pharmaceutical, non clinical and clinical documentation contained in the dossier of the medicinal product for the purpose of examining subsequent applications relating to other medicinal products possessing the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form. <a href="http://www.ema.europa.eu/htms/human/presub/q03.htm">http://www.ema.europa.eu/htms/human/presub/q03.htm</a>
MAA	<b>Marketing Authorisation Application:</b> Across all European markets, plus Australia, New Zealand, South Africa, and Israel (exceptions amongst major markets include USA, Canada, China and Japan), the <b>Marketing Authorization Application</b> (MAA) is a common document used as the basis for a marketing application (an application for approval to market the product based on a full review of all quality, safety, and efficacy data, including clinical study reports). In the USA, the New Drug Application (NDA) is the MAA equivalent. In Canada, the New Drug Submission (NDS) is the MAA equivalent. <a href="http://www.ema.europa.eu/index/indexh1.htm">http://www.ema.europa.eu/index/indexh1.htm</a>

1 2 3 4	Medicinal Product	A finished dosage form, for example, tablet, capsule, solution, etc., that contains an active ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo.
5 6	Multiple Applications	MAAs, where the applicants wish to obtain, either simultaneously or successively, more than one Marketing Authorisation for a specific medicinal product, under different invented names. <a href="http://www.ema.europa.eu/htms/human/presub/q09.htm">http://www.ema.europa.eu/htms/human/presub/q09.htm</a>
7 8 9 10	OD	<b>Orphan Drug</b> A drug for the treatment of a rare serious disease (defined in the EU as a condition that affects not more than 5 in 10,000 persons in the Community, and in the US as a condition affecting fewer than 200,000 people in the US) or for a disease not likely to generate sufficient profit to justify R&D costs. <a href="http://www.ema.europa.eu/htms/human/orphans/intro.htm">http://www.ema.europa.eu/htms/human/orphans/intro.htm</a>
11 12 13 14	PDCO	The main responsibility of the <b>Paediatric Committee</b> (PDCO) is to assess the content of paediatric investigation plans and adopt opinions on them in accordance with Regulation (EC) 1901/2006 as amended. This includes the assessment of applications for a full or partial waiver and assessment of applications for deferrals <a href="http://www.ema.europa.eu/htms/general/contacts/PDCO/PDCO.html">http://www.ema.europa.eu/htms/general/contacts/PDCO/PDCO.html</a>
15 16 17 18 19 20 21	PIP	A PIP sets out a programme for the development of a medicine in the paediatric population. The PIP aims to generate the necessary quality, safety and efficacy data through studies to support the authorisation of the medicine for use in children of all ages including age-appropriate formulation(s). These data have to be submitted to the European Medicines Agency, or national competent authorities, as part of an application for a marketing authorisation for a new medicine, or for one covered by a patent. In some cases, a PIP may include a waiver of the studies in one or more paediatric subsets, or a deferral.
22	Protocol Assistance	The process of giving scientific advice for Orphan Drugs <a href="http://www.ema.europa.eu/htms/human/sciadvic/protocol.htm">http://www.ema.europa.eu/htms/human/sciadvic/protocol.htm</a>
23	SA	<b>Scientific Advice</b> <a href="http://www.emea.europa.eu/htms/human/sciadvic/Scientific.htm">http://www.emea.europa.eu/htms/human/sciadvic/Scientific.htm</a>
24	SA letter	An official written statement expressing the final opinion of the CHMP on the questions raised by the applicant.
25 26 27 28 29	SAWP	The <b>Scientific Advice Working Party</b> is a permanent working party of the CHMP, in charge of Scientific Advice and Protocol Assistance for orphan medicinal products. This is the only Working Party of the EMEA established in the EU legislation <a href="http://www.ema.europa.eu/htms/general/contacts/CHMP/CHMP_SAWP.html">http://www.ema.europa.eu/htms/general/contacts/CHMP/CHMP_SAWP.html</a> .
30 31 32	Scientific Committees	These are composed by experts of all Member States and are established in the legislation. In addition to the CHMP, the Committee for Advanced Therapies is also involved in the evaluation of medicinal products, in particular, gene, cell and tissue engineered medicinal products
33 34 35 36 37 38	Single applications	In the European Union (EU), a company that wishes to bring a medicine to the market may submit a single application to the EMEA for a 'marketing authorisation' (licence) that is valid simultaneously in all EU Member States, plus Iceland, Liechtenstein and Norway. This is called the 'centralised (or 'Community') authorisation procedure', and is mandatory for certain types of medicines and optional for others. (The precise scope is set out in Annex I of Regulation (EC) No 726/2004.) <a href="http://www.ema.europa.eu/index/indexh1.htm">http://www.ema.europa.eu/index/indexh1.htm</a>
39 40 41	SMEs	<b>Small and Medium-sized Enterprises</b> Companies are classified according to their size (micro, small or medium) based on the number of employees and annual turnover. <a href="http://www.ema.europa.eu/htms/human/raguidelines/sme.htm">http://www.ema.europa.eu/htms/human/raguidelines/sme.htm</a>
42 43 44 45	Variation	Modification to the terms of a marketing authorization application (Regulations (EEC) No 2309/93 and Directives 2001/83/EC and 2001/82/EC),. Variations can be minor (type IA and IB) or major (type II), (Commission Regulation (EC) No 1084/2003) <a href="http://www.ema.europa.eu/htms/human/raguidelines/post.htm - type1">http://www.ema.europa.eu/htms/human/raguidelines/post.htm - type1</a> <a href="http://www.ema.europa.eu/htms/human/raguidelines/post.htm - type2">http://www.ema.europa.eu/htms/human/raguidelines/post.htm - type2</a>
46 47 48 49	Waiver	Waivers can be issued if there is evidence 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 adult populations, or that the medicine, or the performance of trials, does not represent a significant therapeutic benefit over existing treatments for paediatric patients.
50 51	Withdrawal	An applicant withdraws the application for evaluation of a medicinal product <a href="http://www.ema.europa.eu/htms/human/withdraw/withdrawapp/background.htm">http://www.ema.europa.eu/htms/human/withdraw/withdrawapp/background.htm</a>
52	Working	The CHMP establishes working parties which have expertise in a particular scientific field, and

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Party	are composed of members selected from the European experts list maintained by the EMEA. <a href="http://www.ema.europa.eu/htms/general/contacts/CHMP/CHMP_WPs.html">http://www.ema.europa.eu/htms/general/contacts/CHMP/CHMP_WPs.html</a>
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**Table 2:** An overview of Article 7, 8 and 30

Regulation (EC) No 1901/2006, as amended	Art. 7	Art. 8	Art. 30 (Paediatric Use Marketing Authorisation)
Existing Marketing Authorisation	No	Yes	No If Yes: not all paediatric needs are covered
Medicinal Product authorised in the Community, protected either by a Supplementary Protection Certificate (SPC) or by a patent which qualifies for granting a SPC	N/A	Yes	No
Mandatory PIP at the time of submission of Marketing Authorisation application	Yes since 26 <sup>th</sup> July 2008	Yes since January 26 <sup>th</sup> 2009	No Voluntary

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3 | **Paediatric Investigation Plans for Pain: painfully slow!**4  
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35 | **Disclaimer:**36 | **The article represents the views of the Authors and should not be understood or quoted as being made on**  
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**Abstract**

*Purpose:* To examine the early impact of the Paediatric Regulation, which entered into force in Europe on 27 January 2007, on the development of pharmaceutical drugs in the therapeutic field of pain submitted to the Paediatric Committee (PDCO) and to the European Medicines Agency (EMA).

*Methods:* Paediatric Investigations Plans (PIPs) submitted with a Decision (outcome) reached between September 2007 and March 2010 were included in the analysis.

*Results:* From seventeen Paediatric Investigation Plans submitted, fourteen have resulted in EMA Decision, three were withdrawn by the applicants, eight were granted a full waiver from development, and one resulted in a negative opinion. Decisions as issued included 15 clinical trials, with at least 1282 children to be recruited into studies across five different products. Neonates were included in four of the products.

*Conclusions:* The small number of submissions indicates a lack of new drugs being developed for the management of pain. Ethical concerns that too many vulnerable children will be recruited into clinical trials must be balanced against limiting the number of off-label prescribing and obtaining age-appropriate information on paediatric use. Now is an opportune time for clinicians, academics, learned societies and industry to collaborate for the benefit of children in pain.

**Key words**

Paediatric, Pain, Clinical trials, Paediatric Regulation, Paediatric Committee (PDCO), Paediatric Investigation Plan (PIP)

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## Introduction

A new piece of legislation (Regulation (EC) No 1901/2006 as amended) namely the 'Paediatric Regulation' governing the development and authorisation of medicines for use in children aged 0 to 17 years was introduced in the European Union in January 2007.

The Paediatric Regulation [6] also brings in many new tasks and responsibilities for the European Medicines Agency (EMA), chief of which is the creation and operation of a Paediatric Committee (PDCO) within the Agency to provide objective scientific opinions on any development plan for medicines for use in children.

Since the Paediatric Regulation entered into force in January 2007, the regulatory environment for paediatric medicines has dramatically changed. The Regulation requires pharmaceutical companies to consider the needs of the paediatric population during the development of their medicinal product.

The objective of the Paediatric Regulation is to improve the health of children in Europe by:

- facilitating the development and availability of medicines for children aged 0 to 17 years,
- ensuring that medicines for use in children are of high quality, ethically researched, and authorised appropriately,
- improving the availability of information on the use of medicines for children,

without:

- subjecting children to unnecessary trials,
- or delaying the authorisation of medicines for use in adults.

The paediatric regulation requires companies to submit a Paediatric Investigation Plan (PIPs; for further description of EMA terms see table 2) for their product, which is evaluated by the PDCO in 60 to 120 days. There is a possible clock stop at D60 to allow companies to respond to requests for modification of the plan. PDCO opinions on PIPs and waivers are transformed into binding European Medicines Agency decisions [7]. The PIP is submitted for review by the PDCO no later than the completion of the relevant human pharmacokinetic studies in adults. A waiver can be granted for a specific product, an indication or a class of products based on of the following three grounds:

- (i) That the specific medicinal product or class of medicinal products is likely to be ineffective or unsafe in part or all of the paediatric population,
- (ii) That the disease or condition for which the specific medicinal product or class is intended occurs only in adult populations or
- (iii) That the specific medicinal product does not represent a significant therapeutic benefit over existing treatments.

For products already authorised, including active substances protected by a supplementary protection certificate, or by a patent eligible for a supplementary protection certificate, Article 8 of the Regulation applies. In these circumstances, companies have the obligation to submit the results of an agreed PIP covering all existing and

1 new indications, new route of administration or new formulation, unless a waiver has been granted by the  
2 PDCO.

3  
4 For medicinal products not yet authorised Article 7 of the Regulation applies, and companies have the obligation  
5 to submit results of an agreed PIP, unless a waiver has been granted by the PDCO. Deferrals for the completion  
6 of trials (not for the submission of PIPs) can also be granted by the PDCO, to protect the safety of children until  
7 additional safety data in adults is available.  
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10 For off-patent products already available on the market for adults only, without information and/or a formulation  
11 appropriate for children of all ages Article 30 can apply, where companies submit a PIP on a voluntary basis  
12 leading to a Paediatric Use Marketing Authorisation (PUMA). The PIP must be agreed and covers paediatric  
13 indication and formulation. An overview of Article 7, 8 and 30 can be seen in Table 1.  
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17 Ethical concerns that too many vulnerable children are recruited into clinical trials must be balanced against  
18 limiting the number of off-label prescribing and obtaining age-appropriate information on paediatric use. Within  
19 the context of a clinical trial safety monitoring can be done rigorously, and any safety concerns noted early on,  
20 minimised or prevented.  
21

22  
23 The PDCO is not responsible for marketing-authorisation applications for medicinal products for paediatric use.  
24 This remains fully within the remit of the Committee for Medicinal Products for Human Use (CHMP) [1].  
25 However, the CHMP or any other competent authority may request the PDCO to prepare an opinion on the  
26 quality, safety and efficacy of a medicinal product for use in the paediatric population if these data have been  
27 generated in accordance with an agreed paediatric investigation plan.  
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31 A review of all the PIPs submitted with a Decision reached between September 2007 and March 2010 was  
32 conducted to examine the impact of the Regulation in the therapeutic field of Pain, not only in terms of numbers  
33 of PIPs received but also in relation to the number and types of clinical trials to be conducted, and the number of  
34 children to be recruited.  
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**Method**

Utilising the EMA Paediatric Database, all the Paediatric Investigation Plans (PIPs) received by the EMA between September 2007 and March 2010 were searched to identify those in the therapeutic field of pain.

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The EMA Paediatric Database includes all PIPs and/or waivers submitted to the PDCO and EMA since June 2007 along with all procedural steps leading to the PDCO Opinion and European Medicines Agency decision (outcome).

It also records scientific data, while streamlining work procedures by producing pre-filled documents and interacting directly with a secure e-mail system to send messages and documents to external addressees (including applicants).

Key word 'pain' was used in search fields 'condition/ indication' and therapeutic area as the main parameter to identify the PIPs of interest.

The Pain PIPs identified were then categorised according to type of product (Table 2): Article 8 for products already authorised, Article 7 for medicinal products not yet authorised and for off-patent products already available on the market for adults only Article 30.

Key word 'diabetes', 'Human Immunodeficiency Virus (HIV)' and 'infectious diseases' were used in search fields 'condition/ indication' and therapeutic area as the main parameters to identify PIPs to be compared in terms of numbers of pharmaceutical drugs that have been submitted with the therapeutic area of pain.

## Results

Seventeen submissions were made to the Paediatric Committee (PDCO) for assessment. Three were withdrawn by the applicants during the procedure; the reasons for withdrawal were not communicated to the European Medicines Agency and PDCO.

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Twelve submissions were for Article 7 and from a known class, with only one of the submissions being a product with a new mechanism of action. The thirteenth submission was for Article 8 and the fourteenth submission was a Paediatric Use Marketing Authorisation request, which was also a well known product widely used for other indications.

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Seven out of the twelve Article 7 submissions were for fixed dose combinations, one of which included development in the adolescent age group while the other was an application for a full waiver. The PDCO did not consider that they offered significant therapeutic benefit to children as fixed combination. Although the effect of the substances on their own was known, the effect of the combination was unknown and would have required studies. However the PDCO was of the opinion that fixed combinations were not appropriate in this case as they do not allow flexibility in the dosing according to age and weight. Therefore waivers for paediatric development were granted for all age groups for these fixed combinations.

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One eighth product was also a request for a Waiver in all age groups, based on the ground that the medicinal product did not represent a significant therapeutic benefit over existing available products. This submission was for an old product well known and widely used, but with a new formulation for intravenous use. In this instance, the PDCO did not agree that the product lacked the potential to meet the current needs; however they had significant concerns about the content of the formulation for this product and about the lack of clinical data for prescribing in the neonatal age group. Discussions with the company regarding these concerns led to the development of a clinical trial designed to specifically investigate these key safety concerns.

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One of the Article 7 submission resulted in a negative opinion; the grounds for refusal cannot be communicated for legal reasons.

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Finally out of the last three PIPs submissions under Article 7 were for the same active substance but included both acute and chronic pain indications, with immediate and prolonged release formulations. The initial application included a request for a partial waiver for the 0-23 months age group. Following extensive discussion with the applicant, the PDCO agreed on PIPs for all the paediatric age groups, in both indications but utilising modelling and simulation of pharmacokinetics in children less than 2 years.

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The last PIP under Article 7 was for acute pain. The initial submission included a request for a partial waiver for the 0-23 months age group. Following discussion with the applicant, the PDCO agreed on PIPs for children from 6 years to less than 18 years and a partial waiver in children from birth to less than 6 years of age. The partial waiver was granted based on the ground that the product does not represent significant benefit over existing treatments.

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The Article 8 PIP submission was refused by the PDCO. The PDCO had concerns that the proposed measures and timelines were not appropriate to generate necessary data in determining the conditions in which the

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1 medicinal product may be used to treat the paediatric population or subsets thereof, nor in adapting a paediatric  
 2 formulation. The PDCO also considered that the product would not bring significant therapeutic benefit. A  
 3 product-specific waiver was granted on PDCO own motion on the grounds that the specific medicinal product is  
 4 likely to be ineffective or unsafe in all the paediatric population.  
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7 Another product submitted a request for a Waiver for children older than 2 years due to expected lack of efficacy  
 8 in this age group and lack of significant therapeutic benefit. The PDCO was in agreement with the data presented  
 9 by the applicant and therefore a Partial Waiver for children over 2 years of age was granted.  
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12 Overall, Opinions as issued by the PDCO following discussion with the applicant resulted in the agreement of 13  
 13 clinical trials, with a total of at least 1282 children to be recruited across five different products. The number of  
 14 studies per product ranged from one to six.  
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17 For two of the products, the PDCO agreed to studies across the full paediatric age range (from birth to 18 years),  
 18 starting with the older children (6 – 17 years) and proceeding in a staggered stepwise manner to the younger  
 19 children (2-5 years followed by the less than 2 years age group). This staggered approach was adopted to  
 20 maximise the safety of the children.  
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23 Following extensive discussion between the PDCO and the company, efficacy did not need to be demonstrated  
 24 in a blinded fashion in two clinical trials, on the grounds that data would be generated in other studies with the  
 25 same compound, all be it in a different pain model.  
 26

27 Evaluation by the PDCO takes account where possible the guidance on Clinical Investigation of Medicinal  
 28 Products for Treatment of Nociceptive Pain (Committee for Proprietary Medicinal Products (CPMP) [10] and  
 29 the Guideline on Clinical Medicinal Products intended for the Treatment of Neuropathic Pain [11]  
 30

32 Four studies for one product were placebo controlled, as there was no pharmacological alternative currently used  
 33 or available in clinical practice. However, the study protocols included clear guidance for 'rescue treatment'.  
 34 Five other studies across three different products were active-controlled, however only two were blinded due to  
 35 complexities in achieving this. Four of the studies were for pharmacokinetics only, and one of the studies was a  
 36 modelling and simulation of pharmacokinetics.  
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39 Neonates were included in four agreed PIPs. Only one applicant had included neonates in their original PIP  
 40 submission, and their inclusion in the other three PIPs was only after evaluation by PDCO, and subsequent  
 41 discussions with the companies. Preterm neonates were included in two agreed PIPs, again following PDCO  
 42 evaluation, with the primary aim of identify pharmacokinetics data in three PIPs. Population-pharmacokinetics,  
 43 micro assay and sparse sampling were agreed in all four PIPs, limiting the individual burden for each infant. This  
 44 is an important step forward given the lack of current available data for many drugs in the neonatal age group,  
 45 while causing minimal pain and distress.  
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 47

49 Three out of the five proposed PIPs were non-opioids intended for mild to moderate pain. One PIP was  
 50 specifically for Procedural pain and the last PIP was for acute pain. Only the new product had the potential to  
 51 work as Step III analgesia, as defined by the World Health Organization three-step analgesic ladder [2].  
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## Formulations

The development of intravenous and age-appropriate oral formulation, in immediate and prolonged release forms, has the potential to be of significant therapeutic benefit to the paediatric population.

Eleven of the fourteen submissions included formulations for oral use, two of the fourteen included intravenous formulation, one submission was for inhalation use and the last submission was for nasal spray. Age-appropriate formulations were not adequately addressed in seven of the original submissions. Following review by the PDCO two of the applicants agreed to develop age-appropriate formulation. This would indicate that the legislation has been able to positively influence the development of age-appropriate formulations where it otherwise may not have been developed.

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## Discussion

Effective management of childhood pain is a high priority. There is now conclusive evidence that paediatric patients of all ages, including the extremely premature neonates [3], are capable of experiencing pain as a result of tissue injuries, medical illnesses, therapeutic and diagnostic procedures, trauma and surgery. A range of medications is available to treat a variety of pain types [4] but not all are suitable for all age subsets. There is increasing knowledge in the understanding of developmental neurobiology, developmental pharmacology and of the psychological needs of children in pain, however a gap remains.

The paediatric population (birth to 18 years) in the European Union is close to 100 million, and up to 10% of these will undergo some type of surgical procedures every year, not to mention other painful conditions. Paediatric patients experience pain in different clinical situations following trauma, during hospital stay and in pathological conditions treated by physicians outside the hospital, such as headache and acute abdominal pain which are common during childhood. An epidemiological survey of 9,000 school children found that one third of seven year old children and half of 15 year olds had headaches. In a survey done in school children in Germany (n=749) [5] 83% of children and adolescents reported experiencing pain during the preceding 3 months. Many of these children, in all age groups will require analgesia.

Prior to the implementation of the Regulation the Paediatric Working Party a temporary working party of the Committee on Medicinal Products for Human Use (CHMP) —conducted an exercise between 2001 and 2007 to establish 'Paediatric Needs' [8]. The lists of paediatric needs as adopted by the Working Party serves as a basis for the inventory of needs that is to be established and published by the Paediatric Committee in accordance with the Paediatric Regulation. This list is intended to guide the Committee when assessing PIPs.

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Another list, the 'Priority List of off-patent medicines' [9] has been set up to direct research on off-patent medicines for which there is a high need in the paediatric population. With the availability of funding, provided through the European Union Framework Programmes, the aim is that more of these medicines will be developed for children and submitted for a Paediatric Use Marketing Authorisation. Conditions with higher therapeutic needs were initially identified as early as 2002-2003, mostly based on the severity of the disease; the paediatric groups affected (with special priority for the neonatal population); the non-availability of treatment alternatives; and the high prevalence of the disease in the paediatric population. For each condition, published therapeutic reviews of medicines used in children were analysed to identify off-label products of therapeutic interest and priorities for research. The list comprises a number of medicines relating to various therapeutic areas and is regularly updated.

Analgesia in the paediatric population was identified as an area with high therapeutic needs in the 'Priority List' and in the 'Paediatric Needs'.

Pain management has one of the highest needs compared to other therapeutic areas, especially when considering the high incidence and prevalence of pain in the paediatric population across all conditions. When comparing the number of PIP submissions in pain to other therapeutic fields in the same time period however we note that the numbers of products being developed are small. In the same period, twenty-one PIPs were submitted in the therapeutic area of Diabetes (Twelve still under review), and twelve submitted for Human Immunodeficiency

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Virus, (Nine still under review). The prevalence and incidence of these indications compared to pain (five still under review) are comparatively much less, but are noted to be very active areas in terms of drug development.

Development in Pain is low in comparison to the high incidence and despite the high therapeutic need identified in the priority list.

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**Conclusion**

There is an apparent lack of innovative drugs being developed for pain, compared to some other therapeutic areas, however this may not be a paediatric only problem. Despite the Paediatric Regulation industry remain at liberty to study in any therapeutic area of their choice. This is an opportune time for clinicians, academia, learned societies and industry to collaborate for the discovery of new products, the generation of new data and the development of new formulations to ultimately benefit the needs of children and neonates in pain. The Paediatric Regulation serves to enforce industry to consider the needs of children in the development plans of their products, while the PDCO serves to ensure that only studies that offer significant value are agreed upon for the final Decisions.

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**Acknowledgements**

The authors would like to thank the Paediatric Committee and the paediatric team at the European Medicines Agency who contribute every day to make better medicines for children. We are very grateful for the cooperation of the children and parents who take part in the clinical research and hope that children will soon benefit from the Paediatric Regulation. It would not be possible without their help and cooperation.

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**Conflict of interest**

The authors declare that they have no conflict of interest.

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7. EMA Decisions on paediatric investigation plans (PIPs), including deferrals and waivers, and on modification of an agreed PIP <http://www.ema.europa.eu/htms/human/paediatrics/decisions.htm>
8. Inventory of Paediatric Needs, 2007 <http://www.ema.europa.eu/htms/human/paediatrics/inventory.htm>
9. Revised Priority list of off-patent medicines, 2009 <http://www.ema.europa.eu/htms/human/paediatrics/prioritylist.htm>
10. Committee for Proprietary Medicinal Products (CPMP) Note for guidance on Clinical Investigation of Medicinal Products for Treatment of Nociceptive Pain, 2003 <http://www.ema.europa.eu/pdfs/human/ewp/061200en.pdf>
11. Committee for Medicinal Products for Human Use (CHMP) Guideline on Clinical Medicinal Products intended for the Treatment of Neuropathic Pain, 2007 <http://www.ema.europa.eu/pdfs/human/ewp/025203enfin.pdf>

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**Table 1** A short description of EMA terms including weblinks (updated from Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency (Eur J Clin Pharmacol (2010) 66:39–48)

Term	Description
Centralised Procedure	A Community registration procedure created by Council Regulation (EEC) No. 2309/93 and amended by Regulation 726/2004 for the authorization of medicinal products, for which there is a single application, a single evaluation and a single authorisation allowing direct access to the single market of the European Community. The opinion of the CHMP is transmitted to the European Commission to be transformed in a further 67 days into a single marketing authorisation applicable to the whole European Union. This procedure is compulsory for medicinal products derived from biotechnology, and in 4 specific therapeutic areas (products against HIV, cancer, neurodegenerative diseases and diabetes), and available at the request of companies for other innovative new products. Applications are submitted directly to the EMEA. <a href="http://ec.europa.eu/enterprise/pharmaceuticals/procedure/cproc_en.htm">http://ec.europa.eu/enterprise/pharmaceuticals/procedure/cproc_en.htm</a> <a href="http://www.ema.europa.eu/index/authorisation.htm">http://www.ema.europa.eu/index/authorisation.htm</a>
Class waiver	The Agency already adopted decisions on class waivers in October 2009 for conditions that do not occur in children, or for products likely to be unsafe or ineffective in children. The list of waivers is regularly updated in light of the advance in knowledge and science in the paediatric field. <a href="http://www.ema.europa.eu/htms/human/paediatrics/classwaivers.htm">http://www.ema.europa.eu/htms/human/paediatrics/classwaivers.htm</a>
CHMP	The <i>Committee for Medicinal Products for Human Use</i> (CHMP) is responsible for preparing the Agency's opinions on all questions concerning medicinal products for human use, in accordance with Regulation (EC) No 726/2004. <a href="http://www.ema.europa.eu/htms/general/contacts/CHMP/CHMP.html">http://www.ema.europa.eu/htms/general/contacts/CHMP/CHMP.html</a>
CHMP Opinion	CHMP's <u>scientific conclusions</u> on issues related to medicinal products, e.g. whether the data <u>submitted allow</u> to conclude that there is an overall positive benefit/risk of a new product in a proposed indication and whether the product should be placed on the market.
Compliance	A compliance check is performed to verify that all the measures agreed in a PIP and reflected in the Agency's decision have been conducted in accordance with the decision, including the agreed timelines. Compliance is one of several prerequisites for obtaining the rewards and incentives provided for in Articles 36 to 38 of the Paediatric Regulation.
EMA	The <i>European Medicines Agency</i> (EMA) created by Council Regulation (EEC) No. 2309/93 of 22 July 1993, and renamed by Council Regulation 726/2004 of 31 March 2004, is based in Canary Wharf, London. The Agency is responsible for coordinating the existing scientific resources put at its disposal by the competent authorities of the Member States for the evaluation and supervision of medicinal products. <a href="http://www.ema.europa.eu">http://www.ema.europa.eu</a>
European Commission	<i>Commission of the European Communities</i> : The "civil service" of the European Union It is the executive organ of the Community. It proposes Community policy and legislation, implements the decisions taken by the Council of Ministers, and supervises the day-to-day running of Commission policies.
Follow-up SA	Any application for SA following the initial application on the same area/condition. For example, the initial advice can be on the pharmacokinetics and the exploratory phase II trial, and later the pivotal Phase III trial could be the subject of a follow-up advice.
Informed Consent applications	According to Article 10c of Directive 2001/83/EC as amended, following the granting of a marketing authorisation, the authorisation holder may allow use to be made of the pharmaceutical, non clinical and clinical documentation contained in the dossier of the medicinal product for the purpose of examining subsequent applications relating to other medicinal products possessing the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form. <a href="http://www.ema.europa.eu/htms/human/presub/q03.htm">http://www.ema.europa.eu/htms/human/presub/q03.htm</a>
MAA	<i>Marketing Authorisation Application</i> : Across all European markets, plus Australia, New Zealand, South Africa, and Israel (exceptions amongst major markets include USA, Canada, China and Japan), the <i>Marketing Authorization Application</i> (MAA) is a common document used as the basis for a marketing application (an application for approval to market the product based on a full review of all quality, safety, and efficacy data, including clinical study reports). In the USA, the New Drug Application (NDA) is the MAA equivalent. In Canada, the New Drug Submission (NDS) is the MAA equivalent. <a href="http://www.ema.europa.eu/index/indexhl.htm">http://www.ema.europa.eu/index/indexhl.htm</a>

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1 2 3 4	Medicinal Product	A finished dosage form, for example, tablet, capsule, solution, etc., that contains an active ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo.	
5 6 7	Multiple Applications	MAAs, where the applicants wish to obtain, either simultaneously or successively, more than one Marketing Authorisation for a specific medicinal product, under different invented names. <a href="http://www.ema.europa.eu/htms/human/presub/q09.htm">http://www.ema.europa.eu/htms/human/presub/q09.htm</a>	Field Code Changed
8 9 10	OD	<b>Orphan Drug</b> A drug for the treatment of a rare serious disease (defined in the EU as a condition that affects not more than 5 in 10,000 persons in the Community, and in the US as a condition affecting fewer than 200,000 people in the US) or for a disease not likely to generate sufficient profit to justify R&D costs. <a href="http://www.ema.europa.eu/htms/human/orphans/intro.htm">http://www.ema.europa.eu/htms/human/orphans/intro.htm</a>	Field Code Changed
11 12 13 14	PDCO	The main responsibility of the <b>Paediatric Committee</b> (PDCO) is to assess the content of paediatric investigation plans and adopt opinions on them in accordance with Regulation (EC) 1901/2006 as amended. This includes the assessment of applications for a full or partial waiver and assessment of applications for deferrals <a href="http://www.ema.europa.eu/htms/general/contacts/PDCO/PDCO.html">http://www.ema.europa.eu/htms/general/contacts/PDCO/PDCO.html</a>	
15 16 17 18 19 20	PIP	A PIP sets out a programme for the development of a medicine in the paediatric population. The PIP aims to generate the necessary quality, safety and efficacy data through studies to support the authorisation of the medicine for use in children of all ages, <b>including age appropriate formulation(s)</b> . These data have to be submitted to the European Medicines Agency, or national competent authorities, as part of an application for a marketing authorisation for a new medicine, or for one covered by a patent. In some cases, a PIP may include a waiver of the studies in one or more paediatric subsets, or a deferral.	Formatted: Highlight
21 22	Protocol Assistance	The process of giving scientific advice for Orphan Drugs <a href="http://www.ema.europa.eu/htms/human/sciadvic/protocol.htm">http://www.ema.europa.eu/htms/human/sciadvic/protocol.htm</a>	Field Code Changed
23 24	SA	<b>Scientific Advice</b> <a href="http://www.emea.europa.eu/htms/human/sciadvic/Scientific.htm">http://www.emea.europa.eu/htms/human/sciadvic/Scientific.htm</a>	Formatted: French (France)
25 26	SA letter	An official written statement expressing the final opinion of the CHMP on the questions raised by the applicant.	
27 28 29	SAWP	The <b>Scientific Advice Working Party</b> is a permanent working party of the CHMP, in charge of Scientific Advice and Protocol Assistance for orphan medicinal products. This is the only Working Party of the EMEA established in the EU legislation <a href="http://www.ema.europa.eu/htms/general/contacts/CHMP/CHMP_SAWP.html">http://www.ema.europa.eu/htms/general/contacts/CHMP/CHMP_SAWP.html</a> .	Field Code Changed
30 31 32	Scientific Committees	These are composed by experts of all Member States and are established in the legislation. In addition to the CHMP, the Committee for Advanced Therapies is also involved in the evaluation of medicinal products, in particular, gene, cell and tissue engineered medicinal products	
33 34 35 36 37 38	Single applications	In the European Union (EU), a company that wishes to bring a medicine to the market may submit a single application to the EMEA for a 'marketing authorisation' (licence) that is valid simultaneously in all EU Member States, plus Iceland, Liechtenstein and Norway. This is called the 'centralised (or 'Community') authorisation procedure', and is mandatory for certain types of medicines and optional for others. (The precise scope is set out in Annex I of <a href="http://www.ema.europa.eu/index/indexh1.htm">Regulation (EC) No 726/2004</a> .) <a href="http://www.ema.europa.eu/index/indexh1.htm">http://www.ema.europa.eu/index/indexh1.htm</a>	Field Code Changed
39 40 41	SMEs	<b>Small and Medium-sized Enterprises</b> Companies are classified according to their size (micro, small or medium) based on the number of employees and annual turnover. <a href="http://www.ema.europa.eu/htms/human/raguidelines/sme.htm">http://www.ema.europa.eu/htms/human/raguidelines/sme.htm</a>	Field Code Changed
42 43 44 45	Variation	Modification to the terms of a marketing authorization application (Regulations (EEC) No 2309/93 and Directives 2001/83/EC and 2001/82/EC),. Variations can be minor (type IA and IB) or major (type II), (Commission Regulation (EC) No 1084/2003) <a href="http://www.ema.europa.eu/htms/human/raguidelines/post.htm - type1">http://www.ema.europa.eu/htms/human/raguidelines/post.htm - type1</a> <a href="http://www.ema.europa.eu/htms/human/raguidelines/post.htm - type2">http://www.ema.europa.eu/htms/human/raguidelines/post.htm - type2</a>	Field Code Changed
46 47 48 49	Waiver	Waivers can be issued if there is evidence 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 adult populations, or that the medicine, or the performance of trials, does not represent a significant therapeutic benefit over existing treatments for paediatric patients.	Field Code Changed
50 51	Withdrawal	An applicant withdraws the application for evaluation of a medicinal product <a href="http://www.ema.europa.eu/htms/human/withdraw/withdrawapp/background.htm">http://www.ema.europa.eu/htms/human/withdraw/withdrawapp/background.htm</a>	Field Code Changed
52 53	Working	The CHMP establishes working parties which have expertise in a particular scientific field, and	Field Code Changed

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Party	are composed of members selected from the European experts list maintained by the EMEA. <a href="http://www.ema.europa.eu/htms/general/contacts/CHMP/CHMP_WPs.html">http://www.ema.europa.eu/htms/general/contacts/CHMP/CHMP_WPs.html</a>
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For Peer Review

**Table 2:** An overview of Article 7, 8 and 30

Regulation (EC) No 1901/2006, as amended	Art. 7	Art. 8	Art. 30 (Paediatric Use Marketing Authorisation)
Existing Marketing Authorisation	No	Yes	No If Yes: not all paediatric needs are covered
Medicinal Product authorised in the Community, protected either by a Supplementary Protection Certificate (SPC) or by a patent which qualifies for granting a SPC	N/A	Yes	No
Mandatory PIP at the time of submission of Marketing Authorisation application	Yes since 26 <sup>th</sup> July 2008	Yes since January 26 <sup>th</sup> 2009	No Voluntary