8 July 2012
EMA/428172/2012
Human Medicines Development and Evaluation
Human Medicines Special Areas Sector

5-year Report to the European Commission

General report on the experience acquired as a result of the application of the Paediatric Regulation

Prepared by the
European Medicines Agency with its Paediatric Committee

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7040
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Table of contents

1. Summary

The objective of the report is to present five years after the entry into force of the Paediatric Regulation, a factual analysis of data collected by the EU Member States and the EMA. The report aims at measuring the initial impact of the Paediatric Regulation in line with its objectives of achieving high-quality ethical paediatric clinical research, increasing availability of authorised medicines that are appropriate for children and producing better information on medicines.

- Paediatric research and development

The Paediatric Committee (PDCO) is responsible for the scientific evaluation of paediatric investigation plans (PIP), which is one of the main pillars of the Paediatric Regulation to foster paediatric research and development. The evaluation of PIPs was completed for 682 medicines up to the end of 2011. Among the opinions adopted, 476 were on the agreement of a PIP (70%) and 30% of a full waiver. Waivers indicate that the use of the medicine in the targeted condition was not of paediatric relevance or interest, or likely to be unsafe. Around 75% of PIPs were for medicines that were not yet authorised at the time of evaluation. All PIP and waiver opinions are made public.

The EMA/PDCO engaged in multiple interactions with external experts on scientific questions raised by paediatric development to improve the plans. The PDCO provided expertise to almost all EMA Scientific Advice / Protocol Assistance procedures addressing paediatric questions, i.e. about 70 per year. In total, about 150 companies benefited from Scientific Advice on paediatric questions, provided by either Member States directly or the EMA/CHMP.

New development approaches included in particular extrapolation of efficacy, required explicitly in 22% of PIPs to protect children against unnecessary trials. Simultaneously, the PDCO required studies in areas with historically no or only very limited paediatric research. Unfortunately, the submission of PIP and waiver proposals was delayed compared to the legal requirements; this did not improve over the years and represents missed opportunity for early regulatory dialogue.

Transparency of ongoing and planned paediatric research is another tool to avoid unnecessary replication of trials. The EudraCT database was developed to include protocol-related information of clinical trials, and this information was made publicly accessible in 2010 as mandated by the Paediatric Regulation. Paediatric trials that are part of an agreed PIP are increasingly visible in EudraCT, with 110 such trials authorised by the end of 2011 and already 21 more submitted for authorisation in 2012 (uploaded into EudraCT as of March 2012). Overall, the number of paediatric trials newly registered in EudraCT is at a constant level of about 350 per year since 2007, while the corresponding numbers of trials with adult participants decreased by about 6% per year from 2007 to 2011 (see limitation of data).

Trials with neonates represent high unmet needs and were requested wherever necessary by the PDCO, including in many cases where these would have been neglected in the past. However, studies with neonates are not necessary for all medicines or in all diseases; studies in this age group were required overall in about one third of the agreed PIPs. EudraCT provides information on temporarily halted or prematurely terminated trials with the paediatric population; monitoring of these situations did not indicate increased concerns on safety or efficacy during clinical trials since the entry into force of the Paediatric Regulation.

The development of 20 off-patent medicines for paediatric use in 15 projects was funded by the EU Framework programme, and the first 7 corresponding PIPs were agreed.

The European Network for Paediatric Research at the EMA (Enpr-EMA), established in 2009, has set up collaboration with 18 networks based on research quality criteria. Concerning support to research and

development, only some Member States have special provisions for paediatrics in addition to the general provisions for research.

- Medicines available to children

By the end of 2011, 29 PIPs (excluding duplicates) had been completed in compliance with the PDCO Decisions. After assessment of the results, the plans led to new paediatric indications (24 medicines) and to new pharmaceutical forms appropriate for children (7 medicines). However, data from 5 completed PIPs provided important information which did not support the use in children and this information was detailed in the Product Information for the benefit of health care professionals.

Between 2008 and 2012, 10 new medicinal products (new active substance) were centrally authorised and received a paediatric indication (out of 113 new active substances in total), under the requirements of the Paediatric Regulation. For 1 of the 10 products, a Paediatric Use Marketing Authorisation (PUMA) had been requested and was granted.

For medicines already authorised centrally or nationally, 18 and 12 respectively, received a new paediatric indication developed under the Paediatric Regulation between 2008 and 2012. Such new indications have increased since 2009, whereas new indications not linked to the Paediatric Regulation have decreased, as expected.

Regarding the development of pharmaceutical forms for use in children, the PIP propoals raised concerns in the majority of cases; issues were mostly related to excipients and/or to appropriateness of formulations to ensure their safe and acceptable use in children. The EMA/PDCO is monitoring how these issues are going to be addressed as well as how PIPs progress in practice.

Annual reports on deferred paediatric studies of authorised medicines indicate that the majority of PIPs are running as programmed. Paediatric research is ongoing at the same rate across therapeutic areas such as oncology, vaccines and immunology-rheumatology-transplantation as estimated by the first trial in agreed PIPs. As expected due to data acquired during medicine development, agreed PIPs need to be modified. The number of modifications of agreed PIPs per year, is about half of that of newly agreed PIPs for that year. The analysis of the reasons for modifications shows variability, for example time lines were changed by one year or less in about half of the modifications.

- Information on medicines and other outcomes

Information on the use of paediatric medicines was improved with the addition of new study data and new recommendations into the Summary of Product Characteristics (SmPC). Contrary to the assumption that very few paediatric data had ever been collected in the past, a huge number of paediatric study data were submitted by Marketing Authorisation Holders to competent authorities (Article 45 of the Paediatric Regulation). Results from more than 18,000 completed paediatric studies of about 1000 active substances have been submitted, including those published in the literature, and are undergoing assessment, in waves. For nationally authorised medicines, the assessment is co-ordinated by the CMD(h) and is ongoing for 248 active substances, prioritised according to the highest paediatric needs. By the end of 2011, the assessment of studies of 149 active substances had been completed, which resulted in 65 SmPC changes.

Rewards for completion of paediatric development in compliance with agreed PIPs are intended to compensate the work done by Marketing Authorisation Holders. By the end of 2011, National Patent Offices in 16 Member States had granted 6-month extensions of the Supplementary Protection Certificate to 11 medicines, resulting in a total of 105 national SPC extensions (not all medicines received the extension in every Member State), as per Article 36(1) of the Paediatric Regulation. In addition, one Paediatric Use Marketing Authorisation benefits from the 10-year protection.

As part of the implementation of the Paediatric Regulation the EMA engaged in projects with external stakeholders and international collaboration. As early as in 2007, a Paediatric Cluster was formed by the EMA and the FDA as part of the confidentiality arrangements. Up to the end of 2011, the cluster held 54 teleconferences, with exchange of information on paediatric development of common interest. Japan and Health Canada joined the teleconferences in 2009 and 2010 respectively. Further international partners of the EMA for the development of paediatric medicines, are the World Health Organization (WHO) with their initiative, Better Medicines for Children, and their Paediatric Medicines Regulators' Network (PmRN), and various academic groups. The EMA is also a partner in the Global Research in Paediatrics project (GRIP).

The EMA also engaged early in the implementation phase in interactions with trade associations and individual pharmaceutical companies (e.g. pre-submission meetings), in particular with Small and Medium Sized Enterprises, including through activities of the business pipeline.

- Conclusions

This report shows that the implementation has already had a positive impact in keeping with the main objectives of the Paediatric Regulation, and that paediatric development is increasing. Systematic paediatric development as set out in PIPs, and contribution to paediatric research and development by all stakeholders is leading to age-appropriate medicines and increasing paediatric information. In principle, PIP Decisions are in place for many authorised medicines that are relevant for children, but do not have a paediatric indication. Hopefully, long-standing gaps in knowledge will be filled in. Achieving the objectives of the Paediatric Regulation is a realistic goal based on the experience gathered so far, but sufficient time is needed as medicines development spans decades. Meanwhile, opportunities for improvement of the processes have been identified and are being addressed to increase the positive impact of the Paediatric Regulation and make medicines available with appropriate information to children.

Figure 1: Highlights of the impact of Paediatric Regulation after 5 years.

2006	2007-2011	End of 2011	Ongoing
Historical situation	**Activities driven by Paediatric Regulation**	**Achievements**	**Areas for improvements**
• Around 75% of all 317 centrally authorised medicines relevant for children, but only half (34%) with a paediatric indication	• Dramatic change with mandatory evaluation of potential paediatric use, for all new medicines and new indications • PDCO sees potential paediatric use in about 80% of medicines and agrees 476 PIPs • PDCO expertise contributes to EMA opinions on paediatric issues • Ongoing shared assessments by Member States of about 18,000 paediatric study reports	• Increasing number and proportion of paediatric trials conducted • PIPs completed for 29 active substances • Authorisation of 13 new medicines, 30 new indications and 9 new pharmaceutical forms for paediatric use, linked to PIPs • Rewards obtained for 12 medicines (SPC extensions for 11 medicines; 1 PUMA exclusivity) • Enpr-EMA established and operational	• Neglected therapeutic areas (e.g., paediatric oncology) • Missed regulatory dialogue opportunities (e.g., late PIP applications) • Simplified procedures; decreased level of details in PIPs • Support to applicants • Increased involvement of patients and learned societies

PIP: Paediatric investigation plan. PUMA: Paediatric Use Marketing Authorisation, SPC: Supplementary Protection Certificate. Enpr-EMA: European Network of Paediatric Research at the EMA.

2. Introduction

Regulation (EC) No. 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (hereinafter 'the Paediatric Regulation') was adopted on 12 December 2006. It was published in the Official Journal of the European Communities on 27 December 2006 and entered into force on 26 January 2007.

In 2013 the Commission has to present *to the European Parliament and the Council a general report on experience acquired as a result of the application of this Regulation (Article 50 (2) of the Paediatric Regulation).*

In order to support the Commission in drafting this report, a working group of the Paediatric Committee has prepared the present document together with the European Medicines Agency secretariat. The document discusses the achievements of the Paediatric Regulation from the view point of the EMA/PDCO. The working group members were: Daniel Brasseur, Maria Jesús Fernández Cortizo, Karl-Heinz Huemer, Dirk Mentzer, Marianne Orholm, Francesca Rocchi, Sylvie Benchetrit, Tsveta Schyns-Liharska, Anne-Sophie Henry-Eude, Ralf Herold and Franca Ligas.

The report includes indicators of activities and outcomes that were agreed in 2011 with the European Commission (list in Annex 12.). These indicators aim to capture the objectives of the Paediatric Regulation, i.e. encouraging ethical high quality paediatric research, making more medicines available to children and increasing information on paediatric medicines. The indicators are therefore presented in this sequence, going from research and development, to availability of medicines for children, to more information for use of medicines for children, complemented by a report on other projects and activities to supports applicants and reduce administrative burdens, and finally to lessons learned. The report includes examples and qualitative information on the impact of the Paediatric Regulation.

The report covers the period from January 2007 to December 2011 ("reporting period"). Data from previous years and data without the application of the Paediatric Regulation are provided as reference, where possible. Throughout the report, the term "children" refers to the whole paediatric population as defined in the Paediatric Regulation (from birth to less than 18 years of age), if not otherwise noted.

Various data sources were used for this report, including national surveys, datasheets of the CMD(h), various EMA business databases, the EudraCT databases as well as data collections of projects necessary to the implementation of the Paediatric Regulation. The surveys were conducted with the EU competent authorities and patent offices of the Member States, and their contributions to the implementation of the Paediatric Regulation and to the report are acknowledged.

As much as possible, the report refers to active substances, to summarise across marketing authorisations, duplicates and marketing authorisation holders (NB: the numbers of PDCO Opinions and EMA Decisions included about 13% duplicates). The report does not include data for generic, biosimilar, hybrid, homeopathic, traditional herbal and well-established medicinal products - which are excluded from the scope of the mandatory development - unless otherwise mentioned. Recitals and Articles refer to the Paediatric Regulation, if not otherwise stated.

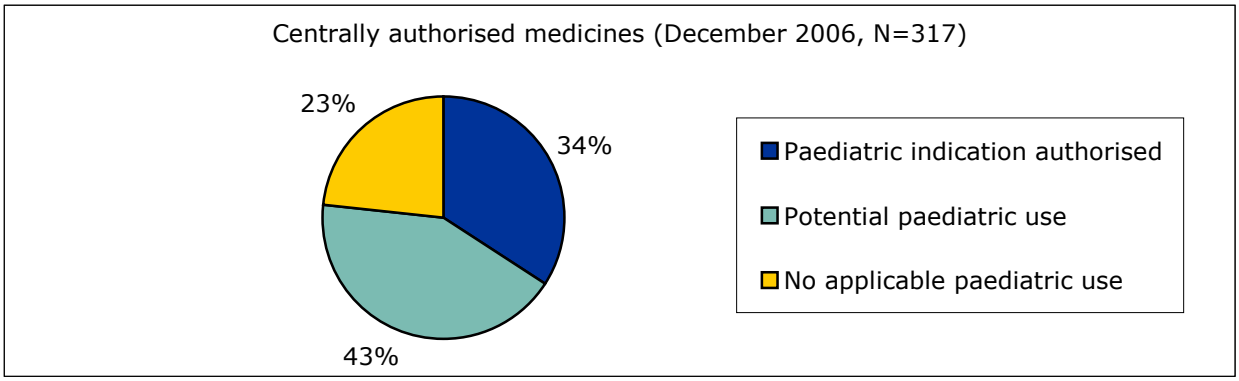
The report is limited by the variable quality of data; this is explained for each indicator.

3. Historical situation for medicines for children up until 2006 - achievements by end of 2011

At the time the Paediatric Regulation came into force (26 January 2007) in the European Union (EU), 50% or more of medicines used in children had never been studied in this population (Conroy et al. 2000), and not necessarily in the same indication or even the same disease in adults (for more details see document EMEA/17967/04 Rev 1 on EMA website).

By the end of 2006, paediatric clinical research was addressed by the guideline ICH E11, which came into force in 2002 following a previous EU guideline (1995). With respect to minors involved in research, the EU Clinical Trial Directive 2001/20/EC was adopted in 2001, transposed in 2004 and covered the research oversight and protection of clinical trials participants. A small number of EMA scientific guidelines (e.g., Addendum on Paediatric Oncology [CPMP/EWP/569/02] and Medicinal products in the treatment of Asthma [CPMP/EWP/2922/01]) explicitly called for paediatric medicines development.

Figure 2: Situation by December 2006: Proportion of medicines among the 317 centrally authorised medicines, for which a potential paediatric indication was identified, already authorised or not applicable in relation to the indication authorised for adults.



Source: EMA analysis of SmPCs in the authorised conditions.

Historically, few paediatric clinical trials which supported medicines development were submitted to regulatory authorities. Some paediatric therapeutic areas and subsets such as neonates were particularly neglected and paediatric clinical research infrequently contributed to medicines development. The lack of paediatric data resulting from the lack of trials on the use of medicines in children is the classical reason cited for the predominance of off-label use in children (e.g., Choonara 2000). There was also a lack of commercial interest into paediatric medicine development due to the length and perceived difficulty of studies, the small fragmented market and the ability to prescribe off-label adult medicines to children.

There was also a consequential lack of age-appropriate formulations. Paediatric health care professionals had to use at best magistral formulas and extemporaneous preparations, which have risks of their own, such as dosing inaccuracy or errors, excipient toxicity, and modified bioavailability and resulted in a higher frequency and seriousness of adverse reactions.

The information on medicines, in particular the Summary of product characteristics, did not systematically identify information relating to special populations such as children. For example, it was often not clear for paediatric health care professionals, whether a paediatric use was authorised, whether there were insufficient data or existing data showed negative effects of the medicine when used in children; often existing information was not even included (e.g., Boos 2003).

The Paediatric Regulation was necessary to make systematic evaluations of the potential paediatric use of medicines by a scientific expert committee, the Paediatric Committee (PDCO). The Committee was established to agree Paediatric Investigation Plans (PIP), deferrals and waivers. A PIP is a development plan aiming at generating the data necessary for a paediatric indication. A deferral allows postponing the initiation and/or the completion of the measures in the PIP so as not to delay the marketing authorisation in adults and to perform studies in children when it is safe to do so. A waiver of the paediatric development can be granted for all (full waiver) or subsets (partial waiver) of the paediatric population on the basis of the lack of efficacy or safety of the medicine, when the disease or condition only occurs in adults, or when the medicine does not have significant therapeutic benefit over existing therapies.

- Major milestones of the implementation of the Paediatric Regulation (summary)

The Paediatric Committee was established and held its first meeting on 1-2 July 2007. It has met monthly since then. Innovative transparency measures were set up and the outcome of the PDCO scientific evaluations of applications for PIPs and waivers were made public each month.

The European Commission Guideline on content and format of applications (2008/C 243/01) was published in September 2008.

Regulatory procedures and the scientific evaluation were set up at the EMA to implement the legal requirements. All were prepared on time, and the deliverables were released without delay..

For the coordination and prioritisation of assessment of paediatric trials completed before the Paediatric Regulation came into force, the Co-ordination Group for Mutual Recognition and Decentralised Procedures – (CMD(h)) set up work-sharing procedures and published the first outcomes in June 2009 (Article 45). Similar procedures for Article 45 and 46 were set up for CHMP in respect of centrally approved products at the same time.

The European Network for Paediatric Research at the EMA (Enpr-EMA) was set up following the adoption of the strategy in 2008 by the EMA Management Board, launched in 2009 and has met regularly since 2010.

The European Union Clinical Trials database (EudraCT) was modified and made publicly accessible (EU-CTR) in March 2011 for paediatric trials included in a PIP or submitted under Article 46. Interventional clinical trials are accessible as soon as the trial is authorised in a first EU Member State, or has received an unfavourable opinion of an Ethics committee. Paediatric trials included in a PIP but performed completely outside of the EU are also available. Since October 2011, the available results of studies submitted under Article 45 are publicly accessible in a separate database.

The results of the survey of all paediatric uses of medicinal products among all Member States in Europe were published in December 2010 (Article 42) and this is the foundation for the inventory of therapeutic needs (Article 43).

The EU funding of projects investigating off-patent medicinal products commenced in 2007 and funding was available every year since then (except in 2011). The EMA / PDCO have annually revised and published a priority list for studies into off-patent paediatric medicinal products to support the research proposals and their evaluation by the European Commission.

4. Better and safer research with children

This chapter reports on the activities and achievements linked to the Paediatric Regulation in terms of its first objective, which is, attaining and conducting better and safer research and development of medicinal products in children. The chapter covers indicators related to the frequency and extent of research and development as well as related to scientific quality and participant safety. Clinical research with children is necessary to develop and make safe and efficacious medicines available for that population.

4.1. Impact of the Paediatric Committee on paediatric development

A multidimensional programme is necessary for the development of better medicines for children, incorporating paediatric therapeutics into the overall development programme, where relevant. The number of PIP submissions and agreed opinions by the PDCO reflect the fulfilment of the legal requirements of the Regulation by the MAHs, i.e., to provide either the results of studies in compliance with an agreed PIP, or their deferral, or a waiver for such studies when filing for marketing authorisation or for certain authorisation variations/line extensions (Article 7 or 8 of the Paediatric Regulation).

EMA Decisions agreeing a PIP (476) represented 70% and EMA Decisions agreeing a full waiver (206) represented 30% of all 682 EMA Decisions by the end of 2011. This does not include modifications of agreed PIPs and negative opinions. At the time of PIP agreement, 356 (75%) of these EMA Decisions were for medicines that were not yet authorised in the EU (Article 7).

It should be noted that the time span between agreeing a PIP and granting a paediatric indication may be several years, taking into account the normal length of medicines development in adults, and considering the time needed for a parallel or deferred paediatric development. The progress of agreed PIPs is addressed in a later section (5.5.).

Whereas Figure 2 shows that only approximately 30% of medicines applied for and obtained a (single subset) paediatric indication before the Paediatric Regulation came into force, the present situation is the reverse, with approximately 70% of all PIPs evaluated by the PDCO proposing or being required to develop indications for the whole or some subsets of the paediatric population.

Table 1 shows the frequency with which paediatric therapeutic areas are addressed by agreed PIPs. Relatively few PIPs were submitted exclusively for the therapeutic area of neonatology, although this subpopulation is known to have the highest need for medicines development. In fact, the neonate is covered under each therapeutic area and about one in four agreed PIPs include specifically the neonatal subpopulation. This is reported in more detail in the following section.

Limitations: In addition to Table 1, Annex I section 15.1. presents the number of EMA Decisions by year and therapeutic area; in both tables, please note that a single PIP may address more than one therapeutic area and, consequently the sum across therapeutic areas may exceed the total number of EMA Decisions.

The relative frequencies of therapeutic areas cannot readily be compared with unmet paediatric therapeutic needs and priorities for medicines for paediatric use. Although the relative frequencies indicate that a reassuringly broad range of paediatric uses is addressed, the prominence of the areas endocrinology-gynaecology-fertility-metabolism and cardiovascular diseases may well be related to the prominence of medicines for such diseases developed in adults.

Table 1: Therapeutic areas addressed by the Paediatric Investigation Plans (PIPs) agreed by the PDCO (a PIP may be for more than one therapeutic area).

Therapeutic areas	Proportion of PIPs (%)
Endocrinology-Gynaecology-Fertility-Metabolism	11
Infectious Diseases	11
Oncology	11
Immunology-Rheumatology-Transplantation	9
Cardiovascular Diseases	8
Haematology-Haemostaseology	8
Vaccines	7
Dermatology	6
Neurology	5
Gastroenterology-Hepatology	5
Pneumology - Allergology*	4
Other	4
Oto-rhino-laryngology	3
Pain, Anaesthesiology	3
Uro-nephrology	3
Psychiatry	2
Neonatology** - Paediatric Intensive Care	2
Other	3

Source: EMA Paediatric database. * Excluding allergen products. ** Applications that exclusively address a use in neonates.

Future directions: The impact of the application of requirements of the Paediatric Regulation to medicines developed for adults will need to be further monitored. Section 5.7. offers preliminary reports on the correspondence between agreed PIPs and unmet paediatric needs, exemplified by the survey of all paediatric uses in the EU.

The figures do not predict the proportion of agreed PIPs that eventually progress to completion of the studies and submission of the results, nor whether an authorisation in children can be granted or not. Although attrition rates as high as 50% are cited for phase 3 of medicinal product development, such high rates may not apply to the PIPs agreed so far, because a sizeable proportion of PIP applications were made late in the overall development, or were for already authorised medicines (about 25%).

To understand better the impact of the PDCO on defining the required paediatric development as set out in PDCO opinions agreeing PIPs, the development approaches and characteristics of paediatric trials were compared systematically, analysing the applicants' proposals and the PDCO opinions, as well as the modifications requested by the PDCO during its evaluation to ensure the generation of the necessary data to establish a paediatric indication. Such information informs applicants on PDCO expectations, and allows better focus in the applications. To some extent, the PDCO has performed such analyses, and already published expectations in articles, guidelines and workshops.

4.2. Addressing unmet therapeutic needs: example of neonates

Whenever relevant, neonates should be included in the clinical development of a medicinal product in order to address their unmet therapeutic needs. Neonates present additional challenges compared to older paediatric age subsets, because they are the most vulnerable population, with the highest dependency on others to respect ethical principles, and because of specific disease characteristics affecting the neonatal population.

This section includes and extends previously published data (Olski et al. 2011). More detailed results with respect to the neonates are presented in Annex I section 15.5.

The following summary shows the impact of the PDCO on product development for neonates, where appropriate. There was no trend over time detectable for the main analyses. Full waivers are excluded from the analysis.

Table 2: Comparison of proposals versus PDCO requirements in respect of neonates.

Applications and PDCO opinions	**Number**	**Proportion**
• Applications proposing to study neonates	60	15%
• Applications proposing to waive neonates, but PDCO opinion requiring to study neonates	50	13%
All PDCO opinions requiring to study neonates	110	28%
Total PDCO opinions agreeing a PIP	395**	100%

Source: EMA applications and opinions. ** Excluding allergen products as these are not relevant for neonates.

Overall neonatal paediatric drug development is specifically mentioned in one out of four PIP applications. This may seem to be a low proportion of PIPs involving neonates but this is likely due to the fact that the majority of condition(s) and indication(s) targeted by the PIP do not exist in neonates and this subpopulation is therefore waived. In contrast, the adolescent age group is rarely waived.

In addition, approximately 60% of trials in neonates required in PDCO opinions were conducted to establish pharmacokinetics and tolerability, i.e., efficacy was extrapolated from older paediatric subsets.

Table 3: Number of trials with neonates required in PDCO opinions, by type of trial and whether the PIP application proposed a study or a waiver for neonates (an opinion can have more than one study with neonates).

Number of types of trials with neonates in PDCO opinions	**Application proposed to study neonates**	**Proportion**	**Application proposed to waive neonates***	**Proportion**
• PK (PD) and tolerability trials	34	57%	24	48%
• Non-controlled safety and activity trials	15	25%	9	18%
• Controlled safety and efficacy trials	32	53%	15	30%
Reference: Total number of applications	60	100%	50	100%

Source: EMA applications and opinions. * Additional studies other than clinical trials may have been required for the neonatal subset.

A detailed analysis of PIPs that were agreed by the PDCO between January and October 2008, revealed that the PDCO increased significantly (from 15 to 26 %) the proportion of PIPs that included younger age groups and neonates in comparison to what was proposed in the applications (Olski et al. 2011) and Annex I, Table 19.

This was confirmed in a similar analysis of PIPs agreed between March and December 2011 (Annex I, Table 20), where the increase was from 24% to 32%. Of note, the proportion of studies including neonates was even higher in 2011 compared to 2008.

Limitations: Due to limited resources, it was not possible to review other relevant aspects of the inclusion of neonates in clinical developments, such as the impact of existing data on study design

features, because this would have required reviewing each PIP application with the EMA / PDCO Summary Report.

Future directions: The efforts towards meaningful studies in the youngest paediatric age subset(s) and lessons learned from such studies should be recorded and monitored. A structured electronic documentation of study details in applicants' proposals and agreed PIPs could allow for a more informative analysis of the neonatal subpopulation. The lack of data and unmet needs do extend to premature neonates as well as young infants.

A recent retrospective review of paediatric studies conducted under US paediatric legislation stated: "Pediatric drug studies remain particularly limited in certain areas, including the use of medications with neonates […]. Many drugs commonly used to treat premature and sick neonates are older drugs that have not been adequately evaluated in studies with this vulnerable age group." (Committee on Pediatric Studies Conducted Under the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) & Board on Health Sciences Policy 2012, p 1-7). The issues are therefore shared across regions.

4.3. Scientific Advice on paediatric development

Applicants may request scientific advice (SA) from EMA and/or National competent authorities on pharmaceutical, non-clinical or clinical issues relating to medicines development. The EMA Scientific Advice is free of charge for paediatric questions (Article 26). SA is a well-known successful procedure to answer specific questions at any stage of the research and development. The procedure is open to pharmaceutical companies as well as to academic and other parties. Advice is offered by EU Competent Authorities as well as by the EMA, where subject matter experts from the European regulatory network collaborate in the Scientific Advice Working Party (SAWP) of the Committee for Medicinal Products for Human Use (CHMP). For orphan-designated medicines, the EMA advice is called Protocol Assistance (PA) and can include questions on significant benefit.

The evaluation of proposed PIPs by the PDCO addresses issues of pharmaceutical, non-clinical and clinical development. As applicants can also request advice on such paediatric development issues, a coordination and mutual involvement of PDCO and SAWP at EMA level is fundamental.

Table 4: Scientific Advice and Protocol Assistance (including follow-ups) provided by the EMA SAWP and CHMP, per year.

Year	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**
Total number of advices (Scientific Advice and Protocol Assistance)*	259	277	321	388	400	433
Sum of paediatric-only and mixed (adult and paediatric development questions) advices*	ND	21	32	74	80	57
Paediatric-only or mixed advices that involved a PDCO member(s) as expert(s)**	ND	ND	ND	68	80	67

Source: EMA databases. * Year of advice letter. ** Year of start of procedure. ND = Not documented

As documented in Table 4, PDCO members are systematically involved as experts in SA/PA procedures in which paediatric questions are raised, with few exceptions. Although PDCO members and alternates have contributed to since 2007, this has only been formally documented since 2009. The PDCO provided paediatric expertise most often on clinical development, but also on pharmaceutical development and non-clinical studies.

While the measures and timelines of the PDCO opinion are binding for the applicant, the SA/PA outcome is not, the applicant as well as the CHMP may justify diverging from the advice received or

provided. A further difference is that a PIP has to address all paediatric issues in the pharmaceutical, non-clinical and clinical development, whereas a SA/PA addresses only questions specifically raised by applicants. A more detailed analysis of EMA SA/PA with respect to paediatric medicine research and development is provided in Annex I, section 15.2.

At national level, in 2010 and 2011, overall 9 EU Member States provided 128 scientific advices on paediatric development to approximately 80 pharmaceutical companies (Confidential Annex III). For 2011 a snapshot of the Member States providing support for paediatric development is provided in Annex II, section 6.1. 15.2.

Limitations: There are no figures, at this time, on the impact of paediatric SA/PA on marketing authorisation. The involvement by the PDCO of SAWP Coordinators in the case of a preceding Scientific Advice, and of the CHMP Rapporteurs in the case of a centrally authorised medicine, is systematically sought during the PIP evaluation. However, this is not yet documented.

Future directions: The collaboration of the PDCO and the SAWP on paediatric development questions will be integrated with a joint procedure and this will be monitored.

4.4. Paediatric research incentives

- European Union funding

Article 40 of the Pediatric Regulation contains a provision for community funding for research into off-patent medicinal products. Off-patent medicines are those not covered by a basic patent or supplementary protection certificate in any Member State. The funding may be provided through the EU Framework Programmes for Research and Technological Development, and should cover the development of off-patent medicinal products with a view to the submission of a Paediatric Use Marketing Authorisation (PUMA) so that the medicine is eventually available to children.

In agreement with the DG Research of the European Commission and in order to ensure that funds are directed into research of medicinal products with the highest needs in the paediatric population, the PDCO has adopted a priority list of off-patent products for which studies are required. The list has been updated in advance of each call for proposals (http://bit.ly/xMS4LE).

To date, 15 projects on at least 20 off-patent medicines (active substances) have received EU funding as part of the area HEALTH-(2007-2011)-4.2-1, and 2 investigator-driven clinical trials for off-patent medicines are funded as part of another area, HEALTH.2011.2.3.1-1. The funding amounts to a total of at least €75 million.

Of note, by the end of 2011, 7 of these 17 funded projects have already obtained agreement on a PIP as indicated in section 15.6. None of the PIPs is completed at this time (April 2012).

The full list of projects is provided in Annex I, section 15.6. of this report.

- National funding

According to the survey of Member States covering the years 2007 to 2011, only 5 Member States out of the 7 providing an answer to this question, had specific incentives and support to paediatric medicine development (Annex II, section 6.2). Concerning clinical trial authorisation procedures, only one Member State reported waiving or reducing fees and offering a priority review for paediatric trials. The national paediatric research incentives were described in the EMA annual report 2010 (http://ec.europa.eu/health/files/paediatrics/2011_report_art50l.pdf).

In brief:

Belgium: The Belgian Paediatric Society granted funding to establish the list of paediatric clinical research centres and researchers in Belgium (which is also the basis for the Belgian paediatric network).

Finland: Although not specific to paediatrics, funding can be applied from the Finnish Funding Agency for Technology and Innovation (http://tekes.fi/) or SITRA, the Finnish Innovation Fund (http://sitra.fi/).

France: Public funding of pediatric clinical research is a priority of the Hospital Program (PHRC).

Italy: The Programme on Independent research on drugs funded by the Italian Medicines Agency (AIFA) continues, with 60 completed projects out of 207 overall.

Malta: Although not specific to paediatrics, Research on medicinal products can be funded under the National Research and Innovation Programme set up by the Malta Council for Science and Technology.

Spain: Since 2007 there have been five annual calls for independent clinical research, including two specifically for paediatric clinical investigations. Additionally, the Spanish Clinical Research Network (CAIBER, http://www.caiber.net/) of the Spanish Ministry of Science and Innovation coordinates and finances national and international clinical trials.

United Kingdom: The Government supports the Medicines for Children Research Network (MCRN, http://www.mcrn.org.uk/), which supported, until the end of 2011, 163 industry studies, of which 90% are part of an agreed PIP. Additionally, 148 academic/health service studies of the MCRN were awarded European, UK and other research grants. A fee waiver applies in certain cases to marketing authorisation or variation applications, such as for a new paediatric formulation or paediatric extension of indication. The priority reviews of applications would include paediatric medicines, but is not specific to such medicines. In 2011, two priority reviews for paediatric medicines were approved.

4.5. Clinical trials with the paediatric population

One of the main achievements of the implementation of the Paediatric Regulation is transparency with the public availability of protocol-related information from EudraCT for registered trials, including all trials with the paediatric population since March 2011. This achievement greatly improves transparency and allows all stakeholders to be informed on trials and enrolment. Transparency will aid in preventing unnecessary trials and finding trials of interest, and will allow the checking of figures and analysis of trends. The initiative is ongoing and should result in the online publication of trial results (phase I to IV in the case of paediatric trials) in the next few years.

Clinical trials with medicinal products are authorised by National Competent Authorities, and the upload in EudraCT can occur either before or after authorisation of the trial. The authorisation is required in each Member State hosting a trial site, but the administrative procedures may vary from one Member State to another.

Table 5 shows that, based on EudraCT data, the number of paediatric clinical trials is stable with an average of 350 per year; however, simultaneously, the number of clinical trials in all populations has decreased between 2007 and 2011.

The first 106 paediatric trials that are part of an agreed PIP had been authorised (or at least uploaded into EudraCT) by the end of 2011, and the proportion of such trials as a percentage of all trials is expected to increase in the future.

The impact of the Paediatric Regulation on paediatric trials will become more obvious in EudraCT in the years to come.

For example, 21 paediatric trials had been uploaded into EudraCT but not yet authorised by the end of 2011, and 114 of these were due to start in 2012. By the end of 2011, 430 EudraCT numbers had been obtained (indicating future submissions of clinical trials) for trials that are part of an agreed PIP (http://bit.ly/GRsu8S). Given that information on the relation to a PIP could only be provided from 2010, the number of paediatric trials that are part of a PIP is likely to be underestimated (see Table 5).

Table 5: Paediatric clinical trials by year of authorisation (or, if not available, by year of protocol upload into EudraCT).

	2005	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**
Paediatric trials (number)	253	315	351	341	401	379	360	
Paediatric trials that are part of an agreed PIP* (number)	1	0	1	4	12	22	70	21**
Proportion of paediatric trials that are part of an agreed PIP among paediatric trials*	0%	0%	0%	1%	3%	6%	19%	
Total number of trials (adults and / or children)	3,327	3,951	4,730	4,506	4,411	4,019	3,622	
Proportion of paediatric trials among all trials	7.6%	8.0%	7.4%	7.6%	9.1%	9.4%	9.9%	

Source: EudraCT Data Warehouse using pre-defined query on 3 April 2012 and counting the first authorised trial only, in case of more than one Member State. As National Competent Authorities of Member States upload data into EudraCT irrespective of the study population, the year of authorisation is a better indicator of the initiation than the year of upload.
* This partial information requires sponsors using a Clinical Trial Application form that was available from November 2009 only, for use with version 8 of EudraCT available from 2011.
** Number of paediatric trials uploaded into EudraCT by 3 April 2012 for authorisation in 2012.

EudraCT may also hold paediatric trials (part of an agreed PIP) that were conducted in the years 2005 to 2009 and that were uploaded into EudraCT only later, when the functionality was available. Agreed PIPs may include ongoing paediatric trials and even completed paediatric trials not yet assessed by competent authorities, nor reflected in the SmPC of the medicine concerned.

The participation of children in clinical trials should be limited to the necessary minimum, as children cannot legally give consent and as a vulnerable population, require additional safeguards. However, to be methodologically correct and interpretable, trials should be adequately powered with a sufficient sample size. Based on data from EudraCT, the planned number of study participants is presented in Table 6.

The increase in the number of paediatric study participants per age group was paralleled by the increase in the number of adults including elderly participants. However, the number of paediatric study participants is highly variable across trials and years (Table 6). A small number of very large vaccine trials in Nordic countries resulted in large increases in the number of newborns, infants and toddlers in some years; Table 6 provides figures excluding those trials but the number of paediatric participants may not have been specified in all clinical trials uploaded to EudraCT.

The main design features of the paediatric trials are presented in Annex I, section 15.4. No change over time was identified in respect of the distribution of clinical development phases, or the types of control in paediatric trials (i.e., no control, placebo or active control).

In many PIPs the PDCO has implemented strategies to extrapolate efficacy from adults to children, reflecting the need to limit the exposure of children in paediatric trials (see section 4.7.).

Table 6: Number of children to be enrolled in clinical trials. In order to exclude large vaccine trials, those for medicines categorised as "immunological medicines" were not included in this analysis.

Number of subjects	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**
Preterm newborns	0	0	0	207	36	2,290
Newborns	0	0	0	64	42	1,051
Infants and toddlers	330	0	15	54	184	2,465
Children	1,910	150	1178	940	1,248	9,345
Adolescents	136	85	1,129	1,543	1,600	8,369
Sum of above	**2,190**	**235***	**2,322**	**1,592**	**2,881**	**22,563**
Reference: number of paediatric trials	254	285	305	332	321	272

Source: EudraCT Data Warehouse using pre-defined query on 3 April 2012, modified by excluding studies for "immunological medicinal products" (http://bit.ly/GQKmLB) * See explanation in text

Limitations: The number of clinical trials conducted in the paediatric population following PIP agreement is difficult to estimate because the EudraCT database is not used for tracking purposes and there are no tracking tools in place. The completeness and quality of data in EudraCT for the purpose of the analysis of trial details and design features is not fully reliable, in part because the provision of information is not mandatory.

The timely execution of trials from agreed PIPs is expected to be reported in PIP annual reports for authorised medicines when there is a deferral, but a proportion of developments of new medicinal products may be discontinued and hence some paediatric trials are never initiated.

To date, the expected correlation between the increasing numbers of agreed PIPs and the numbers of ongoing paediatric trials has not been seen; the relationship to deferred initiations of paediatric studies is unknown. The only general principle is that the development in children follows that in adults.

Future directions: Reporting should ensure a closer follow-up of the execution of agreed PIPs and provide hard data to enable reliable statements to be made rather than assumptions. Study features specific to paediatric trials (Saint Raymond et al. 2010) should be documented for trials in PDCO opinions, and linked to EudraCT details.

4.6. Temporarily halted and prematurely terminated paediatric trials

While it is recognised that clinical research with children is necessary to obtain safe and efficacious medicines for this population, paediatric trials require a controlled and safe environment, in which any evolving risks and signals of lack of efficacy are monitored.

Table 7 shows no increases in the number of safety or efficacy concerns identified as reasons for the discontinuation of paediatric trials. These data are reassuring with respect to the ethical requirements of the Paediatric Regulation, as safety is a major concern in children.

Table 7: Paediatric trials that were prematurely terminated or temporarily halted

Number of trials	2004	2005	2006	2007	2008	2009	2010	2011
Any reason	2	10	15	18	27	18	22	1
P. Reason IMP Quality	0	0	0	0	0	0	0	0
• P. Reason Lack Of Efficacy	0	1	1	0	3	3	2	0
• P. Reason Not Commence	0	5	3	6	9	4	6	0
• P. Reason Safety	1	0	1	2	1	2	0	0
• P. Reason Other	2	10	15	17	24	13	12	1

Source: EudraCT Data Warehouse using pre-defined query.

The analysis is based on data from EudraCT, which are considered reliable in this case, because the Member States are using EudraCT and its messaging system to communicate rapidly on decisions to temporarily halt or to prematurely terminate a trial. The messages include reasons for the decisions, in addition to the categories presented in Table 7, and are automatically exchanged between all Competent authorities in the EU.

There is public access to trials with the paediatric population, including those that are temporarily halted or prematurely terminated, via the EU Clinical Trials Register (EU-CTR, https://www.clinicaltrialsregister.eu/). In addition to checks by public users, the website of the EU Clinical Trials Register permits subscription to an automatic notification system so that interested parties can receive information related to safety and the safeguarding of children, as soon as this information is made public.[1]

Future directions: The data under "P. Reasons Other" need to be further analysed, but this would require trial-by-trial analysis.

4.7. Protecting children from unnecessary trials

- Extrapolation of efficacy approaches

The international guideline ICH E11 (CPMP/ICH/2711/99) and EU Ethical considerations (2008) recommend that clinical trials with the paediatric population are designed in such a way that only the minimum necessary number of children (for the purpose of efficacy at least) are exposed to an investigational medicinal product in a clinical trial.

Whenever extrapolation of efficacy is a possible and valid scientific approach, it should be used to avoid exposing children to invasive, or potentially unsafe investigations and procedures in a clinical trial. ICH E11 provides few details on approaches to extrapolation. Since 2009 the EMA PDCO has analysed, the proposed PIPs and the submitted scientific data systematically to explore the circumstances in which extrapolation can be used.

Moreover, members of the PDCO, the Scientific Advice Working Party and the CHMP are collaborating to draft a paper which develops the concepts underpinning this approach. Preliminary findings and perspectives have already been published (Manolis et al. 2011).

Extrapolation is often supported by modelling and simulation methods. All PDCO opinions given on PIPs up to January 2010 were reviewed (N=210) for such methods. Of these, 47 opinions (22%) included reference to the use of modelling and simulation, which indicates a shift in regulatory thinking towards optimising development before studies are conducted. Modelling and simulation were discussed in an even higher proportion of the summary reports on evaluation of the PIPs.

Limitations: The use of extrapolation of efficacy should be validated based on increasing knowledge and experience. As noted in a recent publication from the US FDA, the development approaches for 13 out of 67 targeted paediatric indications were changed on this basis. In 3 indications, extrapolation was accepted instead of requiring controlled trials (Dunne et al. 2011).

Future directions: The data presented can be used as a baseline and further use of approaches for extrapolation of efficacy should be developed and tracked with a view to minimising the participation of children in clinical trials.

[1] For example, using an internet browser as a client monitoring a user's personalised RSS information feed.

4.8. Innovation in studies of paediatric medicines

In addition to PIPs for new medicinal products, the PDCO should address unmet paediatric needs in areas where there has been no, or only very limited, paediatric research. The collection of case examples provides a qualitative indicator of the introduction of some innovative elements into paediatric research and development by the PDCO.

Inclusion of children of younger ages was required in the clinical development to reflect the specificity of the disease in these subsets:

- This was the case in particular for cholesterol-lowering and anti-hypertensive medicines: hypertension is more frequent as secondary form (whereas it is essential hypertension in adults), is more difficult to treat and thus needs to be studied in younger children.
- Juvenile idiopathic arthritis (JIA) and other auto-immune diseases: the PDCO required studies in younger patients, lowering the minimum age from 6 to 2 years.
- Diabetes mellitus: Anticipating the public health issue of the increasing frequency of type II diabetes mellitus in children, the PDCO required development of oral anti-diabetes medicinal products in the paediatric population from the age of 10 years, when no paediatric data had been requested before.

Reducing off-label use due to lack of data:

- Haemophilia A and B: The PDCO required initiating trials with previously untreated children before the marketing authorisation to reduce prevalent off-label use in this population.
- The PDCO required studies in diseases, or stages of diseases, which so far were never included but corresponded to great paediatric needs, such as persistent pulmonary hypertension of the newborn.

4.9. Optimising animal studies for safer paediatric research and use

Existing data should inform paediatric research and development. However, safety data in adults cannot fully predict adverse reactions and events in children, as they may be different in type, seriousness and severity, and specific effects on growth and maturation cannot be detected. Juvenile animal studies may be justified based on other pharmacology and toxicology data, to provide information before trials in children are initiated. In 2008 the PDCO established a Non-clinical Working Group (NcWG) with specialised non-clinical expertise including assessors from national competent authorities with a view to a facilitating a systematic approach to PIP evaluation and in keeping with the 3Rs principles ("refine, reduce, replace").

The pre-clinical strategies outlined in all 88 PDCO Opinions adopted between March 2011 and December 2011 were compared to that of the respective applications. Juvenile animal studies were proposed or had been completed in 24% of the applications for PIPs (30 juvenile studies in 17 applications). In PDCO opinions, juvenile animal studies were required in 31% of the cases (37 juvenile studies in 22 opinions). In some cases, the PDCO agreed to more than one juvenile animal study (when for example one informs the pharmacology and the other informs the toxicology). An earlier review of 97 PIPs discussed by the NcWG between November 2008 and May 2010 had shown that in about 14% of the PIPs, the NcWG requested either justifications for, or amendments of the juvenile animal studies proposed by the applicants (Carleer & Karres 2011). The review also showed that the number of juvenile animal studies required in the 97 PDCO opinions was greater than the number of juvenile studies initially proposed by applicants, but this was justified by an extension of the use required to include in neonates and infants.

A detailed report on the activities of the NcWG is provided in Annex I, section 22.

4.10. European Network for Paediatric Research at the EMA (Enpr-EMA)

Preparations for the European Network for Paediatric Research at the EMA (Enpr-EMA) began in January 2008 following the adoption of the strategy by the EMA Management Board (Article 44 of the Paediatric Regulation). However, it was not established until 2009, having been delayed due to a lack of resources. The scope and extent of activities of the network will depend on availability of resources at the level of both the EMA and the member networks.

Enpr-EMA is a unique European network of national and European networks, investigators and centres with specific expertise in the design and conduct of studies in the paediatric population. Enpr-EMA is the first transversal network for paediatric research and the first network to be built and operated on research quality criteria. Without the legal basis for Enpr-EMA, no such network would have been founded.

Taking account of the unique responsibility, the EMA strategy sets out a network that is managed mainly by existing networks, and supported by the Agency. The research quality criteria were therefore agreed by the networks themselves, following a documented process. The quality criteria are self-reported, as the EMA does not have the remit to provide accreditation. The information provided by the networks is publicly available (http://bit.ly/yvhMmc) for transparency purpose. To date, 34 networks have submitted self-assessments and are classified in one of the 3 categories of membership in Enpr-EMA.

The quality criteria are aimed at capturing research quality, and encompass research experience and ability, network organisation and processes, scientific competencies and abilities to provide expert advice, quality management, training and educational capacities as well as public involvement. For recognition as an Enpr-EMA member network (category 1), minimum requirements are: at least one ongoing or completed paediatric trial, evidence for organisation and processes, specific access to established expert groups, capacity to respond to external scientific queries, documentation of adherence to GCP and ethical guidelines, evidence of trial monitoring capacities and quality management, examples of involvement with regulatory authorities, training programmes, as well as involvement of patients, parents or their organisations in the design of protocols, information documents and prioritisation of trials with children.

18 networks currently fulfil all the minimum criteria (category 1); 20 networks do not yet fulfil or document all minimum criteria (categories 2 and 3, respectively, see Table 28). The development of new emerging networks is recognised and supported, and their inclusion in Enpr-EMA activities is intended to help deliver high-quality paediatric clinical research.

The number of networks in the Enpr-EMA is about half of the networks identified in an inventory made in 2009. Enpr-EMA does not yet cover all paediatric therapeutic areas. Therefore, one of the most important activities of the Enpr-EMA is to stimulate and foster new European networks where they did not exist previously, such as in paediatric cardiology, gastroenterology, and diabetes, and helping create a larger network for example in neonatology. The activities are performed in collaboration with the relevant learned societies, and existing networks serve as models and mentors.

In March 2011, Enpr-EMA was presented to all stakeholders including academia, regulators and pharmaceutical companies. Enpr-EMA has a scientific Committee, which is the PDCO, and a Co-ordination group composed of 20 members including 2 PDCO members. The EMA co-chairs the network. Enpr-EMA works at an international level with the World Health Organization (WHO) through the EMA's membership of the Paediatric Medicines Regulators' Network (PmRN) and with the United States' Food and Drug Administration (FDA) through the EMA's existing interaction on paediatric therapeutics.

A full report on the activities and the perspectives of the Enpr-EMA is provided (Annex I, section 18.).

4.11. Guidelines and workshops for paediatric medicine development

Since the beginning of the implementation of the Paediatric Regulation in 2007, the PDCO has contributed paediatric expertise to EMA scientific guidelines. Up to the end of 2011, a total of 14 guidelines have been published that include contributions of the PDCO. Twenty two further guidelines are being drafted with PDCO contributions. The list of guidelines is in Annex I, section 15.3.

The EMA / PDCO have also organised 14 expert workshops which targeted specific questions on the development of medicines for children. The outcomes of the workshops are published, and where appropriate, are included in EMA scientific guidelines. See list in Annex I, section 17.1.

4.12. Synergies of the Paediatric and the Orphan medicines Regulation

The following observations can be made from a preliminary review of the experience with the Paediatric Regulation together with the experience on the Orphan medicines Regulation:

- The number of designations of orphan medicines for the treatment of conditions that affect exclusively children, or both adults and children, has increased over recent years to about 60 per year (Annex I, section 16.1.).
- For 17 medicines, pharmaceutical companies have requested orphan designation making explicit reference to the intention to address unmet paediatric therapeutic needs with that medicine, particularly by adapting the pharmaceutical form to the needs of paediatric age groups. For two authorised medicines (Peyona and Mercaptopurine Nova Laboratories), marketing authorisation was obtained as orphan medicinal products for orphan conditions and pharmaceutical forms that address specific needs of the paediatric population. However, no orphan-designated medicine has yet obtained the orphan incentive of two additional years of market exclusivity after completing paediatric studies in compliance with an agreed PIP (Article 37 of the Paediatric Regulation).
- A significant number of orphan designations (about 30%) are for conditions affecting children exclusively; and in some of these, no alternative treatments exist.

Other recent reports on the impact of orphan medicine designations for paediatric medicines availability (Thorat et al. 2012) support this analysis.

At the time of PIP evaluation and creation of the Summary report, the EMA and the PDCO systematically mention whether orphan designation may be applicable for this medicine and the proposed condition, with a view to highlighting opportunities for applicants. The PDCO and the Committee for Orphan Medicinal Products (COMP) interact on an ad-hoc basis to address any potential issues between the orphan-designated condition and the paediatric development.

4.13. Timely planning and conduct of paediatric development

To ensure that the development of medicines for children is appropriate and to avoid any delays in marketing authorisation for adults, the Paediatric Regulation calls for early dialogue with pharmaceutical companies (Recital 10) and requires applications for PIPs to be submitted after the completion of pharmacokinetic (PK) studies in adults (Article 16), considered to be an equivalent of end of phase 1 in adults.

From 2007 to 2009, because the Regulation came into force when most developments were already beyond this stage, most applications were submitted later than the required deadline. Since 2010, the compliance with this requirement is monitored by the EMA, by measuring the time lag between the submission date (first PIP or Waiver) and the declared date of completion of PK studies in adults.

This indicator was reported for the first time in the 2010 Annual report, and included the names of marketing authorisation holders that submitted applications more than 6 months after the date. In some cases, the PIP was submitted when the paediatric studies were completed, putting the PDCO in a difficult situation of finding insufficient studies or trials and being unable to request further data to avoid exposing children to repetitive trials.

The timing had still not improved by the end of 2011 (Table 8). The EMA / PDCO have regularly addressed the issue of timing of submissions in meetings with pharmaceutical industry. The reasons given for late submissions are that preparing PIPs for a number of products for which development will be discontinued would be a waste of resources and that there would be still many unknowns at this stage, possibly leading to multiple modifications of agreed PIPs.

On the other hand, the benefits of early dialogue are a better integration of paediatric needs already in adult development for formulations and pharmaceutical forms, toxicology (reproduction toxicity), animal models and juvenile animal data, modelling and simulation for PK and pharmacodynamic studies. This also avoids delays at the time of submission of the application for adults, if the PIP or waiver has not been agreed on time.

Table 8: Time lag between completion of PK studies and submission of applications for PIP and waiver.

Delayed applications (submissions 6 months or more later than deadline)	**Jan-Jun 2010**	**Jul-Dec 2010**	**Jan-Jun 2011**	**Jul-Dec 2011**
Number of delayed PIP applications Reference: number of all PIP applications	24 47	28 39	21 31	23 43
Time lag in months, median (range)	26 (7-161)	35 (7-121)	20 (9-241)	30 (11-99)
Number of delayed applications for full waiver Reference: number of all applications for full waiver	10 26	11 19	12 22	8 9
Time lag in months for delayed full waiver applications, median (range)	24 (12-71)	19 (8-92)	23 (9-137)	46 (19-134)

Source: EMA Paediatric database.

5. More medicines available for children in the EU

The second major objective of the Paediatric Regulation is to ensure that increasingly more medicines will be available for children in the European Union. Due to the duration of medicine development and of authorisation procedures, the data on this element were gathered over the comparatively short period of time since the Paediatric Regulation came into force. This chapter presents data on new medicines, new indications and new formulations/forms for children. The next chapter covers more information on medicines used in children and changes to the Product Information.

5.1. New medicines (new active substances), new indications and new pharmaceutical forms for use in children

The medicines are presented by type of authorisation procedures. The mandatory scope for centrally authorised products includes, among others, medicines to treat the acquired immune deficiency syndrome, cancer, neurodegenerative disorders, diabetes mellitus, auto-immune diseases and other immune dysfunctions and viral diseases. For variations, the outcome data presented in Table 9 and Table 11 have been summarised across regulatory procedures types. All the analyses and tables exclude generic, biosimilar, hybrid, homeopathic, traditional herbal, and well-established medicinal products or duplicate marketing authorisations.

From 1995 to 2006, 108 of all 317 centrally authorised medicines had a paediatric indication (cumulative, 34%). Since the entry into force of the Paediatric Regulation, 31 new medicines were centrally authorised for paediatric use out of 152 (20%) (Table 9), of which 10 met the conditions of Article 7 of the Paediatric Regulation. Of note, 63% of new medicines intended for both adults and children have a deferral in the agreed PIP. An increasing number of these new approved medicines, 10 so far, have fulfilled some of the requirements set out in the agreed PIP Decisions. However, only 3 of these 10 medicines have completed the PIP. For the remaining medicines, paediatric studies in the PIP are ongoing and should enable later adding to or extending the paediatric indication, and/or authorising a new pharmaceutical form or new route of administration, or modifying the paediatric information. The number of new medicines authorised per year, whether for adults or children, over the same period has decreased (from 2007 to 2011).

In addition, with respect to variations of already authorised medicines, 72 new paediatric indications were authorised, including 29 indications related to Article 8 of the Paediatric Regulation. For 7 already authorised medicines, the new paediatric indication represents the outcome of the assessment of studies submitted under Article 45 (see Table 10).

For authorised medicines, 26 new pharmaceutical forms were authorised for paediatric use, including 15 centrally authorised medicines, and 9 were linked to the requirements of the Paediatric Regulation.

Limitations: The outcome of the procedures (as in Table 9) may be significantly delayed compared to the submission date so the outcomes of recent submissions cannot be included in this analysis.

A full SmPC review to retrieve variations in which non-clinical data had been added was not practically possible. All SmPCs were reviewed for new authorised routes of administration suitable for paediatric use: this was limited to one newly authorised pharmaceutical form.

Table 9: Overview of paediatric medicine changes (by year of authorisation, or variation).

	2007	2008	2009	2010	2011	Sum
Initial marketing authorisation (new active substance) with a paediatric indication:						
• Centralised procedure, linked to requirements of the Paediatric Regulation	NA	0	2	2	6	**10**
• Centralised procedure, not linked to requirements of the Paediatric Regulation	10	6	5	0	0	**21**
Reference: all new centrally authorised medicines (with or without a paediatric indication)	39	25	41	17	30	**152**
• National (DCP, MRP) procedure	0	0	2	0	1	**3**
Newly authorised paediatric indications for already authorised medicine:						
• Centralised procedure, linked to requirements of the Paediatric Regulation	NA	NA	2	1	15	**18**
• Centralised procedure, not linked to requirements of the Paediatric Regulation	7	6	6	2	0	**21**
Reference: Centralised procedure, all extensions of indication	17	28	31	21	31	**128**
• National (DCP, MRP) procedure linked to requirements of the Paediatric Regulation	NA	1[+]	3	5	3	**12**
• National (DCP, MRP) procedure not linked to requirements of the Paediatric Regulation	5	3	8	2	3	**21**
Total Paediatric indications EU	**22**	**16**	**28**	**12**	**27**	**105**
Newly authorised pharmaceutical forms for paediatric use for already authorised medicine:						
• Centralised procedure (line extensions) linked to requirements of the Paediatric Regulation	NA	NA	0	0	3	**3**
• Centralised procedure (line extensions) not linked to requirements of Paediatric Regulation	3	1	2	2	4	**12**
Reference: Centralised procedure, all line extensions	21	15	28	23	21	**109**
• National (MRP, DCP) procedure linked to requirements of the Paediatric Regulation	NA	NA	2	3	1	**6**
• National (MRP, DCP) procedure not linked to requirements of the Paediatric Regulation	1	1	2	0	1	**5**

Sources: Questionnaires to Member States 2009, 2010 and 2011 for national procedures (see Annex II); EMA SIAMED database and Paediatric database; SmPCs of centrally authorised products.
DCP = Decentral procedure, MRP = Mutual recognition procedure
[+] Agreed PIP available for this medicine
NA = Not applicable as requirements of Article 7 and 8 of the Paediatric Regulation were not in force.

Future directions: Collecting the necessary data requires significant resources from the Member States and the EMA; a better use of databases is desirable.

Details are provided in Annex II section 4.1 on newly authorised medicines authorised, in sections 4.2 and 7.2 on new paediatric indications and in sections 4.3 and 7.3 on new pharmaceutical forms for paediatric use.

5.2. Article 29 (Paediatric Regulation) referral procedures

For a co-ordinated and harmonised authorisation of a new paediatric use across Member States, a procedure based on Article 29 of the Paediatric Regulation may be triggered by a marketing authorisation holder when applying for a new indication, new pharmaceutical form or new route of administration for a medicinal product authorised under Directive 2001/83/EC.

The application is assessed by the EMA CHMP, resulting in an opinion followed by a European Commission Decision, with a short timeframe of implementation at national level.

From 2007 to 2010, 8 procedures under Article 29 were completed for 5 active substances: anastrozole, irbesartan, valsartan, atorvastatin and latanoprost. No procedures took place in 2011. Positive opinions on new paediatric indications and new pharmaceutical forms were obtained for all but anastrozole. The future use of this procedure should be monitored.

Details and listings are included in section 5 in Annex II.

5.3. Paediatric Use Marketing Authorisation (PUMA)

The PUMA was established by Article 30 of the Paediatric Regulation. It is an incentive for off-patent medicinal products developed for paediatric use, which offers 10 years of data and marketing protection (8 years of data exclusivity and 2 years of market protection).

In 2011, the first application for a PUMA was submitted to the EMA and authorised through the centralised procedure. The marketing authorisation was granted on 5 September 2011 to Buccolam (midazolam, oromucosal use).

Overall, 40 applications for a PIP have been submitted with a view to submitting a PUMA, as indicated in the PIP application form. In particular, as reported above, an agreed PIP is available for 7 out of the 15 projects adapting off-patent medicines (including 20 active substances) that have received EU funding.

Limitations: The number of future PUMAs cannot be anticipated from what is indicated in PIP applications, because any agreed PIP could be used to apply for a PUMA when the medicine's patent has expired.

Future directions: Although the Paediatric Regulation has led to increased research and development for paediatric medicines, the legal tools to improve the information on and the development of the off-patent medicinal products that are still widely used in the paediatric population, may be too weak to meet this need.

For this group of medicinal products, the incentives such as data exclusivity do not seem to work in many EU Member States, and may not be effective in protecting paediatric formulations or forms.

This may also be linked to reimbursement rules which may not recognise the paediatric marketing use authorisation (PUMA) and may attach little value to old medicines even if they include a new age appropriate formulation/form.

Still, considering the number and scope of therapeutic areas of off-patent medicines projects, the Paediatric Regulation has been successful in stimulating activity and interest in development of older medicinal products for paediatric use.

5.4. Improving the pharmaceutical quality of paediatric medicines

Improving pharmaceutical forms and formulations intended for children is part of the objective of making more medicines available to children. During the evaluation of PIPs, the formulation(s) and pharmaceutical form(s) proposed for paediatric use are systematically reviewed by the PDCO's Formulation Working Group (FWG), a PDCO group created to help the Committee on this aspect. As of December 2011, the group included 13 experts from the EMA PDCO, the Quality Working Party, assessors from EU national regulatory authorities, and experts from hospital and academia.

The three major topics discussed by the PDCO FWG are:

- Safety of excipients for the paediatric population: Applications included insufficient justification of the chosen excipients related to age, daily dose of excipient(s) and insufficient discussion on the possibility to replace excipients with potential safety concern. Potential excipient safety issues are discussed through collaboration with the PDCO NcWG and the Safety Working Party. In an analysis of 84 proposed PIPs that was carried out in 2009, issues with excipients were identified in 102 (82%) out of 125 pharmaceutical forms proposed for children.
- Appropriateness of the pharmaceutical form or formulation: To ensure formulations are suitable for children, or appropriately adapted to the relevant age groups, the PDCO requested sufficient testing of palatability and acceptability of the formulation proposed in children. This was an issue in 50% of the proposed pharmaceutical forms (source as above, 2009).
- Dosing flexibility, accuracy and practical handling: The PDCO focuses on practical aspects of administration, the potential to support correct/accurate dosing with required dosing flexibility, and decreased risks of dosing errors, inappropriate manipulation of adult dosage forms and presentations. This issue concerned 23% of the proposed pharmaceutical forms (source as above, 2009).

The priority of the group is on the youngest age group, i.e. neonates.

The majority of issues discussed by the FWG related to excipients, where there is a need for non-clinical and clinical data to support safe paediatric use, as data have so far been generated for adult use only.

Other frequent issues related to the lack of information on aspects of the pharmaceutical form(s) and of the formulation(s). As a consequence, the EMA standardised the information requested to capture quality information in the electronic application form (http://bit.ly/A6wg0j).

The FWG provides valuable support to the PDCO in the review of the quality and contributes to the quality aspects of the PDCO requests for modification and opinions. In addition, the FWG raises awareness of paediatric formulations issues among applicants, the EU regulatory network and the scientific community. The FWG and the PDCO have contributed to the Guideline on "Pharmaceutical Development of Medicines for Paediatric Use" (EMA/ CHMP/QWP/180157/2011), to provide guidance on the appropriate formulations and forms for use in children and are involved in revision of the EC Guideline on excipients in the label and package leaflet of medicinal products for human use (CPMP/463/00).

A full report of the FWG is in Annex I, section 21.

5.5. Progress towards completion of PIPs

The development of paediatric medicines through the performance of studies and trials in agreed PIPs, is an important indicator of the implementation of the Paediatric Regulation. This indicator is not directly measurable, but can be approached by looking at different sets of data, in particular the analysis of Annual reports for authorised medicines with deferred studies (Article 34(4)), as well as timelines agreed for the first clinical trial in a PIP, and the modifications of agreed PIPs.

- Annual reports on deferred studies in PIPs for authorised medicines

Up to December 2011, the Agency received 91 Annual reports, for 54 centrally or nationally authorised medicines (active substances). The reports should describe the progress of studies in the PIP and any difficulties encountered by the sponsor. For details and template, see http://bit.ly/yo0QNo.

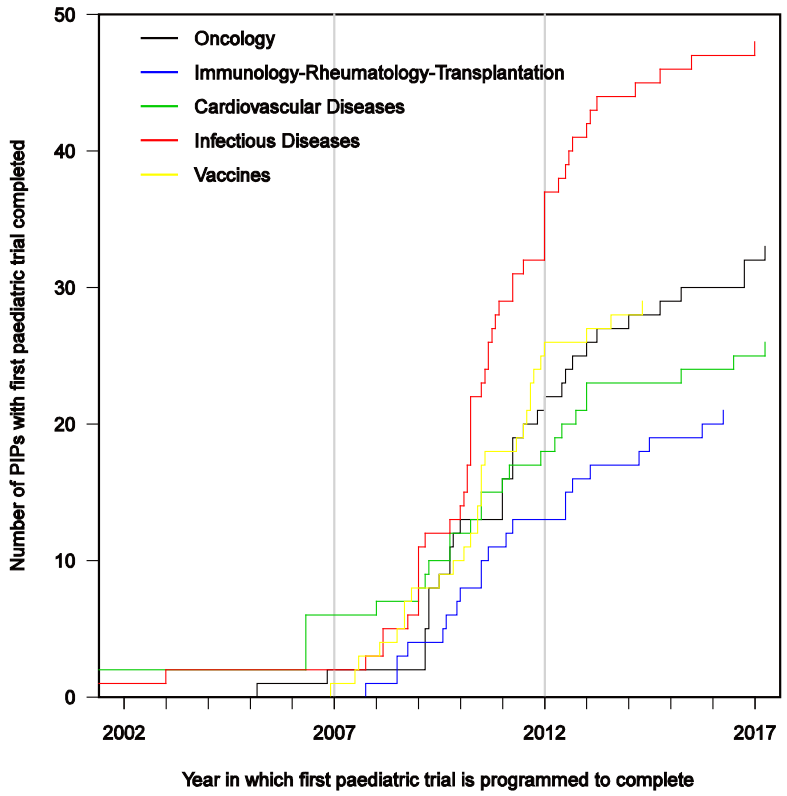
Overall, 58 of the 91 annual reports (64%) stated that the paediatric development was continuing as planned in that reporting year. The most frequent explanations as to why the paediatric development was not continuing as planned, were: difficulties with recruitment (21 annual reports), refusals/problems with Ethics Committees or National Competent Authority(ies) (11), safety (6) or efficacy concerns (3).

During the reporting period (2007-2011), 152 new active substances were centrally authorised for adult and / or paediatric use. For 104 of these active substances, at least one PIP had been agreed and for 50 active substances, the agreed PIP included a deferral. Given that a first Annual report is expected at the latest 18 months after the marketing authorisation, Annual reports were expected for 41 active substances for centrally authorised products, but received for only 30 by December 2011. A reminder of the need to submit Annual reports was sent on 13 April 2012 (http://bit.ly/HWmRWq).

- Planned completion of first trials in PIPs

In addition to the availability of new medicines after authorisation and completion of all studies in an agreed PIP, the participation of children in trials with new medicines can reflect earlier access to new medicines through research, which is desirable in particular for therapeutic areas with high unmet paediatric needs, no or limited therapeutic options, or with broad public health interest. As a possible indicator, it was proposed to monitor the planned end of the first paediatric trial required to be conducted in the agreed PIP. 157 PIPs were analysed, using the EMA Paediatric database.

Figure 3: Planned end of the first trial in agreed PIPs for some therapeutic areas



Source: EMA Paediatric database.

As shown in Figure 3, the first trials in agreed oncology PIPs are planned to complete about at the same rate as those in PIPs for cardiovascular diseases, for vaccines and for immunology-rheumatology-transplantation medicines, even though, due to their design, phase 1 studies in paediatric oncology are expected to take longer than PK / tolerability studies in other areas. In absence of delay, this gives hopes of early access to new medicines in paediatric therapeutic areas with high unmet needs, such as oncology.

- Modifications of agreed PIPs

Once a PIP has been agreed, it can be modified if the applicant encounters such difficulties with its implementation as to render the plan unworkable or no longer appropriate (Article 22). Modifications are expected as part of the normal life cycle with new data generated by the development. A modification can only be initiated by the applicant, but not by the PDCO.

With the increasing number of agreed PIPs, an increasing number of modifications can be expected, in order to take account of new data and of evolving knowledge. PIPs are part of the life cycle of a product.

By the end of 2011, the PDCO had agreed 315 modification opinions, while it had agreed 513 opinions on new PIPs in the same time period. Over the last 3 years (a relatively short period) there was an increase in PDCO modification opinions by about 50 a year. This compares with over 100 newly agreed PIPs per year (excluding the allergen products peak in 2010).

Of all medicinal products with an agreed PIP, less than 30% required a modification so far, but some required several modifications.

An analysis of the scope and reasons for changes was carried out for the first modification ("M01") agreed for any PIP, up to February 2011 (N=100 modification opinions, excluding duplicates). The agreed timelines were changed in 59 opinions, of which 31 (53%) were relatively short delays (i.e., extension of 1 year or less); conversely, 28 opinions agreed significantly longer timelines. Significant timeline extensions were generally not associated with significant changes in study design. Changes to main secondary endpoints, to the dosing, or to the inclusion criteria each occurred in about 9% of the opinions. However, 14% of the opinions had a variety of other changes that seemed of lesser significance for the PIP.

Further analyses will be done to understand if requested modifications of agreed PIPs are scientifically based - as they should be - or if they can be avoided by limiting unnecessary details, for example.

Limitations: Nationally-approved products cannot be fully tracked by the EMA. The analysis of how many studies should have started according to the agreed PIP cannot be performed. The first trial to be completed in a fraction of PIPs was not a paediatric, but an adult bioavailability trial (of the new paediatric pharmaceutical form), and its actual end should be compared to the planned end.

Future directions: The actual conduct of agreed studies should be monitored and become transparent. Links between the information on studies agreed in PIPs and their initiation, conduct, completion, regulatory submission and publication should be available.

As a reflection on the global importance of this indicator and as a matter of comparison, a review of the progress of paediatric studies required under the US PREA legislation showed that up to "78% of drug studies and 54% of studies on biological products (such as vaccines) […] were either not completed or were finished late", compared to their due date in 2007 (Grant 2012, citing Dr Fraterelli).

5.6. Compliance and Statements in Marketing Authorisations

Once a PIP is completed, an applicant may request an opinion from the PDCO under Article 23 of the Paediatric Regulation to verify that all studies have been conducted in compliance with the agreed PIP, including the timelines. Compliance can be checked by Competent Authorities for nationally-approved medicines (the Reference Member State).

A compliance check is necessary at the time of validation of applications for either marketing authorisation (Article 7) or variation/line extensions (Article 8). In order not to delay the validation, an applicant may also request a check of compliance by the PDCO prior to the submission.

By end of 2011, the PDCO had adopted opinions on compliance for 29 agreed PIPs (excluding duplicates). This means that the full paediatric programme was completed for these medicinal products. The number of compliance opinions increased from 3 per year (2008) to 9 (2009), 9 (2010) and 8 per year (2011).

Details of compliance opinions and medicinal products are listed in Annex II, section 1.

Based on the survey of Member States, no Member State had checked compliance of completed PIPs. This may be because the National Competent Authorities had agreed to delegate to the EMA PDCO the check of compliance, or because Marketing Authorisation Holders may prefer to obtain a PDCO Opinion directly.

Following confirmation of compliance during assessment, according to Article 28 (3) of the Paediatric Regulation, a compliance statement is added to the marketing authorisation. This was done for one new medicinal product (a combination of active substances) authorised through a national procedure and for 2 new marketing authorisations of medicinal products authorised centrally. A compliance statement was added to the marketing authorisations for 18 authorised active substances, following a variation/line extension.

The compliance statement is intended for submission to patent offices to obtain the reward of SPC extension. By the end of 2011, National Patent Offices in 16 Member States granted the 6-month extension of SPC to 11 medicines, i.e. a total of 105 national Supplementary Protection Certificates (Article 36(1) of the Paediatric Regulation).

See sections 2 and 3 in Annex II for line listing.

5.7. Addressing paediatric needs and off-label use

Unmet paediatric needs are at the centre of the EU legal and regulatory initiative on paediatric medicines. Information on unmet therapeutic needs in the paediatric population was available from:

1. the EMA's Paediatric Expert Group's "Paediatric needs lists" (http://bit.ly/HZFGG3),
2. the survey of all paediatric uses made in accordance with Article 42 of the Paediatric Regulation (http://bit.ly/HZFGG3),
3. the inventory of therapeutic needs made according to Article 43 and
4. the list of priorities established for the funding of trials with off-patent medicines (http://bit.ly/HZFGG3).

Based on the survey results, including in particular known off-label use, and the list of paediatric needs, the PDCO has worked to establish an updated inventory of paediatric needs.

The PDCO must take account of therapeutic needs when deciding on PIPs. The assessment of whether PIPs (agreed by the PDCO until the end of 2011) did cover unmet needs, found that this was the case

for a substantial proportion of medicines frequently used off-label according to the survey (see section 16.2. in Annex I). Of note, the analysis refers to off-label use before 2008; since then, several new medicines with expected high paediatric use have been authorised for adults, and there is still a risk of off-label use until the PIP is completed and the data are submitted.

Limitations: Member States did not identify any data showing a reduction in off-label use, nor inclusion in SmPC of information (by way of variations) on off-label use for this report. No data were found either for centrally authorised medicines. The PUMA and its incentive has had limited value to reduce off-label uses of older medicines.

Future directions: The priorities and the inventory of therapeutic needs for children (Article 43) should be linked to agreed PIPs and to granted authorisations.

In order to assess the extent of and change in off-label use in children, reporting systems or prescription vs. diagnosis analyses of databases would have to be put in place but will be resource intensive. With the advent of the new pharmacovigilance regulation, it is hoped that data from healthcare settings may be more readily available.

The scope of research and development in agreed PIPs should be measured against a paediatric-weighted representation of therapeutic areas. Eventually, not only the scope of agreed PIPs, but also the change in needs brought about by newly available paediatric medicines should be described and analysed.

6. Increased information on medicines used in children

The third main objective of the Paediatric Regulation is to improve information available on the use of medicinal products in paediatric population. Several provisions address this issue. On the one hand, new paediatric data should support the work of the regulatory authorities in defining and addressing paediatric needs, and on the other hand, additional information should be assessed and made available as recommendations to healthcare professionals and medicines users.

6.1. Assessing available data of existing and new paediatric studies – Recommendations following assessments under Articles 45 and 46

Most data generated in industry-sponsored trials were not accessible to the public or even competent authorities. Articles 45 and 46 of the Paediatric Regulation addressed this gap by requiring that respectively, existing and newly generated paediatric data be submitted to Competent Authorities. Most of the older medicines were nationally authorised and therefore the assessment of data is under the responsibility of the Member States who agreed on a work-sharing procedure. The CMD(h) co-ordinates the work-sharing, and prioritises paediatric therapeutic areas with high unmet therapeutic needs, such as oncology, psychiatry, pulmonology, antibiotics and neonatology.

The CMD(h) and the CHMP have responsibility for assessing paediatric studies submitted under Articles 45 and 46.

Variations following Article 45 or 46 submissions were reported by 13 Member States (Austria, Belgium, Cyprus, Finland, France, Hungary, Italy, Portugal, Romania, Slovenia, Spain, Sweden and United Kingdom) only, but medicines may not be authorised in all 30 Member States (Norway, Liechtenstein and Iceland participate in CMD(h)).

Table 10: Recommended SmPC changes related to Article 45 and 46 submissions (2008 to 12/2011)

Number of	**Article 45 CAP**	**Article 45 DCP, MRP**	**Article 46 CAP**	**Article 46 DCP, MRP**
Active substances with submissions of studies (Article 46) or listings of studies to be submitted (Article 45)	55	994	55	124
Number of concerned medicinal products	61	2175	68	
Study reports	197	≈18,000	105	213
Active substances with completed assessment	60	89	55	27
Recommendations for SmPC changes				
• Paediatric information clarified*	5	34	12	6
• New study data added	NR	9	NR	NR
• Safety information added	5	3	2	1
• New paediatric indication added**	2	7	1	0

Sources: Procedural and work-sharing documentation of the CMD(h), http://www.hma.eu/cmdh.html, using tracking sheet for 31 December 2011. * In sections 4.2, 5.1 or 5.2 of the SmPC. May include that there is insufficient evidence for conclusions on a paediatric use. ** In section 4.1 and / or 4.2 of the SmPC. NR = Not reported separately.

Overall, for both nationally and centrally-approved medicines (Article 45), paediatric data for 205 active substances have been submitted and assessed since 2008, with 73 public assessment reports for nationally authorised medicines and 65 recommendations to update the SmPC (and Package leaflets) with new paediatric information, including 9 with "new" paediatric indications, 39 revisions for

clarity or consistency, 3 for safety and 9 to add study information. However, it should be noted that the conclusions of the assessment by competent authorities were implemented to different extents by Marketing Authorisation Holders. Up to September 2011, 318 studies have been submitted (Article 46) and 25 assessment reports for nationally authorised medicines have been published.

- Recommendations following Article 45 submissions

For centrally-authorised medicinal products, by 2011 the CHMP had completed the assessment of all submitted data, covering 55 active substances in 61 medicinal products. The SmPCs of 12 medicinal products were changed subsequent to the assessment. The publication of all assessment reports / outcomes of the assessment of studies submitted through Article 45 is included in the respective EPAR web pages on the EMA website.

By the end of 2011, for medicinal products authorised through national procedures (MRP, DCP), 73 assessment reports had been made public for 89 active substances after completion by the CMD(h) of the assessment of the submitted studies (http://bit.ly/HeCGCZ). The recommended changes to the SmPCs are in Table 10. For 18 active substances, no change to the SmPC was necessary; these active substances seem to correspond to medicines already authorised for paediatric use.

In October 2011, the first results of the paediatric studies submitted under Article 45 were made publicly accessible in a searchable database on the EMA website (http://art45-paediatric-studies.ema.europa.eu/clinicaltrials/). This is an interim measure to speed up public access, until results of trials can be made publicly available in EudraCT/EU-CTR.

- Recommendations following Article 46 submissions

For data submitted under article 46 for centrally-authorised products, 108 assessment procedures were finalised by 2011, and were managed as follow-up measures (FUM). This may include the same study(ies) submitted for more than one product and for more than one procedure. In 2 of the 108, the data were submitted directly as part of a variation procedure. In total, 55 active substances were involved in 105 studies. The CHMP recommended 15 changes to the product information for 13 active substances, as shown in Table 10.

By the end of 2011, for data submitted under article 46 for nationally-authorised medicinal products, 213 study reports had been submitted resulting in recommendations for SmPC changes as shown in Table 10.

When regulatory action was recommended or necessary (i.e., where amendments to SmPC, labelling and/or PL were identified by the MAH) after an assessment of studies under Article 45 or 46, MAHs were advised to submit a variation containing the paediatric study(ies) within 60 days. In some cases of Article 46, it was agreed that the assessment of the data could be postponed if the MAHs intended to submit a variation procedure within a short period of time.

Details and line listings related to Article 45 and 46 outcomes are in section 8 of Annex II.

6.2. Changes to Product information

Increased information on medicines used in children is provided by adding paediatric information to the Product information (SmPC and / or Package Leaflet). This can be based on paediatric study results resulting in particular from Article 45 or 46 assessment recommendations, or on other information that is relevant for children (e.g., non-clinical study results, findings from pharmacovigilance, or PDCO opinions). Table 11 summarises the paediatric-relevant changes to Product information since the entry into force of the Paediatric Regulation.

Table 11: Increased information on medicines for paediatric use. Figures exclude duplicates.

	2007	2008	2009	2010	2011	Sum
Dosing information for children added to SmPC (section 4.2)						
• Centralised procedure*	14	14	16	15	20	**79**
• National (DCP, MRP) procedure linked to requirements of the Paediatric Regulation	NA	NA	1	2	7	**10**
• National (DCP, MRP) procedure not linked to requirements of the Paediatric Regulation	15	12	13	6	19	**65**
Paediatric study results added to the SmPC (section 5.1)						
• Centralised procedure	11	12	11	23	20	**77**
Paediatric safety information added to the SmPC section 4.8						
• Centralised procedure	8	11	20		28	
Statements on deferral or waiver included or added to SmPC (section 5.1)**						
• Centralised procedure	0	0	2	28	31	**61**
• National (DCP, MRP) procedure	ND	ND	ND	ND	ND	**ND**
Other paediatric information added to other sections of the SmPC (e.g., section 5.2)						
• Centralised procedure	7	13	15	12	19	**66**
PIP data failing to lead to paediatric indication (Annex II, sections 4.7 and 7.7)	NA	0	1	2	2	**5**

Sources: Survey of Member States; EMA databases. DCP = Decentralised procedure. MRP = Mutual recognition procedure. * SmPC guideline wording was updated in further 18 cases. ** Included during either initial marketing authorisation or variation. Counted twice if statement on both deferral and waiver included. ND = No data sufficient for analysis.

Limitations: Data on deferral and waiver statements were provided by only six Member States and in each case, for no more than one year (between 2009 and 2011). Information from the UK on 2 active substances had been included in the 2010 Report to the European Commission (Table 7, p 13); the data indicated that statements on a waiver were included in SmPC for medicines authorised for a paediatric use.

Details and line listings related to variations adding paediatric are in sections 4.2 ff. and 7.2 ff of Annex II for centrally and nationally authorised medicines, respectively.

- Analysis of data from completed PIPs failing to lead to new paediatric indications

By the end of 2011, the completed study results from 5 agreed PIPs did not lead to a new indication as targeted by the respective PIPs. These PIPs were for already authorised medicines and some of them already had a paediatric indication. The outcome of the procedures is summarised below.

Anastrozole: The targeted paediatric indications were treatment of short stature due to growth hormone deficiency and treatment of testotoxicosis. The trial with children with short stature showed that the therapeutic effect was smaller than anticipated in the planning phase, resulting in an unfavourable benefit risk balance when taking into account the safety aspects. Similar conclusions were reached for the trial in children with testotoxicosis, which was confounded by the fact that the rarity of testotoxicosis only permitted a small trial. The assessment report of the non-clinical studies and the paediatric trials is available here: http://bit.ly/IikIz0.

Clopidogrel: The targeted paediatric indication was prevention of thromboembolic events in children at risk. This was addressed in two paediatric trials, including a randomised, double-blind, placebo-controlled, event-driven, multicentre trial, in more than 900 infants with a systemic-to-pulmonary artery shunt as part of the management of their congenital heart disease. No significant differences were found between clopidogrel and placebo for the primary endpoint, an efficacy endpoint composed of clinical outcomes, and for bleeding as the most important adverse reaction. The primary endpoint, however, occurred much less frequently then anticipated in the planning phase, which may be linked to the fact that acetylsalicylic acid was administered as part of the clinical management in as many as 88% of the patients. Lack of efficacy may also be related to variability in response to clopidogrel.

Montelukast: The targeted paediatric indication was the treatment of children from 6 months to less than 6 years of age, who had intermittent but not persistent asthma. The paediatric trial was a parallel group, double-dummy, placebo-controlled, double-blind, multicentre, randomised trial, which was able to enrol more than 1700 children, including more than 800 below 3 years and 190 less than 18 months of age, in a short time. There was no difference for either episode-driven dosing, or continuous dosing of montelukast over 52 weeks compared to placebo on the efficacy endpoint, which led to the conclusion that montelukast does not reduce the number of asthma episodes culminating in an asthma attack in this paediatric subset.

Rizatriptan: The targeted paediatric indication was treatment of migraine in children from 6 years of age onwards. The randomized, double-blind, placebo-controlled, parallel-group, multicentre trial with an enrichment stage was age-stratified and included more than 700 from 12 years of age onwards and also 270 children from 6 years to less than 12 years. The difference in pain freedom between rizatriptan and placebo was about 10% of adolescents and this primary endpoint was statistically significant. However, with respect to pain relief, the placebo effect was higher in children than adults; the difference between rizatriptan and placebo on this supportive endpoint was not significant in children, but was of 20-50% in adults. In the literature, conflicting paediatric data on efficacy of triptans have been discussed in relation to differences in populations, methodologies and outcome measures (e.g., Vollono et al. 2011).

Zoledronic acid: The targeted paediatric indication was treatment of osteogenesis imperfecta. The trial had a randomised, active-controlled, open-label design, evaluating the non-inferiority of the effect of zoledronic acid compared to pamidronate, on bone mineral density. This was a large trial in about 150 children with severe osteogenesis imperfecta, a rare disease. However, methodological weaknesses of the trial (ongoing at time of PDCO review) were recognised, including the lack of validation of the primary endpoint and of the lack of evidence of efficacy for the comparator used in clinical practice. No differences in fracture rates could be demonstrated; adverse reactions were more frequent with zoledronic acid, as were lower extremity long bone fractures. Based on the results, the benefit risk balance was considered unfavourable. The assessment report of the paediatric trials is available here: http://bit.ly/IlQTSu.

Details on the medicinal products are listed in sections 4.7 and 7.7 of Annex II.

- Summary - Increased information on medicines used in children

The Paediatric Regulation has triggered updates of the SmPC for paediatric information in a substantial number of cases as well as given public access to the evaluation of paediatric data in assessment reports (more than 100 so far), mostly based on the results of the paediatric clinical studies conducted before 2007 (Article 45) and also more recently (Article 46).

Data from clinical studies with children have been added to the Summary Product Characteristics (SmPC) and the wording has been improved. The addition and increased visibility of paediatric data and information was one of the most prominent changes to the European Commission guideline on SmPCs (2009), which came into force in 2009. In the past, the lack of information had led to

systematic but unjustified contra-indications in children. Although the SmPC guideline is still recent and many SmPCs remain silent with respect to paediatric use, competent authorities aim to achieve compliance with this guideline; the change in mindset is apparent with co-ordinated efforts to obtain and assess relevant data from marketing authorisation holders, in order to add paediatric data and information to the SmPC.

Even the addition of information on waivers granted is relevant for the paediatric population, because such waivers allow the identification of medicines that do not deserve a paediatric development, including according to the regulatory assessment those likely to be unsafe or not efficacious in children, and may deter unsafe off-label use.

The information on "deferrals" reflects that the regulatory procedure has concluded on the need for paediatric development but accepted the delay to obtain relevant paediatric data when it is safe to do so.

Limitations: The SmPC statements that are proposed by MAHs often include "due to limited data and methodological insufficiencies, no definitive conclusion can be drawn" and "few clinical studies with paediatric patients". This mainly reflects that the data were considered of minor relevance and low added value by the MAH.

To date, MAHs have shown little interest in updating SmPCs and PLs following the worksharing procedures for article 45 or 46. NCAs would require significant resources to ensure that variations are submitted following the assessment for either article 45 or 46. This was clear from the attempt made by a Member State (Austria) to monitor the degree of implementation of the outcome of Articles 45 and 46 procedures; the conclusion was that NCAs should regularly remind MAHs of their obligations in this field. It was also noted that more widespread efforts by many MSs had been useful in increasing compliance by MAHs.

In addition, the implementation of the recommendations can be hampered by dissimilar national product information, differences in national practices or differences in approved formulations. Even when recommendations are not yet implemented in SmPCs, the outcome of the work-sharing procedure is useful to health care professionals and the public, because the assessment reports are made public systematically.

Future directions: The robustness and limited amount of quality paediatric data included in the Article 45 submission should be overtaken by those in PIPs, which are agreed with a full development in mind and after thorough scientific discussion. The outcomes and experience of the assessment of completed paediatric trials may however inform PIPs and Scientific Advices on future paediatric questions.

The inventory of needs should help to drive the prioritisation of resources and of further studies to be assessed under Article 45, although phasing out is expected in the next few years. The assessments made under Article 45 and 46 should be part of the "lessons learned" and, if appropriate, provide information to applicants and the PDCO if new aspects were to be found.

However, it is also important to communicate on the limited evidence and on the weakness of data for many medicines that are used off-label in paediatric practice that have been revealed by these assessments. A discussion with Enpr-EMA and paediatric learned societies on this matter could help identify opportunities for paediatric clinical research. In addition, discussions between assessors of Competent Authorities would be helpful to improve and to draft paediatric recommendations for both SmPC and PL in the most appropriate way. The usefulness of the published assessment reports to health care professionals as well as patients and parents might be enhanced by targeted national communications to learned societies and/or the public.

It is not possible to eliminate off-label use through the assessment of existing paediatric data under Article 45, but a prospective approach defining priorities in the necessary paediatric research and development in PIPs may be a way to minimise off-label use in the future.

7. Other projects necessary for the implementation of the Paediatric Regulation

7.1. Participation of children and young people in PDCO Activities

In addition to the participation of patients' representatives (families) as full member of the Paediatric Committee, there is a well-established and recognised need to involve patients and families in clinical research and in the development of medicines for their needs.

Article 24(1) of the Charter of Fundamental Rights of the European Union of 7 December 2000 stipulates that 'Children shall have the right to such protection and care as is necessary for their well-being. They may express their views freely. Such views shall be taken into consideration on matters which concern them in accordance with their age and maturity.'

Based on this article, and on relevant articles within the Universal Declaration of Human Rights and the Convention on the Rights of the Child, in 2011 the European Medicines Agency has initiated an innovative project aimed at facilitating the direct participation of children and young people of different cultures and backgrounds in PDCO activities, in a manner that would be age-appropriate, authentic / honest and which would bring an additional and meaningful dimension to the scientific aspects of the paediatric investigation plan evaluation process. Such plans are in keeping with the Agency's policy on the involvement of patients in scientific committees.

The project involved gathering information from international projects, EU initiatives and also from Enpr-EMA members. The exact framework and specific process for the participation of children and young people in PDCO activities is being defined. An Agency standard operating procedure is being written and will include the definition of a necessity test for youth participation in specific product assessments and the areas in which young people may be expected to contribute their experience, as well the potential formats for such participation. A pilot phase will be conducted in 2012-13. Young people themselves will be surveyed on how they believe they can best contribute in a meaningful way.

7.2. International activities

7.2.1. Paediatric Cluster with US FDA, PMDA Japan and Health Canada

The Paediatric Medicines team at the EMA and the FDA Office of Pediatric Therapeutics (OPT) formed the Paediatric Cluster in 2007. By the end of 2011 OPT had coordinated fifty-four teleconferences in order to exchange information related to paediatric medicines. Members of the OPT and of the FDA divisions participate on a regular basis; PDCO Rapporteurs and Peer Reviewers are also invited and participate if possible. During these teleconferences, the participants discuss the contents of Paediatric Investigation Plans (PIPs), studies mandated under the US Paediatric Research Equity Act and studies in Written Requests issued by the FDA. General questions have also been addressed, such as the types of paediatric studies applicable to certain paediatric therapeutic areas, extrapolation of efficacy and choice of endpoints. Where relevant, the discussions in the teleconferences are reflected in EMA / PDCO Summary Reports.

The Japanese authorities (MHLW and PMDA) joined the Paediatric Cluster teleconferences in November 2009 and Health Canada joined in September 2010, following the establishment of the respective confidentiality agreements.

Since the end of 2009, FDA colleagues regularly participate in the virtual meetings of the PDCO Non-Clinical Working Group and the PDCO Formulation Working Group. In addition, staff exchanges included visits of 5 EMA Paediatric Medicine staff members to the FDA, where they were given the

opportunity to observe the FDA Pediatric Review Committee (PeRC) meetings, as well as visits of several FDA OPT staff to observe some activities of the EMA, including PDCO meetings. The EMA has provided remote access to FDA colleagues to its Paediatric database.

A report on all interactions of the EMA and the US FDA (September 2010) is available (http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/06/WC500107900.pdf).

7.2.2. Global collaboration for regulating development and safeguarding children - Paediatric medicines Regulatory Network at the WHO

Various national or regional activities for developing and making paediatric medicines available are ongoing throughout the world. The Paediatric medicines Regulators' Network (PmRN) was created in 2010 as part of the WHO's Better Medicines for Children initiative. It is chaired by the European Medicines Agency. Currently, the PmRN has members from 28 medicines regulatory authorities (NMRAs) from all regions of the world (http://www.who.int/childmedicines/paediatric_regulators/en/).

The network has carried out a review of ethical guidelines, and has developed guidance on paediatric forms and formulations and an assessor guidance for the evaluation of paediatric trials. A public section has been established on the WHO website, with a restricted access page allowing regulators to exchange questions, information on the safety of medicines and other relevant information.

These activities contribute to the objective of building regulatory competences on paediatric medicines and in particular to ensure that paediatric trials are scientifically designed whilst providing the necessary safeguards for the participants.

7.2.3. Contributing to Global Research in Paediatrics (GRIP) project

GRIP is a project consortium that has received 5-year funding from the EU 7th framework programme to establish a training programme on paediatric pharmacology (http://grip-network.org/). The project includes building up infrastructure to stimulate and facilitate the development and safe use of medicines in children.

The EMA as a partner is contributing regulatory and scientific knowledge to some of GRIP's work packages. In addition to the training programme, the work packages include, work on paediatric formulations, pharmacoepidemiology on the use of medicines in children (safety oriented), outcome measures, methodology, and neonatology. For example, defining regulatory acceptable endpoints for paediatric trials requires validating them and ensuring that this is reflected in the relevant EMA scientific guidelines for medicinal product development.

7.3. Minimising administrative burden and supporting applicants

The European Medicines Agency and the EU network have always engaged in efforts to support applicants and to minimise the administrative and procedural burdens. The EMA has contributed to many information sessions (e.g., DIA, TOPRA, EFGCP, RAPS) and participated in several groups involving stakeholders (such as meetings with the EFPIA Paediatric Subgroup).

In addition to reducing administrative burdens through electronic workflow, EMA has implemented continual process improvement to simplify the regulatory processes wherever possible. In addition, information is published systematically and Questions and Answers documents are updated for frequently asked questions.

7.3.1. Business Pipeline meetings with applicants and pre-submission meetings for specific medicines

Since 2003, the EMA has developed an activity of business intelligence and forecasts of applications (Business Pipeline). Pharmaceutical companies are invited to or can request to have confidential meetings to present their portfolio of medicines and to discuss development or regulatory issues. During the reporting period, 24 pipeline meetings were held on medicines for a paediatric (and possibly adult) use, PIPs or Waivers, compared to 16 pipeline meetings exclusively on medicines for adults. The annual number of pipeline meetings addressing paediatric medicines has increased with time.

The EMA has also set up pre-submission meetings for paediatric activities. These were not available initially due to resource constraints. Since 2009, pre-submission meetings were held with applicants before the submission of applications for PIP and / or waiver, or before requests for modification of agreed PIPs.

As part of the activities of the SME office to support small and medium-sized companies with less regulatory experience, EMA held pre-submission meetings to discuss PIP applications for 3 medicines and exchanged information on PIP applications in writing or by teleconferences for a further 13 medicines. SME briefing meetings were held for 6 more medicines to address PIP requirements and the legal basis for the submission for marketing authorisation. An EMA workshop on paediatric medicines was held for SMEs in 2009.

7.3.2. Administrative harmonisation and simplification of PIP applications

For the efficient management of applications for Paediatric Investigation Plans and Waivers at the EMA, an electronic workflow was implemented in 2007 and has been extended incrementally. Applicants complete "intelligent" electronic forms, automatically from their systems (data are stored in a standard generalised mark-up language), or manually with many fields pre-filled with standard terminology from the EuTCT). The electronic forms are uploaded into the paediatric database at the EMA. The database manages the administrative and procedural aspects and the scientific content; it produces the necessary documents using the validated and standardised data, including the EMA / PDCO Summary Report and the PDCO Opinion (and eventually will produce the Decision).

The electronic application form was introduced in 2007, extended in 2009 and a standardised form for non-clinical studies and clinical trials was added in 2010. In addition the electronic forms were adapted and simplified. The collection of data on pharmaceutical forms and formulations to describe the pharmaceutical quality was added in 2011, to harmonise the information submitted on complex quality data.

Overall, this electronic management of applications and evaluation has received support from stakeholders. It has reduced resources needed at the EMA to manage the extremely high number of procedures, including in the initial phase. This initiative has served as a model for other procedures, e.g. the management of marketing authorisation and variation applications.

7.3.3. Class waivers and confirmation of applicability

"Class" or conditions waivers were issued early (2007) in the implementation as a way to decrease the administrative burden of applying for product-specific waivers for products intended for diseases or conditions that only occur in adults (Articles 11, 12, 14). The EMA PDCO has issued 44 class waivers on conditions and 1 waiver for a class of medicinal products (current). A few have been revoked and the list is updated annually (http://bit.ly/y0yom8).

As condition waivers are written in broad terms, the EMA PDCO offered to confirm whether or not the indication proposed by applicants was covered by EMA Decisions. This was intended to avoid failures of the validation of the marketing authorisation which would delay the authorisation for adults. There were 209 requests to confirm the applicability of an existing class/condition waiver up to the end of 2011.

The review of the applicability of a class waiver is also an opportunity for the PDCO to recommend medicines development in paediatric conditions with unmet needs, when the mechanism of action of the medicine justifies development. This was particularly the case for medicines used in adult oncology that can be used, based on their mechanism of action, in different cancers in children with high unmet needs. The PDCO recommended development for a number of medicines. Sadly, no PIP application was received in response to such PDCO recommendations.

7.4. Interaction with external experts and stakeholders

The EMA PDCO engaged in multiple stakeholder interactions. Stakeholders included experts and (paediatric) learned societies (in expert groups and public and dedicated workshops); patients' organisations (in expert groups and public and dedicated workshops); pharmaceutical companies (through interactions with trade associations, company hearings and public workshops); and patent offices in collaboration with the European Commission.

Patients' representatives are part of the Committee and may participate in the evaluation. In addition, the PDCO with the COMP initiated a joint 'job description' of a patient representative in an EMA Committee to define the expectations and added value of their presence. This was subsequently discussed and endorsed by the EMA patients and consumer Working Party.

The 14 workshops on paediatric medicine development conducted by the EMA so far, involved the PDCO and experts from the EU regulatory network and informed the development of scientific guidance (see section 4.11.).

Sixty seven external experts have been involved in the evaluation of proposals for PIPs by the EMA PDCO. They represent all paediatric therapeutic areas. Overall, 212 persons with expertise relevant to paediatric medicines have been nominated, and so far 156 of them have been involved in paediatric medicines workshops, discussions with the PDCO of general aspects of paediatric diseases and medicines, or in product-specific PIP evaluations.

Interactions with external experts and with stakeholders are included in the PDCO monthly reports.

7.5. Awareness of the Paediatric Regulation in external publications

Publications in scientific journals were recorded to judge of the awareness of the Paediatric Regulation and interest of stakeholders, principally the academic community. Publications can also reflect agreement on or objections to the Regulation. The EMA (both secretariat and PDCO) has published proactively to increase transparency of the processes and outcomes, to allow scrutiny and to ensure trust in the regulatory system.

A search in PubMed and EMBASE identified publications in scientific journals. The publications focus on the expected changes (e.g., availability of medicines and formulations relevant for paediatric medical care), the possibilities to comment on paediatric guidelines, and the lists of needs and priority lists as opportunities to collaborate (e.g., as external expert, as investigator).

Table 12: Publications on the Paediatric Regulation and its implementation.

Number	2007	2008	2009	2010	2011	Total
Publications by external authors	8	22	13	10	14	67
Publications by EMA staff or PDCO members	1	8	6	7	26	46

Source: EMA publications database and search.

The search criteria and the list of publications are in Annex I, section 18.1.

Future directions: Publications by external authors may identify areas for improvement in relation to the measures introduced by the Regulation, such as ethical concerns, availability of children participants for trial recruitment. Scientific publications, by increasing awareness and ensuring transparency of the processes, serve also the objectives of the Paediatric Regulation.

8. Resources used by the Member States and EMA

The successful implementation and operation of the Paediatric Regulation required extensive scientific, regulatory, and financial resources from the EMA and the European network of National Competent Authorities. The Member States have contributed resources in kind in the following activities, which are for most of them non-fee attracting.

- Not only do Paediatric Committee members appointed by the Member States provide on their own significant time and expertise to the work of the Committee, but many of them benefit from extensive input from assessors and additional experts at national Agency level. As an indicator of the contribution of the Member States, Annex 19. presents the break-down of rapporteurships (including peer-review) in the PDCO over the 5 years.
- The Member States approve paediatric clinical trials performed in their territories and upload information in EudraCT.
- Member States experts are involved in national and EU paediatric scientific advice, and the assessment, compliance check and update of the Summaries of Product Characteristics for paediatric data relating to nationally approved products.
- The Member States with the CMD(h) contribute actively to the evaluation of the huge amount of older data submitted under article 45 of the Paediatric Regulation.
- The CMD(h) created a specific paediatric subgroup to coordinate paediatric activities and regulatory procedures.
- The Member States have performed a survey of all uses of medicines in children collated and published in December 2010 (Article 42-43), which was the basis for the on-going work on the inventory of needs.
- Member States submitted the inventory of national incentives, and every year report on companies who benefit from or infringed the Paediatric Regulation (in collaboration with their Patent Offices).

The European Medicines Agency also contributed significant resources to support paediatric activities, to prepare for the implementation of the paediatric legislation, for the setting up of the PDCO and its activities, for the scientific evaluation of PIPs and Waivers, for the secretariat of the Paediatric Committee and of the CMD(H), for legal and regulatory procedures, for the training of assessors and the collection of Member States data (e.g. survey, inventory, annual reports).

Significant resources from both Member States and the EMA were devoted to the preparation of this report. The resources from the EMA secretariat devoted to the preparation of this report represent about 140 man/day.

9. Lessons learned and opportunities for improvement

The implementation of the Paediatric Regulation by the European regulatory network was a complex process, as the Regulation changed the development and authorisation of medicines, the conduct and transparency of clinical trials with the paediatric population, as well as the awareness of paediatric needs in regulatory interactions. The experience with the implementation raised a number of difficulties and challenges ranging from administrative, regulatory, legal issues to difficult scientific matters, which the EMA PDCO and the EU network are eager to identify and address.

The EMA, in particular the Paediatric Committee members, have reflected on the experience with the Paediatric Regulation. The data in this report support the expectation that the main objectives of the Paediatric Regulation will be achieved. There is already evidence of increased and better research, increased availability of paediatric medicines and age-appropriate information, which are filling in gaps in knowledge on paediatric medicines. However, there are also expectations of achieving the objectives more efficiently, with respect to the agreement and conduct of studies in PIPs, requiring feasible studies with children, identifying priority medicines for use in children, progressing regulatory science on paediatric medicine development, decreasing administrative burden for example in decreasing the number of minor changes to agreed PIPs, therefore indicating a range of opportunities for research and for improvement.

Throughout the implementation of the Paediatric Regulation, the EMA PDCO have engaged a large number of stakeholders, including those from the pharmaceutical industry and medical and scientific communities, with open dialogue and exchange, recognising their roles and responsibilities in making medicines available for children.

The report explains how some improvement actions were already undertaken, how applicants were supported and sets out future directions. From the specific aspects reported, a number of lessons have been identified with opportunities for improvement.

- Paediatric medicine development and availability

After 5 years with the Paediatric Regulation, new medicines have been authorised with a paediatric use, a number of authorised medicines were granted new paediatric indications, or the authorisation was extended to include a pharmaceutical form relevant to paediatric use. More could have been hoped for as some paediatric studies were already ongoing when the Paediatric Regulation came into force, but at the same time the completion of all studies in a PIP takes several years (and may additionally be deferred).

At this point in time, there is still uncertainty on the progress of research and development for agreed PIPs. The need to submit annual reports only applies to authorised medicines on PIPs with a deferral, and not all have been submitted. The analysis of those available shows that most developments are ongoing as programmed; however, these reports cannot provide the full picture as most agreed PIPs concern products that are not yet approved, The EMA PDCO are looking into possibilities to monitor the progress of agreed PIPs, which may involve linking databases and networking paediatric health research communities, including those in Enpr-EMA.

It is disappointing, and perhaps surprising for the Committee, that many healthcare professionals do not recognise the need for evidence-based paediatric prescribing, achieved through the conduct of paediatric clinical trials (Mukuttash et al. 2011). The EMA PDCO considers that this unexpected hurdle should be addressed by all stakeholders.

The timely conduct and feasibility of PIPs is always considered by the EMA PDCO, but more work with Enpr-EMA, external experts and academic communities would be useful to ensure that the most appropriate and high-quality studies are required (see e.g., Eichler & Soriano 2011).

Regardless of the high number of PIPs proposed by pharmaceutical companies and agreed by the PDCO, conditions covered by PIPs do not fully match the known but evolving unmet paediatric needs. Diseases that occur frequently or exclusively in children are both underrepresented and poorly addressed (e.g., for pain, Davies et al. 2010, for paediatric malignancies Paolucci et al. 2008) because the main driver of pharmaceutical research remains the adult indication and market. Pharmaceutical companies' motivations to propose a PIP are probably driven by a genuine interest in meeting paediatric needs, stimulated by the legislative force of the Paediatric Regulation, and by prospects of financial gain from the (limited) paediatric market as well as the additional protection reward (at times significant). The EMA PDCO are monitoring the alignment of agreed PIPs with paediatric needs, taking into account the EU inventory (Article 43). Furthermore, the elaboration of model PIPs for underrepresented diseases is ongoing, to attract PIPs for conditions that are not otherwise falling under the requirements of the Paediatric Regulation.

Additionally, the EMA and the PDCO are exploring how PIPs for different medicines for similar conditions can generate complementary instead of similar paediatric data, which would progress paediatric research and reduce feasibility issues.

Further steps are considered necessary to achieve the main objectives of the Paediatric Regulation for paediatric therapeutic areas such as paediatric oncology where little progress has been made in the last five years in part due to the difference in clinical conditions between adults and children. In view of the unmet therapeutic needs in paediatric oncology, taking into account the mechanism of action that is of great interest and relevance to the treatment of paediatric malignancies is necessary. The scope of the PIP or the waivers should be driven by the potential paediatric use, i.e. the data (existing or to be generated as part of a PIP) on the mechanism of action, or on the target of the anti-cancer medicine where the anti-cancer adult indication is under development.

So far, only one Paediatric Use Marketing Authorisation (PUMA) has been granted. This new type of marketing authorisation and the related incentive were expected to encourage small and medium-sized enterprises and generic companies to develop off-patent medicines for children (Recital 20). Many off-patent medicines are relevant for the treatment of children, but are lacking a paediatric formulation and data for safe and appropriate use in subsets of the paediatric population, as detailed in the list of priorities for studies, updated regularly by the EMA / PDCO. However, the few PIPs for PUMAs (as can be identified) so far and the uncertainties around future PUMAs cast doubts on the success of this measure of the Paediatric Regulation. Considerations could be given to limit the studies required in a PIP for a PUMA to those set out in the priority list, or limit to a particular needy subset. In this context, marketing authorisations made under a legal basis that does not fall under the Paediatric Regulation (in particular the so-called hybrid applications) may have potential paediatric use and represent missed opportunities.

In addition to the Paediatric Regulation as the provision with the highest potential impact on making new medicines available to children, national authorities could consider encouraging the development and use of new paediatric medicines through therapeutic guidelines and adaptation of reimbursement rules.

- Availability of more information relevant for the paediatric population

Huge efforts and resources from the European regulatory network are involved to assess paediatric studies completed before the Paediatric Regulation for nationally authorised medicines. Variable quality but substantial information existed that had not been provided to Competent Authorities. This further

justifies the prospective requirement to submit results of paediatric studies and trials as soon as completed, whether part of a PIP or not (Article 46).

The assessments under Articles 45 and 46 (for studies outside of a PIP) should have led to a greater number of Product information changes relating to paediatric use. The assessments have revealed methodological issues in these paediatric trials, which are lessons to be learned for future PIPs.

Considering the priorities for some therapeutic areas with highest paediatric need under Article 45, future assessments may have less impact on product information for the paediatric population. The experience gathered supports the conclusion that addressing gaps in knowledge on medicines for children requires a prospective scientific approach to agreed PIPs, with a systematic, comprehensive and prospective collection of necessary data.

The visibility, understanding and use of the published Assessment reports and Product information by health care professionals and patients / parents is less than optimal in paediatrics as for adults. It is hoped that recent changes to the Product information may be effective but other approaches should be envisaged.

- Administrative burden minimisation and efficient handling of PIP applications

The Paediatric Regulation and the European Commission Guideline on the format and content of applications […] (2008/C 243/01) defined a set of obligations that apply to pharmaceutical companies. Despite the new mindset developed in pharmaceutical companies, the integration of paediatric needs early in the process of medicine development is still incomplete, as exemplified by late submissions of applications for a PIP or waiver. At this time, there are no data to demonstrate the benefits of early submissions (such as possibilities to link paediatric with adult formulation measures, to refine non-clinical studies for paediatric endpoints, and to avoid that off-label use prevents the necessary paediatric trials). Future research should address the question. The EMA has information on the reasons provided for late submissions of PIP and waivers and this will be analysed in 2012.

The EMA PDCO are conscious of the resource implications and of development uncertainties, and are striving to minimise potential obstacles to early PIPs. The electronic workflow introduced in 2007 allows applicants to re-use previous submission data. Work is well advanced to promote less detailed PIP proposals, including the key elements in PIP opinions. The simplification of applications and subsequently of PDCO opinions should benefit early PIP applications, in which studies can be based on knowledge about the paediatric disease / condition, while data on the medicine are limited. This should in turn reduce the need for modifications of agreed PIPs, and leave sufficient flexibility for applicants to implement and conduct the study.

Modifications of agreed PIPs are considered part of the life cycle of a medicinal product to respond to new data and evolving knowledge, therefore modifications do not indicate that the original PIP failed or was inappropriate in the first place. However, modifications of agreed PIPs should be scientifically based, rather than administrative. The large number of modifications of minor details is recognised as an issue and a better description of the reasons for modifications will be made in the near future, to continue simplifying and improving PIP opinions.

Given the extensive interactions between the PDCO and the SAWP for Scientific Advice, a single joint procedure is under development, to form a single view at the EMA on the scientific questions to meet the applicants' interests.

Based on the experience of the EMA PDCO from pre-submission meetings, validation issues and positive and negative PDCO opinions for PIP and waivers, the link between the indication(s) developed in adults and the condition(s) to be addressed in the PIP or the waiver was not predictable. Work is ongoing to develop such a framework, in order to allow anticipation of the requirements of the

Paediatric Regulation. Since the start of the implementation of the Paediatric Regulation, a high level of transparency on the paediatric procedures has been introduced and developed, for the benefit of applicants, health care professionals and patients / parents. The EMA / PDCO Summary Report on PIPs or waivers may be further improved to clarify the reasoning and conclusions of the PDCO as well to identify uncertainties on scientific (and sometimes ethical) questions, and to specify how the PDCO suggests to address these questions.

Recognising that plans, timelines, and target indications may change during the development of a medicine, and that some authorised medicines are developed for further indications, it is legitimate to protect the chances of applicants to obtain rewards or use incentives offered by the Paediatric Regulation should remain possible to be obtained. To this end, the EMA is working on a policy to facilitate changes in development plans.

Finally, the main procedure defined in the Standard Operating Procedure (SOP/H/3207 available on EMA website) will be revised again in 2012, taking into account the experience gathered with a view to simplify procedures.

- Monitoring and reporting

Despite significant efforts and resources at the level of Member States and the EMA, collecting and analysing data for this report, presented a number of difficulties. For the monitoring of the implementation and of the outcomes of the Paediatric Regulation, paediatric data need to be documented specifically in various regulatory activities. Such information is either not tracked routinely or spread over several databases and documents (e.g., the SmPC and other parts of the EPAR), creating difficulties and impacting exhaustivity and reliability.

Considering the need to collect and compile data for the soon to come 10-year report under Article 50(3), the annual reports under Article 50(1), and any public presentations by members of the network, it is necessary to streamline and agree early on some indicators with methodological advantages (based on SMART criteria, for example). The EMA PDCO will continue to use the data on the impact and implementation of the Regulation to learn about possible administrative and scientific improvements, with the intention to facilitate high-quality paediatric research and to remove any unnecessary administrative burden.

The indicators used for this report may not reflect all aspects of the impact of the Paediatric Regulation and the changes brought about for the paediatric population. For example, the current report cannot capture the mid-term impact (e.g., improvements in quantity and quality of paediatric research) nor the impact of long-term changes (e.g., integration of paediatric needs early during pharmaceutical development with long lasting changes). The EMA PDCO are therefore developing further indicators, with the view to capture the involvement and efficiency of interactions with stakeholders, the general awareness and perception by stakeholders, as well as the progress of generating data on medicines that are relevant for the paediatric population.

Annex I

10. References

For the methodology for retrieving references related to the Paediatric Regulation see section 18.1.

Publications by EMA and / or PDCO related to the Paediatric Regulation

1. Baiardi P, Ceci A, Cantarutti L, Girotto S, Sturkenboom M, Baraldi E. How the European paediatric regulation is reducing the gap. Acta Paediatrica, Int J Paediatrics. **2010** 99 (10) (pp 1446). AN: 2010485302
2. Bensouda-Grimaldi L, Chalumeau M, Mikaeloff Y, Pons G. [Pharmaco-epidemiology to evaluate medicines in pediatric patients]. Arch Pediatr. **2008** Jun;15(5):814-6.
3. Bouillon-Pichault M, Jullien V, Bazzoli C, Pons G, Tod M. Pharmacokinetic design optimization in children and estimation of maturation parameters: example of cytochrome P450 3A4. J Pharmacokinet Pharmacodyn. **2011** Feb;38(1):25-40
4. Brasseur D. Paediatric research and the regulation "better medicines for the children in Europe". Eur J Clin Pharmacol. **2011** May;67 Suppl 1:1-3.
5. Brasseur D. What has become of extemporaneous mixtures? Ann Dermatol Venereol. **2007** Mar;134(3 Pt 2):2S37-9. PMID: 17563713
6. Carleer J, Karres J. Juvenile animal studies and pediatric drug development: a European regulatory perspective. Birth Defects Res B Dev Reprod Toxicol. **2011** Jun 2
7. Ceci A, Giaquinto C, Aboulker JP, Baiardi P, Bonifazi F, Della Pasqua O, Nicolosi A, Taruscio D, Sturkenboom M, Wong I. The Task-force in Europe for Drug Development for the Young (TEDDY) Network of Excellence. Paediatr Drugs. **2009**;11(1):18-21. PubMed PMID: 19127946.
8. Chiron C, Dulac O, Pons G. Antiepileptic drug development in children: considerations for a revisited strategy. Drugs. **2008**;68(1):17-25.
9. Davies EH, Ollivier CM, Saint Raymond A. Paediatric investigation plans for pain: painfully slow!.J Clin Pharmacol. **2010** Nov;66(11):1091-7
10. Eichler I, Sala-Soriano E. Close collaboration between academia, industry and drug regulators is required in the development of allergen products for specific immunotherapy in children. Allergy: European Journal of Allergy and Clinical Immunology. **2011**;66 (8) (pp 999-1004)
11. Wirth S, Kelly D, Sokal E, Socha P, Mieli-Vergani g, Dhawan A, Lacaille F, Saint Raymond A, Olivier S, Taminiau J. Guidance for clinical trials for children and adolescents with chronic hepatitis C. J Pediatr Gastroenterol Nutr. **2011** Feb;52(2):233-7.
12. Heidmets LT, Metsvaht T, Ilmoja ML, Pisarev H, Oselin K, Lutsar I. Blood Loss Related to Participation in Pharmacokinetic Study in Preterm Neonates. Neonatology. **2011** Mar 2;100(2):111-115
13. Herold R, Saint Raymond A. Preamble may not improve consent and assent process [letter]. Pediatr Blood Cancer. **2011** Feb;56(2):327; author reply 328
14. Hirschfeld S, Saint Raymond A. Pediatric regulatory initiatives. Pediatric Clinical Pharmacology. Handbook of Experimental Pharmacology. 205 (pp 245-268), **2011**

15. Karres J, Tomasi P, Saint Raymond A. The development of pharmacological treatment of obesity in children. A European regulatory perspective. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. **2011** May;54(5):570-6

16. Kimland E. Nydert P. Odlind V. Böttiger Y. Lindemalm S. Paediatric drug use with focus on off-label prescriptions at Swedish hospitals – a nationwide study. Acta Paediatr. **2012** Mar 8. doi: 10.1111/j.1651-2227.2012.02656.x

17. Knellwolf AL, Bauzon S, Alberighi OD, Lutsar I, Bácsy E, Alfarez D, Panei P. Framework conditions facilitating paediatric clinical research.Ital J Pediatr. **2011** Feb 23;37:12.

18. Kubiak C, de Andres-Trelles F, Kuchinke W, Huemer KH, Thirstrup S, Whitfield K, Libersa C, Barraud B, Grählert X, Dreier G, Grychtol R, Temesvari Z, Blasko G, Kardos G, O'Brien T, Cooney M, Gaynor S, Schieppati A, Sanz N, Hernandez R, Asker-Hagelberg C, Johansson H, Bourne S, Byrne J, Asghar A, Husson JM, Gluud C, Demotes-Mainard J. Common definition for categories of clinical research: a prerequisite for a survey on regulatory requirements by the European Clinical Research Infrastructures Network (ECRIN). Trials. **2009** Oct 16;10:95

19. Lass J, Irs A, Pisarev H, Leinemann T, Lutsar I. Off label use of prescription medicines in children in outpatient setting in Estonia is common. Pharmacoepidemiol Drug Saf. **2011** May;20(5):474-81

20. Lass J, Käär R, Jõgi K, Varendi H, Metsvaht T, Lutsar I. Drug utilization pattern and off-label use of medicines in Estonian neonatal units. Eur J Clin Pharmacol. **2011** Jun 11

21. Lehmann B, Mentzer D, Fischer T, Mallinckrodt-Pape K. Clinical trials in children--between the expectations of scientific requirements, the assurance of proven treatment and ethical demands. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. **2009** Apr;52(4):410-6. German

22. Lehmann B. Regulation (EC) No 1901/2006 on medicinal products for paediatric use & clinical research in vulnerable populations. Child Adolesc Psychiatry Ment Health. **2008** Dec 8;2(1):37.

23. Lehmann B. Review of the development in European Legislation on the harmonisation of the laws for medicinal products. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. **2008** Jul;51(7):713-21. Review. German.

24. Manolis E, Osman TE, Herold R, König F, Tomasi P, Vamvakas S, Saint Raymond A. Role of modeling and simulation in pediatric investigation plans. Paediatr Anaesth. **2011** Mar;21(3):214-21

25. Manolis E, Pons G. Proposals for model-based paediatric medicinal development within the current European Union regulatory framework. Br J Clin Pharmacol. **2009** Oct;68(4):493-501.

26. Mentzer D. Regulatory aspects of clinical trials in children. Arb Paul Ehrlich Inst Bundesamt Sera Impfstoffe Frankf a.M. **2009**;96:203-7; discussion 207-9

27. Muntoni F. Meeting Steering Committee and TREAT-NMD Network. The development of antisense oligonucleotide therapies for Duchenne muscular dystrophy: report on a TREAT-NMD workshop hosted by the European Medicines Agency (EMA), on September 25th 2009. Neuromuscul Disord. **2010** May;20(5):355-62

28. Neugebauer B, Drai C, Haase M, Hilger A, Keller-Stanislawski B, Laitinen-Parkkonen P, Mentzer D, Rasmussen C, Ratignier C, Seitz R. Factor VIII products and inhibitor development: concepts for revision of European regulatory guidelines. Haemophilia. **2008** Jan;14(1):142-4.

29. Olski TM, Lampus SF, Gherarducci G, Saint Raymond A. Three years of paediatric regulation in the European Union. Eur J Clin Pharmacol. **2011** Mar;67(3):245-52

30. Olsson J, Kimland E, Pettersson S, Odlind V. Paediatric drug use with focus on off-label prescriptions in Swedish outpatient care -- a nationwide study. Acta Paediatr. **2011** Sep;100(9):1272-5.

31. Paolucci P, Cioni V, Bigi E, Lucaccioni L, Cano C. Endpoints in paediatric oncology. Eur J Clin Pharmacol. **2011** May;67 Suppl 1:33-40.

32. Paolucci P, Jones KP, del Carmen Cano Garcinuno M, Catapano M, Iolascon A, Ceci A. Challenges in prescribing drugs for children with cancer. The Lancet Oncology. 9 (2) (pp 176-183), **2008**

33. Rocchi F, Paolucci P, Ceci A, Rossi P. The European paediatric legislation: benefits and perspectives. Ital J Pediatr. **2010** Aug 17;36:56

34. Rocchi F, Tomasi P. The development of medicines for children. Part of a series on Pediatric Pharmacology, guest edited by Gianvincenzo Zuccotti, Emilio Clementi, and Massimo Molteni. Pharmacol Res. **2011** Sep;64(3):169-75

35. Ruperto N, Eichler I, Herold R, Vassal G, Giaquinto C, Hjorth L, Valls-i-Soler A, Peters C, Helms PJ, Saint Raymond A. A European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA). Arch Dis Child. **2012** Mar;97(3):185-8. epub 2011 Nov 27

36. Russo R, Capasso M, Paolucci P, Iolascon A. TEDDY European Network of Excellence. Pediatric pharmacogenetic and pharmacogenomic studies: the current state and future perspectives. Eur J Clin Pharmacol. **2011** May;67 Suppl 1:17-27

37. Saint Raymond A. Regulatory aspects of drug development in children: change and resistance to change. Expert Rev Clin Pharmacol. **2010** Sep;3(5):593-5.

38. Saint Raymond A, Hill S, Martines J, Bahl R, Fontaine O, Bero L. CONSORT 2010. Lancet. **2010** Jul 24;376(9737):229-30

39. Saint Raymond A, Seigneuret N. The European paediatric initiative: 1 year of experience. Paediatr Drugs. **2009**;11(1):9-10

40. Sala Soriana E, Eichler I: Spotlight. Joined-up Thinking. EPC **2012**;36-37

41. Silva-Lima B, Due Theilade-Thomsen M, Carleer J, Vidal JM, Tomasi P, Saint Raymond A. Juvenile animal studies for the development of paediatric medicines: a description and conclusions from a European Medicines Agency workshop on juvenile animal testing for nonclinical assessors. Birth Defects Res B Dev Reprod Toxicol. **2010** Dec;89(6):467-73

42. Stoyanova-Beninska VV, Wohlfarth T, Isaac M, Kalverdijk LJ, van den Berg H, Gispen-de Wied C. The EU paediatric regulation: effects on paediatric psychopharmacology in Europe. Eur Neuropsychopharmacol. **2011** Aug;21(8):565-70.

43. Tod M, Jullien V, Pons G. Facilitation of drug evaluation in children by population methods and modelling. Clin Pharmacokinet. **2008**;47(4):231-43..

44. Tomasi P. In Search of Safe and Effective Medicines. European Pharmaceutical Contractor, 2011

45. van den Berg H, Tak N. Licensing and labelling of drugs in a paediatric oncology ward.Br J Clin Pharmacol. **2011** Sep;72(3):474-81. doi: 10.1111/j.1365-2125.2011.03977.x

46. van den Berg H, Taminiau JA. Better medicines for children: European measures. Ned Tijdschr Geneeskd. **2008** Jul 5;152(27):1537-40. Dutch

47. Wirth S, Kelly D, Sokal E, Socha P, Mieli-Vergani G, Dhawan A, Lacaille F, Saint Raymond A, Olivier S, Taminiau J. Guidace for clinical trials for children and adolescents with chronic hepatitis C. J Pediatr Gastroenterol Nutr. **2011** Feb;52(2):233-7

External publications on the Paediatric Regulation

1. Allegaert K, Rayyan M, Vanhaesebrouck S, Naulaers G. Developmental pharmacokinetics in neonates. Expert Review of Clinical Pharmacology. 1 (3) (pp 415-428), **2008**. AN: 2008389165

2. André N, Leblond P, Verschuur A. [Specificity of paediatric oncology pharmacology]. Bull Cancer. **2010** Feb;97(2):191-8. French. PubMed PMID: 19812009.

3. Arenas-López S, Fajardo C, Valls i Soler A, García-Corzo JR, Lima-Rogel MV, Calle G, Leite R, Lobos E, Hume-Wright Q, MacLeod S. Pediatric clinical trials in Latin America and Guyana: present views of local practitioners and ways to embrace the future. Paediatr Drugs. **2011** Aug 1;13(4):257-65. doi: 10.2165/11590350-000000000-00000. PubMed PMID: 21692549.

4. Auby P. Pharmaceutical research in paediatric populations and the new EU Paediatric Legislation: an industry perspective. Child Adolesc Psychiatry Ment Health. **2008** Dec 8;2(1):38. PubMed PMID: 19063723; PubMed Central PMCID: PMC2629463.

5. Breitkreutz J. [Dosage forms for children. After the EU Reform]. Pharm Unserer Zeit. **2009**;38(1):30-7. Review. German. PubMed PMID: 19132675.

6. Breitkreutz J. European perspectives on pediatric formulations. Clin Ther. **2008** Nov;30(11):2146-54. PubMed PMID: 19108802.

7. Broekmans AW. [Better medicines for children: European measures]. Ned Tijdschr Geneeskd. **2008** Aug 30;152(35):1945; author reply 1945. Dutch. PubMed PMID: 18808086.

8. Calderon M, Mösges R, Hellmich M, Demoly P. Towards evidence-based medicine in specific grass pollen immunotherapy. Allergy. **2010** Apr;65(4):420-34. Epub 2009 Dec 21. Review. PubMed PMID: 20028374.23:

9. Jago C. SMi's Conducting Clinical Trials in Europe. I Drugs. 2009 Dec;12(12):754-9. PubMed PMID: 19943216.

10. Cave E. Seen but not heard? Children in clinical trials. Med Law Rev. 2010 Winter;18(1):1-27. Epub **2010** Feb 3. PubMed PMID: 20129995.

11. Choonara I. Ethical and safety aspects of clinical trials in neonates. Early Hum Dev. 2009 Oct;85(10 Suppl):S19-20. Epub **2009** Sep 22. PubMed PMID: 19775839.

12. Dewit O.E, Tiner R. Working with the pharmaceutical industry in relation to paediatric clinical trials. A British perspective. Paediatric and Perinatal Drug Therapy. 8 (4) (pp 140-144), **2008**. AN: 2008386474

13. Donnelly F. EU initiatives for research involving children. Eur J Pediatr. **2008** Jul;167(7):837-8. Epub 2008 Feb 6. PubMed PMID: 18253749.

14. Duarte D.M, Silva-Lima B. Juvenile animal studies in the development of pediatric medicines: Experience from European medicines and pediatric investigation plans. Birth Defects Research Part B - Developmental and Reproductive Toxicology. 92 (4) (pp 353-358), **2011**. AN: 2011467475

15. Dunne J. The European Regulation on medicines for paediatric use. Paediatr Respir Rev. 2007 Jun;8(2):177-83. Epub **2007** May 30. Review. PubMed PMID: 17574163.

16. Fortinguerra F, Maschi S, Clavenna A, Bonati M. Pain management in the paediatric population: the regulatory situation in Europe. Arch Dis Child. 2010 Sep;95(9):749-53. Epub **2010** Jun 28. Review. PubMed PMID: 20584850.

17. Hawcutt DB, Smyth RL. Drug development for children: how is pharma tackling an unmet need? IDrugs. **2008** Jul;11(7):502-7. Review. PubMed PMID: 18600597.

18. Hawcutt DB, Smyth RL. The new European regulation on pediatric medicines: regulatory perspective. Paediatr Drugs. **2008**;10(3):143-6. PubMed PMID: 18454566.

19. Himmel HM. Safety pharmacology assessment of central nervous system function in juvenile and adult rats: effects of pharmacological reference compounds. J Pharmacol Toxicol Methods. 2008 Sep-Oct;58(2):129-46. Epub **2008** Jun 8. PubMed PMID: 18585470.

20. Hoppu K, Anabwani G, Garcia-Bournissen F, Gazarian M, Kearns GL, Nakamura H, Peterson RG, Sri Ranganathan S, de Wildt SN. The status of paediatric medicines initiatives around the world-what has happened and what has not? Eur J Clin Pharmacol. **2012** Jan;68(1):1-10. Epub **2011** Jul 6. PubMed PMID: 21732178.

21. Hoppu K. Can we get the necessary clinical trials in children and avoid the unnecessary ones? Eur J Clin Pharmacol. **2009** Aug;65(8):747-8. Epub 2009 Jun 12.PubMed PMID: 19521694.

22. Hsien L, Breddemann A, Frobel AK, Heusch A, Schmidt KG, Läer S. Off-label drug use among hospitalised children: identifying areas with the highest need for research. Pharm World Sci. 2008 Oct;30(5):497-502. Epub **2008** Jan 26. PubMed PMID: 18219585.

23. Jacqz-Aigrain E. Drug policy in Europe Research and funding in neonates: current challenges, future perspectives, new opportunities. Early Hum Dev. **2011** Mar;87 Suppl 1:S27-30. Epub 2011 Jan 26. Review. PubMed PMID: 21269785.

24. Johannesson M, Berglund EG. [The Medical Products Agency's preparations prior to the new EU regulation on children and drugs]. Lakartidningen. 2007 Jul 11-24;104(28-29):**2009**. Swedish. PubMed PMID: 17702388.

25. Kemper EM, Merkus M, Wierenga PC, Van Rijn PC, Van der Werff D, Lie-A-Huen L, Offringa M. Towards evidence-based pharmacotherapy in children. Paediatr Anaesth. **2011** Mar;21(3):183-9. doi: 10.1111/j.1460-9592.2010.03493.x. Epub 2010 Dec 28. Review. PubMed PMID: 21199133.

26. Khan-Boluki J, Hundt F. Children in clinical trials: survey on the current situation in paediatric university clinics in Germany. Ger Med Sci. **2008** Mar 10;6:Doc01. PubMed PMID: 19675729; PubMed Central PMCID: PMC2703255.

27. Knellwolf AL, Bauzon S, Alberighi OD, Lutsar I, Bácsy E, Alfarez D, Panei P. Framework conditions facilitating paediatric clinical research. Ital J Pediatr. **2011** Feb 23;37:12. Review. PubMed PMID: 21345195; PubMed Central PMCID: PMC3055809.

28. Kölch M, Märsch C, Fegert JM, Lippert HD. [Clinical trials with minors in Germany--effects of the 12th amendment to the German Drug Code on the numbers of applications to Institutional Review Boards (IRB)]. Gesundheitswesen. **2009** Mar;71(3):127-33. Epub 2009 Feb 16. German. PubMed PMID: 19221985.

29. Kölch M, Schnoor K, Fegert JM. The EU-regulation on medicinal products for paediatric use: impacts on child and adolescent psychiatry and clinical research with minors. Eur Child Adolesc Psychiatry. 2007 Jun;16(4):229-35. Epub **2007** Apr 7. PubMed PMID: 17417746.

30. Laughon MM, Benjamin DK Jr, Capparelli EV, Kearns GL, Berezny K, Paul IM, Wade K, Barrett J, Smith PB, Cohen-Wolkowiez M. Innovative clinical trial design for pediatric therapeutics. Expert

Rev Clin Pharmacol. **2011** Sep;4(5):643-52. PubMed PMID: 21980319; PubMed Central PMCID: PMC3184526.

31. Lindner U, Hilgendorff A, Frey G, Gortner L. Drug utilisation in very preterm infants: any changes during the past decade? Klin Padiatr. **2008** Jul-Aug;220(4):238-42. Epub 2008 Apr 9. PubMed PMID: 18401813.

32. McIntosh ED. Paediatric drug development and clinical trials. Adv Exp Med Biol. **2009**;634:153-9. PubMed PMID: 19280857.

33. Mensonides-Harsema M, Otte A. European regulatory framework on the use and development of pharmaceuticals and radiopharmaceuticals for pediatrics. Hell J Nucl Med. **2011** Jan-Apr;14(1):43-8. Review. PubMed PMID: 21512665.

34. Mensonides-Harsema M, Otte A. European regulatory framework on the use and development of pharmaceuticals and radiopharmaceuticals for pediatrics. Hell J Nucl Med. 14 (1) (pp 43-48), **2011**. Date of Publication: January-April 2011. AN: 2011235120

35. Mukattash T, Hawwa AF, Trew K, McElnay JC. Healthcare professional experiences and attitudes on unlicensed/off-label paediatric prescribing and paediatric clinical trials. Eur J Clin Pharmacol. **2011** May;67(5):449-61. Epub 2011 Jan 18. PubMed PMID: 21243345.

36. Napoleone E, Mele G. The FIMP Medicines for Children Research Network. Ital J Pediatr. **2010** Jun 30;36:46. PubMed PMID: 20591168; PubMed Central PMCID: PMC2909954.

37. Napoleone E. Excellence in Family Paediatricians: the FIMP-MCRN (Medicines for Children Research Network) becomes a member of ENPR-EMA (European Network of Paediatric Research at the European Medicines Agency). Ital J Pediatr. **2011** Jan 19;37:7. PubMed PMID: 21247483; PubMed Central PMCID: PMC3037309.

38. Naraynassamy C. Maintaining good clinical research practices in paediatric studies. Paediatric and Perinatal Drug Therapy. 8 (3) (pp 131-133), **2007**. AN: 2008393483

39. Neubert A, Planner C, Cranswick N. The new European regulation on paediatric medicines: safety and ethics perspectives. Paediatr Drugs. **2008**;10(3):147-9. PubMed PMID: 18454567.

40. Pandolfini C, Bonati M, Rossi V, Santoro E, Choonara I, Naylor C, Sammons H, Jacqz-Aigrain E, Zarrabian S, Arnau JM, Castel JM, Danés I, Fuentes I. The DEC-net European register of paediatric drug therapy trials: contents and context. Eur J Clin Pharmacol. **2008** Jun;64(6):611-7. PubMed PMID: 18351329.

41. Pandolfini C, Bonati M. European paediatric research and children's therapeutic needs. A trial review. Acta Paediatr. **2008** Sep;97(9):1232-7. Epub 2008 May 13. Review. PubMed PMID: 18489618.

42. Pandolfini C, Bonati M. Something is moving in European drug research for children, but a more focused effort concerning all therapeutic needs is necessary. Arch Dis Child. **2008** Aug;93(8):715. PubMed PMID: 18644943.

43. Permanand G, Mossialos E, McKee M. The EU's new paediatric medicines legislation: serving children's needs? Arch Dis Child. **2007** Sep;92(9):808-11. Review. PubMed PMID: 17715445; PubMed Central PMCID: PMC2084007.

44. Perucca E. Designing clinical trials to assess antiepileptic drugs as monotherapy: difficulties and solutions. CNS Drugs. **2008**;22(11):917-38. Review. PubMed PMID: 18840033.

45. Pinxten W, Dierickx K, Nys H. Ethical principles and legal requirements for pediatric research in the EU: an analysis of the European normative and legal framework surrounding pediatric clinical trials. Eur J Pediatr. **2009** Oct;168(10):1225-34. Epub 2009 Jan 14. PubMed PMID: 19142660.

46. Prandstetter C, Tamesberger M, Wagner O, Weissensteiner M, Wiesinger-Eidenberger G, Weidinger I, Lechner E. [Medical prescriptions to premature and newborn infants in an Austrian neonatal intensive care unit]. Klin Padiatr. **2009** Sep;221(5):312-7. Epub 2009 Aug 25. German. PubMed PMID: 19707996.

47. Pugsley MK, Gallacher DJ, Towart R, Authier S, Curtis MJ. Methods in safety pharmacology in focus. J Pharmacol Toxicol Methods. **2008** Sep-Oct;58(2):69-71. Epub 2008 Jul 22. PubMed PMID: 18707009.

48. Radziszewska B. European Union regulatory requirements. Front Neurol Neurosci. 2009;25:66-70. Epub **2009** Mar 19. PubMed PMID: 19478499.

49. Rose K. Challenges in pediatric drug development: a pharmaceutical industry perspective. Paediatr Drugs. **2009**;11(1):57-9. PubMed PMID: 19127957.

50. Rose K. Ethical, regulatory and scientific challenges in paediatric drug development. Pharmaceutical Medicine. 22 (4) (pp 221-234), **2008**. AN: 2008447875

51. Rose K. Integration of pediatric aspects into the general drug development process. Ernst Schering Res Found Workshop. **2007**;(59):123-34. Review. PubMed PMID: 17117719

52. Sammons H. Ethical issues of clinical trials in children: a European perspective. Arch Dis Child. **2009** Jun;94(6):474-7. Epub 2009 Feb 10. Review. PubMed PMID: 19208673.

53. Seibert-Grafe M, Butzer R, Zepp F. German Paediatric Research Network (PAED-Net). Paediatr Drugs. **2009**;11(1):11-3. PubMed PMID: 19127943.

54. Sinha G. EU law mandates drug testing in children. J Natl Cancer Inst. 2008 Jan 16;100(2):84-5. Epub **2008** Jan 8. PubMed PMID: 18182609.

55. Smyth AR, Barbato A, Beydon N, Bisgaard H, de Boeck K, Brand P, Bush A, Fauroux B, de Jongste J, Korppi M, O'Callaghan C, Pijnenburg M, Ratjen F, Southern K, Spencer D, Thomson A, Vyas H, Warris A, Merkus PJ. Respiratory medicines for children: current evidence, unlicensed use and research priorities. Eur Respir J. **2010** Feb;35(2):247-65. Epub 2009 Oct 19. Review. PubMed PMID: 19840958.

56. Tafuri G, Trotta F, Leufkens HG, Martini N, Sagliocca L, Traversa G. Off-label use of medicines in children: can available evidence avoid useless paediatric trials? The case of proton pump inhibitors for the treatment of gastroesophageal reflux disease. Eur J Clin Pharmacol. 2009 Feb;65(2):209-16. Epub **2008** Sep 17. PubMed PMID: 18797857; PubMed Central PMCID: PMC2714890.

57. Tassinari M.S, Benson K, Elayan I, Espandiari P, Davis-Bruno K. Juvenile animal studies and pediatric drug development retrospective review: Use in regulatory decisions and labeling. Birth Defects Research Part B - Developmental and Reproductive Toxicology. 92 (4) (pp 261-265), **2011**. AN: 2011467465

58. Thirstrup S, Heisterberg J; Dansk Selskab for Klinisk Farmakologi. [Children on the drug development map. The Danish Society of Clinical Pharmacology]. Ugeskr Laeger. **2008** Mar 17;170(12):1039. Danish. PubMed PMID: 18397657.

59. van Riet-Nales D.A, de Jager K.E, Schobben A.F, Egberts T.C.G, Rademaker C.M. The availability and age-appropriateness of medicines authorized for children in the Netherlands. British Journal of Clinical Pharmacology. 72 (3) (pp 465-473), **2011**. AN: 2011431934

60. van Riet-Nales DA, de Jager KE, Schobben AF, Egberts TC, Rademaker CM. The availability and age-appropriateness of medicines authorized for children in The Netherlands. Br J Clin Pharmacol. **2011** Sep;72(3):465-73. doi: 10.1111/j.1365-2125.2011.03982.x. PubMed PMID: 21477143; PubMed Central PMCID: PMC3175516.

61. van Riet-Nales DA, Schobben AF, Egberts TC, Rademaker CM. Effects of the pharmaceutical technologic aspects of oral pediatric drugs on patient-related outcomes: a systematic literature review. Clin Ther. **2010** May;32(5):924-38. Review. PubMed PMID: 20685501.

62. Vassal G, Will children with cancer benefit from the new European Paediatric Medicines Regulation? European Journal of Cancer **2009**. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19419857 [Accessed May 11, 2009].

63. Vergely C. [Impact of parent organisations in social aspects of cancer childhood care]. Rev Prat. **2007** May 31;57(10):1104-8. French. PubMed PMID: 17844805.

64. Welzing L, Harnischmacher U, Weyersberg A, Roth B. Consequences of Directive 2001/20/EC for investigator-initiated trials in the paediatric population--a field report. Eur J Pediatr. **2007** Nov;166(11):1169-76. Epub 2007 Feb 27. PubMed PMID: 17333274.

65. Westra AE, Engberts DP, Sukhai RN, Wit JM, de Beaufort ID. Drug development for children: how adequate is the current European ethical guidance? Arch Dis Child. **2010** Jan;95(1):3-6. Epub 2009 Mar 25. PubMed PMID: 19321505.

66. Zisowsky J, Krause A, Dingemanse J. Drug development for pediatric populations: Regulatory aspects. Pharmaceutics. 2 (4) (pp 364-388), **2010**. AN: 2011121680

67. Zivkovi Z. [Medicine for children: the European initiative in the regulation of new drugs and clinical studies]. Srp Arh Celok Lek. **2007** Nov-Dec;135 11-12:686-8. Serbian. PubMed PMID: 18368912.

68. Zwaan CM, Kearns P, Caron H, Verschuur A, Riccardi R, Boos J, Doz F, Geoerger B, Morland B, Vassal G. The role of the 'innovative therapies for children with cancer' (ITCC) European consortium. Cancer Treatment Reviews. 36 (4) (pp 328-334), **2010**. AN: 2010311369

Publications cited in the report

1. Bailey GP and Marien D. What have we learned from pre-clinical juvenile toxicity studies? Reprod Toxicol 28, 226-229, **2009**.

2. Boos J. Off label use - label off use? Annals of Oncology 14, 1-5, **2003**. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12488285 [Accessed May 18, 2010].

3. Choonara I. Clinical trials of medicines in children. BMJ 321, 1093-1094, **2000**. Available at: http://www.bmj.com/content/321/7269/1093 [Accessed March 19, 2012].

4. Conroy S. et al. Survey of unlicensed and off label drug use in paediatric wards in European countries. BMJ 320, 79-82, **2000**. Available at: http://www.bmj.com/cgi/content/abstract/320/7227/79 [Accessed April 20, 2010].

5. Dunne J et al. Extrapolation of Adult Data and Other Data in Pediatric Drug-Development Programs. Pediatrics **2011**. Available at: http://pediatrics.aappublications.org/content/early/2011/10/20/peds.2010-3487.abstract [Accessed October 27, 2011].

6. EMA. European Medicines Agency policy on the handling of potential conflicts of interest. **2012**. Available at: http://bit.ly/Im5CxQ

7. EMA. Guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications. EMEA/CHMP/SWP/169215/2005, **2008**. Available at: http://bit.ly/JuYQCB [Accessed January 30, 2012]

8. EU Ethical considerations. Ethical considerations for clinical trials on medicinal products conducted with the paediatric population (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). **2008**. Available at: http://ec.europa.eu/health/files/eudralex/vol-10/ethical_considerations_en.pdf [Accessed March 19, 2012]

9. European Commission. Communication from the Commission - Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies (2008/C 243/01, Official Journal C 243, 24/9/2008 p. 1 - 12), **2008**. Available at: http://ec.europa.eu/health/files/eudralex/vol-1/com_2008_jo243/com_2008_243_en.pdf [Accessed March 19, 2012]

10. European Commission. Guideline on Excipients in the label and package leaflet of medicinal products for human use. ENTR/F2/BL D(2003), **2003**. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003412.pdf [Accessed January 30, 2012]

11. European Commission: A guideline on summary of product characteristics (SmPC) September 2009, **2009**. Available at: http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf

12. European Medicine Agency. List of paediatric networks at the (EMA), **2011**. Available at: http://bit.ly/IC21ur

13. Grant B. Are the Kids Alright? The Scientist, **2012**. Available at: http://the-scientist.com/2012/03/01/are-the-kids-alright/ [Accessed March 7, 2012].

14. ICH Topic E 11 Clinical investigation of medicinal products in the paediatric population. CPMP/ICH/2711/99, **2001**. Available at http://bit.ly/Il3gOG

15. IOM Committee on Pediatric Studies Conducted Under the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) & Board on Health Sciences Policy. Safe and Effective Medicines for Children: Pediatric Studies Conducted Under BPCA and PREA - Institute of Medicine. **2012.** Available at: http://www.iom.edu/Reports/2012/Safe-and-Effective-Medicines-for-Children.aspx [Accessed March 2, 2012].

16. Mukattash T et al. Healthcare professional experiences and attitudes on unlicensed/off-label paediatric prescribing and paediatric clinical trials. European Journal of Clinical Pharmacology, 67, 449–461, **2011**.

17. Regulation (EC) no 1901/2006 of the European parliament and of the Council of 12 December2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004. Official Journal of the European Union **2006**; L 378: 1-19. Available at: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf

18. Ruperto N, Eichler I, Herold R et al. A European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA). Arch Dis Child doi, **2011**: 10.1136/archdischild-2011-300286

19. Sukkar E. European researchers are urged to do more trials in children, conference hears. BMJ, 344, p.e2350, **2012**. Available at: http://www.bmj.com/content/344/bmj.e2350?etoc= [Accessed March 30, 2012].

20. The European paediatric initiative: History of the Paediatric Regulation. EMEA/17967/04 Rev 1, **2007**. Available at: http://bit.ly/ItcM09

21. Thorat C et al. What the Orphan Drug Act Has Done Lately for Children With Rare Diseases: A 10-Year Analysis. Pediatrics, **2012**. Available at: http://pediatrics.aappublications.org/content/early/2012/02/22/peds.2011-1798 [Accessed February 29, 2012].

22. Vollono C et al. Triptans other than sumatriptan in child and adolescent migraine: literature review. Expert Review of Neurotherapeutics 11, 395–401, **2011**.

11. Glossary/Abbreviations

- Age groups: newborns: from birth to 28 days of age, infants: from 1 month to less than 12 months, toddlers: from 1 year to less than 2 years of age, children: from 2 years to less than 12 years, adolescents: from 12 years to less than 18 years (see also "Paediatric population" below, reference: ICH E11)
- CT: clinical trial as defined in Directive 2001/20/EC
- EudraCT: European Union drug regulating authorities' clinical trials database. Public access is via the "EU Clinical Trials Register", https://www.clinicaltrialsregister.eu/
- EuTCT: European Union Telematics Controlled Terms System, http://eutct.ema.europa.eu/
- Paediatric population: the population aged between birth and 18 years (Article 2.1)
- PUMA: Paediatric use marketing authorisation, with Article 30 of Regulation (EC) 1901/2006 in conjunction with Article 8(3) of Directive 2001/83/EC, as amended, as the legal basis for the marketing authorisation
- SmPC: Summary of Product Characteristics. In case of variations of the SmPC, new paediatric data are to be reflected in SmPC section(s) 4.5, 4.8, 5.1 and / or 5.2. Recommendations in relation to any paediatric use are in section(s) 4.1, 4.2 and / or 4.4. The SmPC has the following sections:
  - Section 4.1 Indication(s)
  - Section 4.2 Posology and method of administration
  - Section 4.4 Special warnings and precaution for use
  - Section 4.5 Interactions
  - Section 4.8 Undesirable effects
  - Section 5.1 Pharmacodynamics properties
  - Section 5.2 Pharmacokinetic properties
- US BPCA and PREA legislation: Best Pharmaceuticals for Children Act and Pediatric Research Equity Act

12. Indicators used for this report

The following indicators were agreed in 2011 with the European Commission.

12.1. Better and safer research and development

1. Number of Clinical trials (CTs):
    1.1. requested by the PDCO as a result of the assessment of a PIP and that were not initially proposed in the PIP at the time of submission
    1.2. suppressed from the PIP upon request from PDCO
2. Number of juvenile toxicity studies requested by the PDCO as a result of the assessment of a PIP and that were not initially proposed in the PIP at the time of submission / number of juvenile toxicity studies suppressed from the PIP upon request from PDCO
3. Decrease in number of children to be included in CTs upon request from PDCO further to the assessment of PIP
4. Number of scientific advices given at National and EMA level for paediatric use only, or for paediatric and adult use
5. Comparison between 2010 and 2011 to see if PIP are submitted earlier in the development
6. List of funding at National level and at EU level (DG Research)
7. Development of the paediatric network according to Article 44 of the paediatric regulation
8. Number of publications and workshops on paediatric aspects published by the EMA / EMA staff
9. EudraCT: number of CTs stopped and reason, number of CTs conducted in EU or outside of EU

12.2. More medicines available for children in the EU

1. Number of new products authorised, with Paediatric indication only or paediatric and adult indication
2. Number of variations to extend the therapeutic indication to include paediatric population
3. Number of article 29 referrals to extend the therapeutic indication to include paediatric population
4. Number of PIPs for a later PUMA agreed
5. Number of annex II procedure to add a new paediatric pharmaceutical form or a new route of administration for children
6. Number of products with new paediatric information in the dosage recommendation section of the SmPC (section 4.2)
7. List of medicines available for children as prepared according to Article 42 of the paediatric regulation
8. List of therapeutic needs for children as prepared according to Article 43 of the paediatric regulation. A link between these identified therapeutic needs and new paediatric indications granted could be done in the report.
9. Off label use could be investigated liaising with Member States, academia.

12.3. More information on children in the SmPC

1. Number of statements on deferrals and waivers included in the SmPC
2. Number of variations leading to additional information on paediatric population in SmPC including and identifying number of Article 45 and 46 of the paediatric regulation leading to a change in the SmPC
3. Number of assessments according to of Article 45 and 46 of the paediatric regulation performed even if not leading to changes in the SmPC

- Number of failure to show any paediatric indication according to Article 36 of the paediatric regulation that leads to information added in the SmPC

13. Description of methods and data sources for the report

Unless stated otherwise, data on Paediatric investigation plans (PIPs) and waivers refer to EMA Decisions, excluding withdrawn applications or prematurely terminated procedures for agreement of a PIP and / or a waiver. Modifications of PIPs do not count as another EMA Decision. Data on PIPs and waivers are presented by the year of the PDCO opinion. In principle, there is one EMA Decision for one PDCO opinion on one application for agreement of a PIP and / or waiver. The number of EMA Decisions, however, is higher than the number of different active substances, because duplicate applications can be made for the same active substance. Separate applications were also made, for example, for conditions that were and those that were not orphan designated. Second and subsequent applications account for only 13% of all EMA Decisions. Therefore the report uses the number of all applications and EMA Decisions as denominator, recognising this may change in future reports.

Some analyses specially consider or exclude 118 "allergen products" (allergen extract products for the specific immunotherapy of allergic rhinitis and rhinoconjunctivitis), for which a high number of applications were handled in 2009 and 2010 subsequent to a change of pharmaceutical law in a Member State (Germany) (see Eichler and Soriano, 2011, and http://bit.ly/znsbX8).

The survey queries to Member States and National Patent Offices are provided in the annexes.

Data from EudraCT are based on data submitted in the Clinical Trial Authorisation (CTA) application form (EudraLex Vol. 10, Chapter I, http://bit.ly/b54eUC), fields A.7, E.7, F.1.1.2 to F.1.3, F.4.

14. Additional data: Historical situation for medicines for children by 2006

Figure 4: Case example on lack of availability of centrally authorised medicines for paediatric oncology

Through the centralised procedure, 29 new anti-cancer medicines were authorised between December 2000 and January 2007, for the treatment of 21 different diseases.

- For the 7 of the diseases that occur in adults and children, 6 out of the 7 medicines have a paediatric indication.
- 18 out of the 23 medicines without a paediatric indication have a paediatric interest, based on a clinical or strong biological and / or non-clinical rationale, and should be evaluated in the paediatric population.

Source: modified from (Vassal 2009)

15. Additional data: Better and safer research with children

15.1. Number of agreed PIPs

Table 13: Number of agreed PIPs addressing therapeutic areas

Therapeutic area addressed	**2008**	**2009**	**2010**	**2011**	**Sum**
Infectious Diseases	4	22	29	33	88
Endocrinology-Gynaecology-Fertility-Metabolism	4	23	21	32	80
Immunology-Rheumatology-Transplantation	4	19	26	28	77
Oncology	6	17	12	33	68
Vaccines	4	18	21	21	64
Pneumology-Allergology	3	10	108*	35*	156
Cardiovascular Diseases	7	16	11	20	54
Haematology-Haemostaseology	1	7	19	24	51
Dermatology	1	9	16	13	39
Neurology	3	6	11	15	35
Gastroenterology-Hepatology	5	4	14	10	33
Psychiatry	2	4	4	10	20
Pain	1	11	2	5	19
Uro-nephrology		3	7	8	18
Other	1	4	10	5	19
Oto-rhino-laryngology		2	1	10	13
Ophthalmology	1	4	4	3	12
"Neonatology"** - Paediatric Intensive Care		2	3	3	8
Diagnostic use		2		3	5

Source: EMA Paediatric Business database using query. * Including 118 allergen products (Eichler and Soriano 2011) ** Applications that specifically address a use in neonates or in paediatric intensive care, only; PIPs agreed for other therapeutic areas however may also include neonates in the development.

15.2. Scientific advice

Summary of Scientific Advices provided by the MEA:

- Questions related to paediatric development were addressed in 133 EMA Scientific Advice procedures (including follow-up advices and Protocol Assistance). Number of such advices per year: 21 (2007), 23 (2008), 30 (2009), 32 (2010) and 27 (2011)
- Approximately 70 companies benefited from the European Medicines Agency free paediatric Scientific Advice during the years 2007 through 2011. Out of the 133 advices, 24 were obtained by a small, micro or medium-sized enterprise (SME) company.

In Table 14, the phases of the clinical development may refer to the stage of the adult development, even if the majority of paediatric related SAs were for paediatric-only questions, because almost all of the advices were for medicines developed for both adult and paediatric use.

It appears that advice is asked increasingly later during the development, which could be speculated to be the result of the PDCO evaluation of a proposed PIP taking place earlier in the overall development.

Table 14: Scientific advices (SA) and Protocol Assistances (PA) provided by the EMA SAWP per year

Number	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**
Reference: Scientific advices in total	201	214	265	311	332	355
Reference: Protocol assistance in total	58	73	56	77	68	78
Reference: Sum of above	259	277	321	388	400	433
Paediatric only, SA	NA	14	13	14	19	21
Paediatric only, FU SA	NA	4	5	9	4	2
Paediatric only, PA	NA	0	5	4	6	3
Paediatric only, FU PA	NA	3	0	3	3	1
"Mixed" (Paediatric and adult), SA	NA	NA	6	21	25	12
Mixed, FU SA	NA	NA	1	8	6	7
Mixed, PA	NA	NA	1	12	12	7
Mixed, FU PA	NA	NA	1	3	5	4
Sum of paediatric-only and mixed advices and follow-up advices	NA	21	32	74	80	57
Paediatric quality issues	ND	7	7	7	13	6
Paediatric pre-clinical issues	ND	15	12	22	16	13
"Paediatric population" issue in development	ND	17	20	21	27	23
Paediatric only, SA+FU+PA+FU, Phase I	NA	3	7	4	8	1
Paediatric only, SA+FU+PA+FU, Phase II	NA	4	10	9	11	5
Paediatric only, SA+FU+PA+FU, Phase III	NA	9	15	15	14	10
Paediatric only, SA+FU+PA+FU, Phase IV	NA	0	1	2	5	0

Source: EMA Scientific Advice database. ND = Not documented

15.3. Guidelines

Summary:

- The PDCO contributed to the development and publication of 12 guidelines
- Some guidelines already included sections that specifically addressed the development for use in children; for others, the PDCO developed paediatric addenda to address the recommendations for paediatric development

Table 15: EMA Guidelines in which the PDCO was involved

Publication date	Title	Document reference
22/01/2009	Requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD) in adults and for use in the treatment of asthma in children and adolescents	CPMP/EWP/4151/00 Rev. 1
25/06/2009	Guideline on the Investigation of medicinal products in the term and preterm neonate	
01/11/2009	Guideline on the Clinical Development of Medicinal Products for the Treatment of Cystic Fibrosis	CHMP/EWP/9147/08
01/01/2010	Addendum to the note for guidance on evaluation of medicinal products indicated for treatment of bacterial infections to specifically address the clinical development of new agents to treat disease due to Mycobacterium tuberculosis	CHMP/EWP/14377/08
01/01/2010	Guideline: Reflection Paper On Ethanol Content In Herbal Medicinal Products	EMA/HMPC/85114/2008
01/01/2010	Clinical investigation of medicinal products in the treatment of epileptic disorders	CPMP/EWP/566/1998 Rev. 2 Corrigendum
01/03/2010	Guideline on Alcohol Dependence after public consultation as well as an overview of the comments on this GL	CHMP/EWP/20097/2008
01/07/2010	Clinical investigation of medicinal products for the treatment of attention-deficit/hyperactivity disorder (ADHD)	CHMP/EWP/431734/2008
01/02/2011	Guideline on medicinal products for the treatment of insomnia	EMA/CHMP/16274/2009
01/08/2011	Guideline on clinical investigation of recombinant and human plasma-derived factor IX products	CHMP/BPWP/144552/09
01/08/2011	Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products	CHMP/BPWP/144533/09
01/08/2011	Guideline on the treatment of Premenstrual Dysphoric Disorder	EMA/CHMP/607022/2009

Publication date	Title	Document reference
01/09/2011	Reflection paper on the necessity of initiatives to stimulate the conduct of clinical studies with herbal medicinal products in the paediatric population	EMA/HMPC/833398/2009
01/02/2012	Paediatric addendum to the CHMP guideline on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension	CHMP/EWP/213972/10

15.4. Clinical trials with the paediatric population

Table 16: Overview of clinical trials with the paediatric population by year of authorisation (or, if not available, by the year of upload of the protocol-related data into EudraCT)

Number of	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**
Paediatric trials (trials with the paediatric population)	251	310	354	340	402	374	302
Paediatric trials planned as							
• Phase 1	17	18	23	25	30	50	28
• Phase 2-4	227	286	336	310	365	324	281
• Controlled (various types of control)	186	226	250	240	268	244	189
• Active controlled	40	33	56	59	60	85	42
• Placebo controlled / placebo use	85	92	103	107	117	93	91
Paediatric trials planned to be conducted							
• in EEA only	171	220	229	243	271	232	169
• in and outside of EEA	80	90	125	97	131	142	133
• only outside of EEA					1		
Reference: All trials (adults, elderly and / or children)	3314	3912	4734	4495	4412	4002	3488

Source: EudraCT using pre-defined query counting the first authorised trial only, in case of conduct in more than one Member State. Data were uploaded by the National Competent Authorities.

It was assumed that the extraordinary high number of adult participants planned to be enrolled (Table 6) could correspond to large post-authorisation (Phase 4) trials and pharmaco-epidemiological studies that were uploaded into EudraCT, but may not have required authorisation. The following table has been created excluding all entries in EudraCT that were only marked as "phase 4" trials.

Table 17: Number of subjects planned to be enrolled in clinical trials registered in EudraCT. As Table 6, but excluding trials marked as "phase4" only.

Number of subjects	2005	2006	2007	2008	2009	2010	2011	2012
Preterm newborns					22		1,059	
Newborns			98		59	6	184	24
Infants and toddlers	13	330	98	15	54,560	1,847	7,629	1,390
Children	163	1,810	248	178	869	845	14,203	1,379
Adolescents	183	50	85	129	1,449	1,276	14,964	810
Sum of above	**359**	**2,190**	**529**	**322**	**56,959**	**3,974**	**38,039**	**3,603**
Reference: in utero			98				210	
Reference: adults including elderly	5,003	9,834	49,642	14,555	85,298	98,116	408,396	56,877

15.5. Analysis of clinical trials with the neonatal population in applications and PDCO opinions agreeing paediatric investigation plans

Material and methods: A retrospective analysis of the opinions for Paediatric Investigation Plans (PIPs) adopted by the PDCO from 2007 until end of 2011 (first opinion adopted in January 2008), was performed.

Opinions represent complete data sets without missing data. Applications withdrawn before opinion were not included in the analysis of outcomes. Applications which failed the validation step were not included in the analysis. Duplicates of medicines share a single development, therefore in these cases a single PIP was considered in our analysis. As the opinion is produced several months after the application, the starting date for the analysis of opinions was 23 January 2008, including the very first opinions adopted under this legislation, seven months after the establishment of the Paediatric Committee; the cut-off date is 31 December 2011.

We analysed, to which extent the neonatal age group was covered in agreed PIPs. It was analysed for how many PIP-opinions the PDCO had requested the inclusion of neonates in the clinical development programme where initially the applicants had requested a waiver for that age group. It was analysed which types of studies the PDCO asked that neonates were investigated in. In particular it was looked at, which types of studies neonates were asked to be enrolled in, when initially a waiver for that age group had been requested.

In addition, a closer look was taken at more specific clinical trial parameters proposed to and requested by the PDCO for the procedures that reached an opinion during the first 10 months between 23 January 2008 and 17 October 2008 and during the latest 10 months between March 2011 and December 2011. The content of scientific opinions adopted by the Paediatric Committee was compared to the proposals submitted by industry. We analysed the changes in the age groups to be included, changes to the need for randomisation, changes to blinding, and inclusion of an active or a placebo comparator.

First, global results are presented in section 4.2. of the core report.

Table 18: Sum of number of studies with neonates required in PDCO opinions per year of opinion, presented by type of study for PIP applications proposing a study or a waiver for neonates. A PDCO opinion can have more than one study with neonates.

Number of types of studies with neonates required in PDCO opinions	**Sum**
PK (PD) and tolerability studies	
• application proposed any neonate study	34
• application proposed waiver for neonates	24
Controlled safety and efficacy studies	
• application proposed any neonate study	32
• application proposed waiver for neonates	15
Non-controlled safety and activity studies	
• application proposed any neonate study	15
• application proposed waiver for neonates	9

Table 19: Jan-Oct 2008: Age groups which were covered by PIP applications, additionally requested by the PDCO and eventually covered in PDCO opinions (adapted from Olski et al., 2011 REF)

Age group	**Covered in PIP application**	**Additionally requested by PDCO**	**Covered in PDCO opinion**
12 to less than 18 years	76% (41/54)	7¥	81% (44/54)
6 to less than 12 years	67% (36/54)	7	74% (40/54)
2 to less than 6 years	46% (25/54)	5	54% (29/54)
Subset of 2 to less than 6 years	9% (5/54)	3	13% (7/54)
28 days to less than 2 years	28% (15/54)	7*	35% (19/54)
Subset of 28 days to less than 2 year	17% (9/54)	3	17% (9/54)
Birth to less than 28 days	15% (8/54)	7	26% (14/54)

¥ in 1 PIP, the PDCO requested to cover the entire age group instead of only a subset of the age group
* in 3 PIP, the PDCO requested to cover the entire age group instead of only a subset of the age group

Table 20: Mar-Dec 2011: Age groups which were covered by PIP applications, additionally requested by the PDCO and eventually covered in PDCO opinions

Age group	**Covered in PIP application**	**Additionally requested by PDCO**	**Covered in PDCO opinion**
12 to less than 18 years	79% (65/82)	2	80% (66/82)
6 to less than 12 years	87% (71/82)	5	93% (76/82)
2 to less than 6 years	87% (62/82)	4	80% (66/82)
28 days to less than 2 years	44% (36/82)	7	50% (41/82)
Birth to less than 28 days	24% (20/82)	6	32% (26/82)

When initially a study comprised the neonatal age group as part of a larger trial that encompassed many age groups, the request for modification by the PDCO could have resulted in a separation of the trial and the request for a trial specifically for the neonatal age range. This could not be analysed specifically. However, based on the data collected, an attempt was made to estimate in how many cases the neonatal age group was part of a larger trial encompassing older patients and in how many cases separate trials for neonates exclusively were part of the opinion. This data was retrieved for analysis also subdivided by size of the trial.

However, as a qualitative finding, there were a number of medicine developments for which the PDCO required to study neonates separately from older children, in an additional study exclusively for neonates, even though the PIP application proposed to study these age groups together in a single study.

For the number of newborns that were requested per study, there is no apparent pattern that they were enrolled particularly in large or small trials when looking at the entire time span 2008-2011.

There is also no clear trend towards inclusion into larger or smaller trials, when looking at PIP-opinions where a waiver initially requested for newborns.

Study design features such as blinding and type of control were compared between PIP proposals by applicants and PDCO opinions, analysing all age groups during the same time periods used in the preceding section (Jan-Oct 2008 and Mar-Dec 2011).

The requests of the PDCO appear to remain consistent over time, however with a slight decrease in active-controlled trials during the last 10 months compared to the first 10 months, including 2 dose-comparative parallel-group trials.

Table 21: Jan-Oct 2008: Number of trials for specific design features as proposed by the applicants and as additionally required in PDCO opinion (Olski et al. EJCP, 2011 REF)

Number of trials	**Proposed by applicant**	**Additionally required in PDCO opinion**	**Sum**
Double-blind	33 (53%)	11 (47.8%)	44 (52%)
Placebo control	12 (19%)	12 (52.2%)	24 (28%)
Active control	35 (57%)	6 (26.1%)	41 (48%)
Active and placebo control	4 (7%)	0	4 (5%)
Sum	62 (100%)	23 (100%)	85 (100%)

Table 22: Mar-Dec 2011: Number of trials for specific design features as proposed by the applicants and as additionally required in PDCO opinion

Number of trials	**Proposed by applicant**	**Additionally required in PDCO opinion**	**Sum**
Double-blind	70 (34%)	9 (15%)	79 (32%)
Blinded	86 (42%)	22 (36%)	101 (41%)
Placebo control	55 (27%)	10 (16%)	65 (27%)
Active control	38 (18%)	11 (18%)	50 (20%)
Active and placebo control	3 (1%)	2 (1%)	5 (2%)
Sum	207 (100%)	61 (100%)	245 (100%)

However, when following the number of neonates included in trials over the last 4 years, there appears to be a trend from 2008 towards 2011 of including a larger number of newborns in trials, in particular, when looking at the number of neonates included in 2011.

Is the increased number of newborns enrolled especially in 2011 a result of proposals by applicants or a result of requests from the PDCO? The detailed analysis of applications vs. opinions in 2011 (Mar-Dec) supports the notion that the PDCO's requests to companies played a significant part in enrolling more newborns in larger trials. The PDCO increased the number of trials with more than 100 neonates from 5 to 7. It increased the number of trials with 11 to 50 neonates from 0 to 3.

Table 23: Number of newborns included in studies as proposed and agreed by the PDCO (from Mar-Dec 2011). The values for the number of neonates are separated depending on how the age range was specified in the opinion

	0-28 days	**0-2 yrs***	**0-6 yrs***	**0-12 yrs***	**0-18 yrs***
As proposed by applicants					
1-10 patients	0	1*	2*	0	0
11-20 patients	0	3*	6*	2*	0
21-50 patients	0	2*	4*	0	2*
51-100 patients	0	0*	0	2*	0
> 100 patients	5	0*	0	0	4*
In opinions agreed by PDCO					
1-10 patients	0	3*	1*	0	0
11-20 patients	1	3*	7*	0	1*
21-50 patients	2	1*	7*	0	2*
51-100 patients	0	0	0	0	1*
> 100 patients	7	0	0	0	5*

*: These fields contain more than just the neonatal age group, as a broader age range was specified in the opinion.

15.6. List of projects on off patent medicines funded by the European Commission through the EU Framework programme

Health: area 4.2 results, Off-patent medicines calls 2, 3, 4 and 5.

- HEALTH-2007-4.2-1 Adapting off-patent medicines to the specific needs of paediatric populations
- HEALTH-2009-4.2-1 Adapting off-patent medicines to the specific needs of paediatric populations
- HEALTH.2010.4.2-1 Off-Patent Medicines for Children. FP7-HEALTH-2010-single-stage
- HEALTH-2011.4.2-1 Investigator-driven clinical trials on off-patent medicines for children

Table 24: Funded off patent medicines projects (start up to 01 January 2012) and agreed PIPs, if available. Information on the projects is available on this web page: http://bit.ly/wUPuOb. Agreed PIPs for active substances addressed in projects are available via this web page: http://bit.ly/xTshyn.

No.	Acronym	Year start	Objectives (active substance[s] in bold)	Agreed PIP
1	KIEKIDS	2011	To develop an innovative, age-adapted, flexible and safe paediatric formulation of **ethosuximide** for the treatment of absence and of myoclonic epilepsies in children	NA
2	NEO-CIRC	2011	To provide safety and efficacy data for **dobutamine**, to perform pre-clinical studies, to develop biomarker of hypotension and to adapt a formulation for newborns	NA
3	TAIN	2011	To develop a neonatal formulation of **hydrocortisone** for the treatment of congenital and acquired adrenal insufficiency and for use in oncology (brain tumours and leukaemia)	NA
4	DEEP	2010	To evaluate PK & PD of **deferiprone** in in 2-10 years old children in order to produce an approved Paediatric Investigational Plan to be used for regulatory purposes	EMEA-001126-PIP01-10
5	HIP Trial	2010	Evaluates the efficacy safety, PK, PD of **adrenaline** and **dopamine** in the management of neonatal hypotension in premature babies and to develop and adapt a formulation of both suitable for newborns in order to apply for a Paediatric Use Marketing Authorisation (PUMA)	EMEA-001105-PIP01-10
6	TINN2	2010	To evaluate PK & PD of **azithromycin** against urea plasma and in BPD in neonates.	NA
7	NEMO	2009	Evaluates the efficacy safety, PK, PD, mechanisms of action of **bumetanide** in neonatal seizures, including the effect on neurodevelopment and to develop and adapt a bumetanide formulation suitable for newborns in order to apply for a Paediatric Use Marketing Authorisation (PUMA).	NA
8	NeoMero	2009	European multicentre network to evaluate pharmacokinetics, safety and efficacy of **meropenem** in neonatal sepsis and meningitis	EMEA-000898-PIP01-10
9	PERS	2009	Focuses on two indications, the use of **risperidone** in children and adolescents with conduct disorder who are not mentally retarded, and the use of risperidone in adolescents with schizophrenia	EMEA-001034-PIP01-10
10	EPOC	2008	To evaluate pharmacokinetics and pharmacodynamics of	NA

No.	Acronym	Year start	Objectives (active substance[s] in bold)	Agreed PIP
			doxorubicin	
11	LOULLA & PHILLA	2008	Development of oral liquid formulations of **methotrexate** and 6-**mercaptopurine** for paediatric acute lymphoblastic leukaemia (ALL).	NA / NA
12	NeoOpioid	2008	Compares **morphine** and **fentanyl** in pain relief in pre-term infants	EMEA-000712-PIP01-09
13	NEUROSIS	2008	Efficacy of **budesonide** (BS) in reducing bronchopulmonary dysplasia (BPD)	EMEA-001120-PIP01-10
14	O3K	2008	Oral liquid formulations of **cyclophosphamide** and **temozolomide**	EMEA-000530-PIP02-11 / NA
15	TINN	2008	Aims to evaluate PK & PD of **ciprofloxacin** and **fluconazole** in neonates	NA

NA = Not available

- HEALTH.2011.2.3.1-1 Investigator-driven clinical trials of off-patent antibiotics

Table 25: Investigator-driven clinical trials of off-patent antibiotics

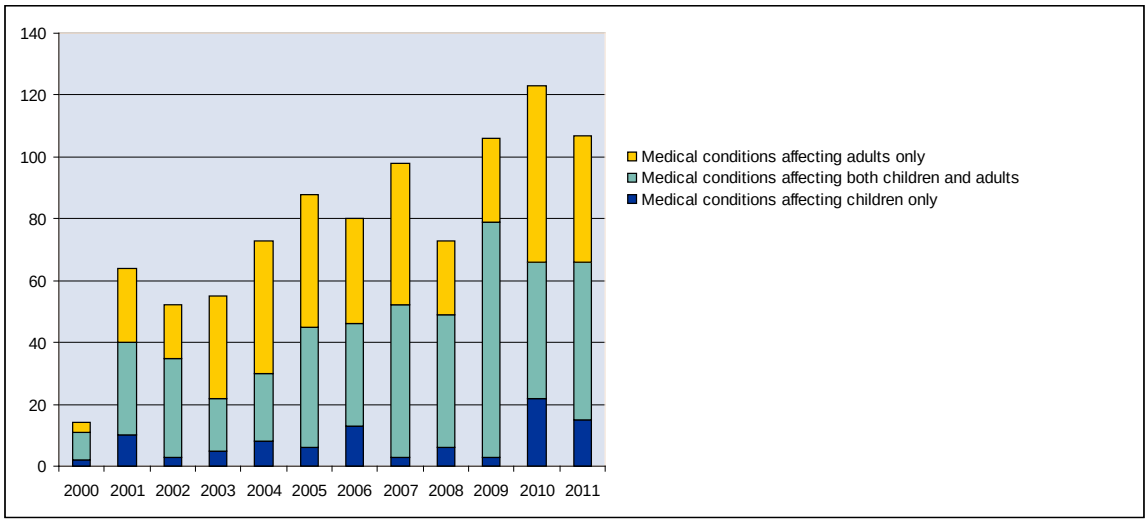
No.	Acronym	Year start	Objectives (active substance[s] in bold)	Agreed PIP
1	MAGICBULLET	2012	Optimisation of treatment with off-patent antimicrobial agents of ventilator-associated pneumonia (VAP)	NA
2	AIDA	2011	Assessment of clinical efficacy by a pharmacokinetic / pharmacodynamic approach to optimise effectiveness and reduce resistance for off-patent antibiotics	NA

NA = Not available

16. Additional data: More medicines available for children in the EU

16.1. Orphan medicine designation for paediatric uses

Figure 5: Total number of orphan designated medicines by year



16.2. Paediatric medicine development in PIPs correlated with survey of all paediatric uses

Table 26: Therapeutic needs in the paediatric population according to the Survey of all paediatric uses (EMA/794083/2009) and projects addressing the needs

Paediatric therapeutic area	**Paediatric use**	**Active substance / class of substances**	**Addressed by (FP6, FP7, PIP etc.)**	**Comments**
Infectious diseases	Treatment of bacterial infections in very young children	• Macrolides • Betalactamines plus beta-lactamase inhibitors • Carbapenems	• No PIP • No PIP • Doripenem (EMEA-000015-PIP01-07)	PIPs agreed for quinolones
Cardiovascular diseases	Treatment of hypertension (primary and seconddary)	• Renin-angiotensin inhibitors • Beta-blocker	• Aliskiren (EMEA-000362-PIP01-08), Alizisartan (EMEA-000237-PIP01-08), Candesartan (EMEA-000023-PIP01-07) • No PIP	
Cardiovascular diseases	Treatment of arrhythmia	• Antiarrhythmics	• No PIP	
Gastroenterology	Treatment of reflux disease	• Proton pump inhibitors • H2-receptor antagonists	• Rabeprazole (EMEA-000055-PIP01-07), esmeprazole (EMEA-000331-	

Paediatric therapeutic area	Paediatric use	Active substance / class of substances	Addressed by (FP6, FP7, PIP etc.)	Comments
			PIP01-08) • No PIP	
Pulmonology / respiratory medicine	Treatment of asthma	• Antiasthmatics (including montelukast, salbutamol)	• Montelukast (EMEA-000012-PIP01-07) • Tulobuterol (EMEA-000763-PIP01-09)	PIPs agreed for long acting beta agonists
Psychiatry	Treatment of depressive disorder	• Selective serotonin reuptake inhibitors • Serotonin-norepinephrine reuptake inhibitors • Tricyclic antidepressants	• No PIP • Desvenlafaxine (EMEA-000523-PIP01-08, waiver) • No PIP	Others: LUAA21004 (EMEA-000455-PIP02-10)
Dermatology	Treatment of atopic eczema	• Glucocorticosteroids, topical use	• No PIP	
Endocrinology	Prevention of pregnancy	• Oral contraceptives	9 unique PIPs agreed (EMEA-000148-PIP01-07, EMEA-000305-PIP01-08, EMEA-000475-PIP01-08, EMEA-000474-PIP01-08, EMEA-000250-PIP01-08-M01, EMEA-000518-PIP01-08, EMEA-000526-PIP01-08, EMEA-000546-PIP01-09, EMEA-000606-PIP01-09, EMEA-000658-PIP01-09, EMEA-000305-PIP01-08-M01, EMEA-000250-PIP01-08-M02, EMEA-000305-PIP01-08-M02)	
Endocrinology	Various uses	• Dexamethasone, systemic use	• No PIP	
Endocrinology	Not specified	• Multivitamin preparations	• No PIP	

16.3. Survey on all existing paediatric uses

One of the legal requirements of the Paediatric Regulation was the collection of available data on all existing uses of medicinal products in the paediatric population. In accordance with Article 42 of the Regulation, the PDCO/EMA requested data from the 27 EU Member States2. The 3 EEA states which are not EU Member States (Iceland, Norway and Liechtenstein) were also invited to provide data.

The majority of the submitted data focused on the existing off-label use in children; the few datasets referring to the existing authorised use of medicines are therefore difficult to extrapolate.

The analysis of these data was subject to a number of limitations, due to format heterogeneity in the submitted data from different Member States, many datasets could only be considered representative for specific paediatric subsets in the different individual countries (e.g. only OTC setting, only hospital, different age groups not equally covered etc.). Some Member States did not submit any data. Several datasets used the terms authorised, unauthorised and off-label use in different definitions. Most datasets could not link the use to treatment of a specific condition.

Both hospitalised children and out-patients are frequently treated with medicines used outside the terms of their marketing authorisation. Higher rates were reported in the premature (up to 90% of prescribed medication) and term neonates and in infants, as well as in patients having serious conditions and being admitted in the intensive care units (both neonates and paediatric). Medicines are mainly used "unapproved" for the treatment of children, with lower figures for prophylactic uses. Not surprisingly, there are differences with regard to the unapproved medicines use across the EU, partially explained by different prescribing habits, but also by the regulatory status (approved or not, in all or some subsets) of the medicinal product in different countries.

The most frequent medicines used off-label and unauthorised belong to the following therapeutic classes: anti-arrhythmics, antihypertensives (rennin-angiotensin inhibitors and beta-blockers), proton pump inhibitors and H2-receptor antagonists, antiasthmatics, and antidepressants (mainly selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and tricyclic antidepressants). A high rate of off-label use of oral contraceptives was encountered in adolescents, mainly reported in Scandinavia. There is extensive off-label use of antimicrobials (macrolides, beta-lactamines plus beta-lactamase inhibitors and carbapenems) in very young children. Corticosteroids (dexamethasone) are frequently reported to be used off-label in the systemic treatment of very young children. Some steroids for systemic use (e.g. dexamethasone) are not even authorised in some countries (Norway). Most other steroids used off-label in children were topical medicines for dermatologic use. There is a need for clinical trials and supporting evidence for safety and efficacy of anti-asthmatics in children, especially since long term safety concerns were recently reported for the long-acting beta agonists (LABA). This is all the more important as asthma affects principally children. The use of anti-infectives requires supportive evidence in the younger age groups. Although scarce, the data submitted confirm that the neonates, in particular preterm neonates, have high unmet needs. The future will have to address those needs through dedicated trials despite the feasibility issues.

The analysis of the pharmaceutical forms shows that both oral and parenteral formulations are being used unauthorised or off-label, pointing out at a common reason which is the lack of appropriate dosages and strengths for the treated age groups.

EMA/PDCO assembled a comprehensive report on this data which is also available on the EMA website. This review is not exhaustive and analysed very heterogeneous data. However, it is clear there are wide unmet needs everywhere in Europe. The outcome does not provide sufficient information on safety.

These data among others are currently also used to revise the inventory of paediatric therapeutic needs in the Paediatric Inventory Working Group of PDCO. This effort is aiming to update information to fulfil the requirements of Article 43 of the Paediatric Regulation, that is, to define research priorities to improve information on use of medicines in paediatrics based on prevalence, seriousness and availability and suitability of alternative treatments.

[2] http://www.ema.europa.eu/pdfs/human/paediatrics/5756962007en.pdf

17. Additional data: Increased information on medicines used in children

17.1. EMA / PDCO workshops on paediatric medicine development

The slides presented for discussion and outcomes are available here: http://bit.ly/H5Fx4W.

Table 27: Scientific workshops conducted specifically on the development of paediatric medicines

No.	Topic	Date	Stakeholders participating (approximate participant number)
1	Ethical considerations for paediatric trials - how can ethics committees in the European Member States and the Paediatric Committee at the European Medicines Agency work together?	29-30/11/2011	Pharmaceutical industry, Ethics committees, PDCO, EMA, European regulatory network experts (95)
2	Expert meeting on clinical investigation of new drugs for the treatment of chronic hepatitis C in the paediatric population	04/04/2011	
3	High-grade glioma expert group meeting	03/12/2010	Paediatric neuro-oncologists, adult neuro-oncologists, neuro-surgeons; biologists; pathologists; experts from PDCO, SAWP and COMP; members of FDA (30)
4	Expert group meeting on paediatric heart failure	29/11/2010	
5	Paediatric rheumatology expert group meeting	17/11/2010	
6	Expert meeting on paediatric gastroenterology and rheumatology	28/06/2010	
7	Expert meeting on neonatal and paediatric sepsis	08/06/2010	
8	Expert meeting on specific immunotherapy	18/01/2010	
9	Paediatric rheumatology expert group meeting	04/12/2009	
10	Paediatric epilepsy expert group meeting	01/09/2009	
11	Meeting of the paediatric diabetes mellitus expert group	17/04/2009	
12	Meeting of the paediatric human immunodeficiency virus (HIV) expert group	26/05/2009	
13	European Medicines Agency workshop on modelling in paediatric medicines	14-15/04/2008	
14	Workshop on FP7 and off-patent medicines developed for children	06/06/2007	

18. Additional data: Other projects necessary for the implementation of the Paediatric Regulation

18.1. Literature related to the Paediatric Regulation

The following key words and limits were used in various combinations to identify scientific publications directly related to the implementation of the Paediatric Regulation or scientific publications on data that explicitly respond to or address the Paediatric Regulation by providing data or methods. The abstracts of literature search results were manually reviewed and relevant publications were categorised by authors' affiliation to either external stakeholders or to the EMA and / or PDCO. The found literature is listed in section 10. "References".

PubMed:

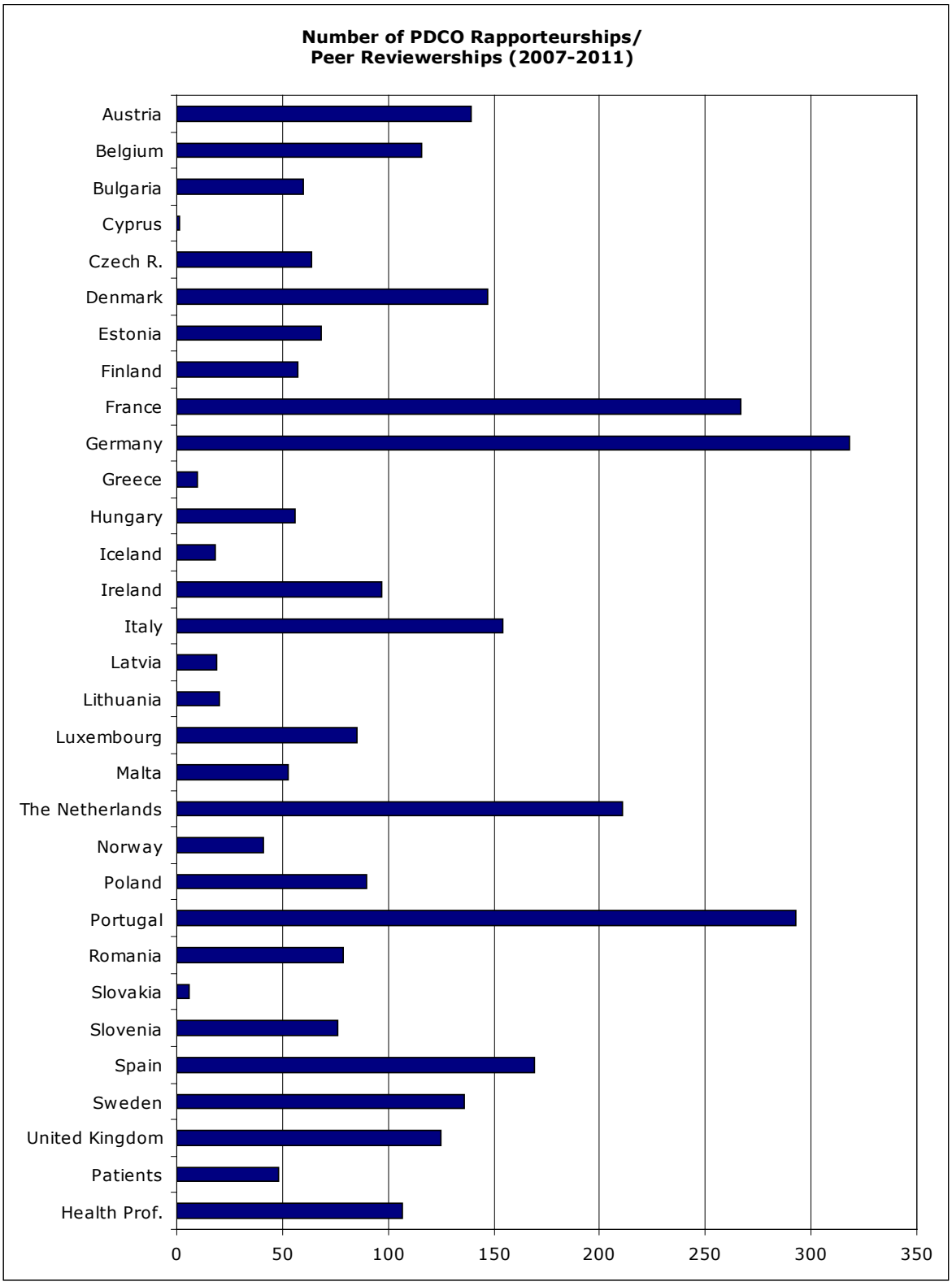
- "Paediatric regulation" OR "Pediatric regulation" OR "Paediatric legislation" OR "Pediatric legislation"
- ("2007/01/01"[PDAT] : "2012/01/31"[PDAT])
- "Clinical trials"[All Fields], "Paediatric trials"[All Fields], "Pediatric trials"[All Fields]
- ("Child"[Mesh] OR "Infant"[Mesh] OR "Infant, Newborn"[Mesh]), (child* OR pediatr* OR paediatr*)
- "Europe"[Mesh], "European Union"[Mesh], "european regulation", "european legislation", "Legislation as Topic"[Mesh], "Legislation, Pharmacy"[Mesh], "Legislation, Drug"[Mesh]
- "Pharmaceutical Preparations"[Mesh]

Embase:

- ("paediatric regulation" or "pediatric regulation" or "paediatric legislation" or "pediatric legislation").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
- limit 2 to yr="2007 - 2011"
- exp clinical trial/ or exp "clinical trial (topic)"
- (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>))
- *Europe/ ("european regulation" OR "european legislation") {Including Related Terms}, *regulatory mechanism/

19. Additional data: Resources used by the Member States

Figure 6: Number of rapporteurships/peer reviewerships for PIP or waiver applications, by Member State (2007-2011)



20. European Network for Paediatric research at the EMA (Enpr-EMA)

Introduction

Article 44 of the Paediatric regulation required the European Medicines Agency (EMA) to develop a European Network of existing national and European networks, investigators and centres with specific expertise in the performance of studies in the paediatric population. To meet this objective the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) has been established, officially launched and presented to all stakeholders in March 2011 as a network of research networks, investigators and centres with recognised expertise in performing clinical studies in children (full list of Enpr-EMA milestones below). Enpr-EMA aims to foster ethical research on quality, safety and efficacy of medicines to be used in children. It serves as platform for industry providing access to competent, high quality paediatric research networks and encourages inter-network trans-European collaboration.

In order to aid achieving the successful creation of Enpr-EMA an Implementing Strategy (http://bit.ly/AqfjRV) was adopted in January 2008 by the Management Board at EMA, where the definition of a network was given as a virtual structure defined by a formal agreement between individuals, organisations or structures sharing and collaborating towards the same objectives, goals and quality standards. The implementing strategy was largely based on the outcome of previous discussions/meetings held by the EMA during 2005 and 2006 with representatives of existing or developing paediatric networks.

As a next step, the EMA prepared a formal inventory of paediatric networks, investigators and centres with specific expertise in the performance of studies in the paediatric population. Sixty networks were identified at that time, and these were subdivided in various categories such as national networks, European Networks publicly funded, paediatric sub-specialty networks (e.g. rheumatology, HIV), age-related networks (e.g. neonatology) and activity or structure-related networks (e.g. pharmacovigilance, community-practitioners). The implementing strategy also identified interested 'stakeholders' including patients, parents, families and organisations representing them; Paediatric and other relevant learned societies; Academia (EU and international); National Competent Authorities; Ethics Committees; Paediatric health care providers; Pharmaceutical industry; Clinical Research Organisations and Hospital pharmacists.

The main objectives of Enpr-EMA were identified as building up and strengthening scientific, technical and/or administrative competences in the performance of paediatric clinical trials through effective collaboration in order to avoid duplication of work and efforts, making the use of facilities more efficient and profitable and developing common methods of working with special attention to quality assurance. Additional benefits are the facilitation of recruitment of patients, and avoiding unnecessary studies in children. Finally the EU network aims at strengthening the foundations of the European Research Area by promoting European Commission framework programme applications. For more detailed goals of the network see the implementing strategy published on the EMA website.

Operational structure

From 2009, two working groups with members of identified networks were tasked to elaborate the operational structure of Enpr-EMA and to define recognition criteria which will have to be fulfilled to become a member of Enpr-EMA (http://bit.ly/I6w22Z). Both tasks were completed by February 2010 and a workshop was organised in March 2010 (http://bit.ly/IJdbvW) to present the proposals to a larger group of networks, and to come to an agreement. Twenty-two networks were represented by 27

participants. As stated in the implementation strategy the operational centre of Enpr-EMA is a co-ordinating group (CG) which is responsible for the network's long- and short-term strategy. During the workshop it was agreed that the co-ordinating group should be as diverse as possible to represent various types of networks: networks focusing on specific therapeutic areas, specific needs/age subsets (e.g., neonatal /adolescent networks) or specific activities (e.g., pharmacovigilance), as well as organisational networks (e.g., national networks linking together either several clinical trial centres or community paediatricians), accommodating for regional differences throughout Europe with regards to how the medical care of children is organised. Consensus was reached regarding the total number of members for the CG: 18 networks fulfilling all minimum recognition criteria and 2 PDCO representatives. A maximum of four additional members may attend the CG meetings as observers, including patient/family representatives, representatives of ethics committees as well as the EC.

It was further agreed that Pharmaceutical Industry will not be represented in the Co-ordinating Group; however, regular communication with industry as major stakeholder must be ensured. Membership of the Co-ordinating Group shall be for 3 years only, to ensure sufficient renewal and involvement of various members. The main tasks of the CG were identified as follows: to facilitate access of the pharmaceutical industry to paediatric clinical study centres and experts; to discuss and solve operational and scientific issues for the network; to act as a forum for communication; to identify new networks and inviting them to join Enpr-EMA; to develop common educational tools for children and parents, to increase their willingness to take part in clinical trials; and to report to the Paediatric Committee, which acts a scientific committee of Enpr-EMA.

The European Medicines Agency will provide the secretariat and organise and host the meetings.

For further details on the composition and tasks of the CG please see the Report on Second Workshop (http://bit.ly/IJdbvW).

Recognition criteria to become member of Enpr-EMA

A set of recognition criteria and quality standards were elaborated following the Delphi and nominal group techniques (Ruperto et al. 2011). Six quality criteria were identified: Research experience and ability; Network organisation and processes; Scientific competencies and ability to provide expert advice; Quality management; Training and educational capacity to build competences; Public involvement. Each category was further subdivided with detailed information being requested in each of them. From this list a minimum set of recognition criteria that have to be fulfilled in order to become a member of Enpr-EMA was agreed at the workshop in 2010 and was published on the EMA website allowing networks to assess themselves (http://bit.ly/I6w22Z). Networks submitting a self-assessment are expected to provide evidence for their claims to allow public scrutiny. Self-assessment reports together with the supplementary documentation are reviewed by the EMA secretariat and published on the EMA website once all the potential clarifications/questions have been addressed by the corresponding network. All self-assessment reports have to be annually revised and updated.

Following a call for expressions of interest in 2010, Enpr-EMA published a full list of applicants for membership in January 2011 (http://bit.ly/IvoGI5). To date 34 networks have submitted their self-assessment reports to the EMA (http://bit.ly/IJcz9E). During the reviewing process performed by EMA secretariat networks were classified according to 3 categories: category 1 networks fulfilling all minimum criteria for membership of Enpr-EMA; category 2 networks potentially fulfilling all minimum criteria but in need of clarifying some issues before becoming a member of Enpr-EMA; and category 3 networks currently not yet fulfilling minimum criteria. To date 18 networks are recognised as category 1; 2 are recognised as category 2; and 14 are recognised as category 3 (Table 28).

Table 28: Enpr-EMA networks . Networks were classified according to 3 categories. Category 1: networks fulfilling all minimum criteria for membership of Enpr-EMA; Category 2: networks potentially fulfilling all minimum criteria but in need of clarifying issues before becoming a member of Enpr-EMA; and Category 3: networks currently not yet fulfilling minimum criteria.

Type or therapeutic area of network	Category 1 networks	Category 2 networks	Category 3 networks
National	NIHR-MCRN, FinPedMed, MCRN-NL, MICYRN, Scotmcn, CICPed		IPCRN, NCCHD, BLF, RIPPS, Futurenest CR, BPDN
Oncology (solid / haematologic malignancies)	Newcastle-CLLG, ITCC, IBFMSG, EPOC	CLG of EORTC	
Diabetes / Endocrinology / metabolic disorders / Gynaecology			AMIKI
Gastroenterology / Hepatology			ESPGHAN
Allergology / Immunology/ Rheumatology	PRINTO		JSWG of PRES
Stem Cell and Organ Transplantation / Haematology (non malignant) / Haemostaseology	EBMT		IPTA
Respiratory diseases / Cystic Fibrosis	ECFS-CTN		
Cardiovascular diseases / Nephrology			
Psychiatry / Neurology	EUNETHYDIS		
Infectious diseases / Vaccinology	PENTA, UKPVG		PENTI
Special Activities / Age groups			
Intensive Care / Pain / Anaesthesiology / Surgery		Network of Excellence for research in paediatric clinical care-NL	
Neonatology	GNN		EuroNeoNet, Neo-circulation, INN
European Paediatric Pharmacists			
Special Activities (pharmacovigilance, long-term follow up, community paediatricians)	FIMP-MCRN		
Expertise in Clinical Trial Methodology			TEDDY*, PRIOMEDCHILD*, ECRIN*, GRIP*

* Unable to provide self-assessment report, as based on different objectives

Presentation of Enpr-EMA to all stakeholders

Enpr-EMA was officially launched in 2009 and introduced to a wider audience in March 2011 during a 2 day workshop organised by the Agency (http://bit.ly/Im7Ygg). On the first day of the March 2011 meeting, open to networks only, Enpr-EMA's co-ordinating group was established and Professor Peter Helms, director of the Scottish Medicines for Children Network, was elected as chair of the co-ordinating group. Priority tasks for the CG were defined as establishing Enpr-EMA as platform for communication with industry and patient organisations; linking activities between Enpr-EMA's

members; developing common educational tools for patients/parents to increase willingness to participate in paediatric trials; collaborating with the Paediatric committee (PDCO) on the development of so called "model paediatric investigation plans in selected therapeutic areas; defining a policy of transparency in line with the EMA policy on the handling of potential conflicts of interest (EMA 2012) with the aim to balance the need to ensure that experts involved have no interests which could affect their impartiality with the need to secure the best (specialist) scientific expertise.

The second day of the workshop was open to all stakeholders, particularly patient organisations, clinical researchers, and pharmaceutical industry staff responsible for paediatric studies. More than 160 participants attended. During the second day expectations from various stakeholders were discussed (http://bit.ly/Im7Ygg). The views from pharmaceutical industry were represented by large pharmaceutical industry, small and medium sized enterprises (SMEs) and companies developing medicines for rare disease. The networks perspective was addressed by representatives of three different types of paediatric networks: a large national network, an oncology network and a neonatal network. The parent/patients' expectations were addressed by the secretary general of the Patients Network for Medical Research and Health (EGAN) and one PDCO member representing patients' organisations. Several parallel break-out groups discussed proposals for the effective use of Enpr-EMA.

Following the conclusion of the workshop, the first meeting of the newly form CG took place in June 2011 where the outcome of the workshop and the first tasks identified were discussed. Enpr-EMA also elaborated and submitted a common response document to the Clinical Trials Directive consultation and this was sent to the European Commission. EMA secretariat and the coordinating group worked closely to elaborate the mandate of the coordinating group, the mission statement, the policy on transparency and the working plan for Enpr-EMA, all published on the Enpr-EMA website in early 2012.

In order to fill the identified gap of networks in several therapeutic areas, Enpr-EMA organised a meeting to "kick-start" paediatric research networks in three specialties: Paediatric Cardiology, Paediatric Gastroenterology and Paediatric Diabetes and Endocrinology. The workshop took place in November at the EMA with the aim of bringing together relevant experts in the paediatric specialties mentioned above in order to stimulate the development of European-wide new clinical trials networks (CTNs) in these therapeutic areas by sharing experience with existing CTNs, and scoping the possibilities for networks in these specialties. Representatives for each of the three potentially new networks were selected and will report on the progress of their initiatives at the fourth annual Enpr-EMA-workshop in March 2012.

In addition one of the key areas Enpr-EMA has been working on is to raise awareness on the need to perform ethical research in children in order to ensure that a medicinal product is safe, of high quality and effective for use in the paediatric population. Enpr-EMA has established intense collaborations with the Patients and Consumers Working Party (PCWP) at the EMA, with the result of one of their members (Jose Drabwell) being elected as their representative to interact with Enpr-EMA; Jose Drabwell has now become a co-opted member of the CG of Enpr-EMA.

Other key tasks that Enpr-EMA has identified include the elaboration of Model PIPs. The first step will be to develop a priority list of areas for model PIPs. Another area of work has been to increase the visibility of Enpr-EMA. A logo for Enpr-EMA has been created and a link (to the Enpr-EMA pages) on the EMA website has been established. Enpr-EMA secretariat has submitted two project proposals to the EMA for a website and a resource database that will increase visibility and efficiency of the network. In addition a paper on Enpr-EMA has recently been published in Archives of Disease in Childhood5 as well as a short report in the European Pharmaceutical Contractor.

One of the key tasks for Enpr-EMA is to deal with queries coming from pharmaceutical industry. To this end Enpr-EMA is working to develop an operational procedure to deal with these queries. The potential issues from industry point of view are confidentiality of the information submitted to Enpr-EMA and

how this information will be distributed amongst all the members of Enpr-EMA. This will be one of the major topics in the upcoming Workshop in March 2012, where representatives of pharmaceutical industry are expected to attend and give their views and ideas on how to establish a sound system. From Enpr-EMA side, a conflict of interest policy has been developed and all members will have to sign to a confidentiality agreement to protect Industry interests.

Conclusion

The establishment of Enpr-EMA has been a significant achievement, and even though more work is needed the way ahead for Enpr-EMA is clear. Enpr-EMA aims to become the platform for access to competent, high quality networks with recognised expertise in performing clinical studies in children across Europe. Enpr-EMA is able to provide reassurance on quality of networks being recognised members of Enpr-EMA, and to ensure that networks contacted in parallel for one specific study interact and communicate between each other achieving a high level of collaboration between networks avoiding potential duplication of studies. Enpr-EMA anticipates an ever increasing pool of key players and networks with capacity to conduct paediatric drug trials to provide timely and well informed scientific advice and to act as advocates for the needs of children as far as the safe and effective use of medicines is concerned.

Table 29: Enpr-EMA Milestones

2005-2006:
- Inventory of existing paediatric networks
- Several meetings at EMEA with existing networks
- Voluntary participation
- Understanding the difficulties, the issues, the needs
- Preparing the strategy by discussing objectives

2007:
- 01/2007 Entering into force of Paediatric Regulation
- 07/2007 Establishing PDCO
- Consultation of Paediatric Committee on Network strategy
- Public consultation on strategy

2008:
- 01/2008 Adoption of "Implementation strategy for " The Network of Paediatric Networks at the EMEA" by EMA Management Board
- 07/2008 Call for European Paediatric Research Networks sent to 15 European and International Paediatric and general scientific journals – to identify additional networks

2009:
- 02/2009 first network workshop
- 04/2009 establishing 2 working groups

- "implementation working group" (WG 1) to elaborate on the structure and operational model for the European network and on communication strategies
- WG 2 to define definition of quality standards and recognition criteria.
  - 04-06.2009 WG 2 identified available information on quality standards/recognition criteria for networks
  - 06/2009 WG 1 meeting – deliverable: proposal for structure and communication strategy
  - 07/2009
- WG 2 T-conference: agreeing to use the Delphi Technique and Nominal Group Technique to define recognition criteria.
- first round of Delphi survey sent to all identified networks and learned societies
  - 08-09/2009
- summarising responses from Delphi survey
- preparing second round of Delphi survey
- sending out second round of Delphi survey
  - 09/2009
- Informing learned societies and networks in writing about

i) proposed organisational structure of Enpr-EMA
ii) the need for grouping of existing networks and centres to ensure adequate representation in the coordinating group,
iii) asking for proposals on how and with which other network(s) collaboration could be envisaged

- 10-11/2009: analysing responses from second round of Delphi survey
- 12/2009: face to face meeting WG 1 and WG2: finalising proposal for recognition criteria

2010:

- 01/2010 test phase for self-assessing recognition criteria by network members of WG1 and WG2
- 02/2010 public consultation of recognition criteria
- 03/2010 second workshop:

- agreement of final recognition criteria
- agreement of organisational structure and composition of coordinating group

- 05/2010 Publication of recognition criteria
- 05-09/2010 self-assessment period for networks
- 06/2010 First internal meeting with EnCEPP to discuss ways for collaboration
- 10-12/2010

- checking self-assessment reports submitted to Agency and requesting additional clarifications as needed

2011:

- 01/2011

- Publication of self-assessment reports received and list of networks becoming member of Enpr-EMA
- T-conference with new members of Enpr-EMA to discuss composition of coordinating group (CG) and call for expression of interest to chair CG
- second internal discussion meeting with EnCEPP

- 03/2011 third network workshop:

- first day only networks: election of chair of coordinating group and discuss priority tasks of CG
- second day: first meeting between networks and industry and patient organisations

- 06/2011 First face to face meeting of coordinating group at EMA
- 07/2011 creation of Enpr-EMA Banner on EMA webpage with direct link to Enpr-EMA webpages
- 07/2011 Adoption of Policy on transparency and handling of research Interests
- 08/2011 Adoption of Mandate of Coordinating group (CG)
- 09/2011 Adoption of Enpr-EMA Mission statement
- 10/2011 Second meeting of CG
  - representative of Patients and Consumers Working Party (PCWP) at the EMA agreed to become co-opted member of coordinating group[
- 11/2011 Workshop on emerging networks in the therapeutic area of cardiology, Endocrinology and Gastroenterology

2012:

- 01/2012 Third meeting of CG
- 01/2012 Follow up TCs with 3 emerging networks (in the therapeutic area of cardiology, Endocrinology and Gastroenterology)
- 03/2012 fourth annual workshop
  - first day: open meeting between networks and industry and patient organisations
  - second day: only networks

21. Formulation working group

The Paediatric Committee's (PDCO) Formulation Working Group (FWG) was established in February 2008 as the PDCO identified a need for specialised expertise in paediatric formulations.

Composition

The FWG started with 11 members in 2008, increased to 13 in December 2011. It is composed of formulation experts from the EMA PDCO, the Quality Working Party, assessors from EU national regulatory authorities, experts from hospitals and academia.

Two representatives from the United States Food and Drug Administration (FDA) also attend the meetings by teleconference as observers. Their participation is within the framework of the Agency's confidentiality arrangement with the FDA.

Role

The Group supports the PDCO in the review process of the quality section of paediatric investigation plans (PIPs), through monthly teleconference meetings, the week before the PDCO plenary. At each meeting, recommendations are made regarding age-appropriate paediatric formulations in PIPs for discussion at the next PDCO plenary, and questions for the PIP Request for Modifications as well as key binding elements for the PIP Opinions are proposed.

The FWG reviews the proposed paediatric formulations of a PIP for the first time before the Day 30 PDCO discussion and suggests modifications to the PDCO if appropriate.

The Group's comments are reflected in the summary report and, if endorsed by the PDCO, in the request for modification sent to the applicant.

The FWG is usually also involved later on in the process, once the responses to the request for modification have been received from the applicant, to evaluate the appropriateness of the applicant’s proposals and suggest some key binding elements for the PIP Opinion.

In addition, the Group provides advice on formulation-related aspects upon request of the PDCO (e.g. interaction with other EMA committees), or during drafting/revision of scientific guidelines.

Achievements

- The major topics discussed by PDCO FWG relate to the safety of excipients in the paediatric population, the appropriateness of the pharmaceutical form and the intended dosing/need for dosing flexibility. Focus has been put on the youngest age groups, in particular neonates, to optimise formulations with regard to appropriate dose, safe excipients, minimising risk of medication errors and optimising practical handling.
  - Safety of excipients for the paediatric population: Better justification of the chosen excipients, in relation to age and daily dose of excipient, replacement of excipients with potential safety concern. Input from/collaboration with the PDCO NcWG and the CHMP SWP for further discussion of potential excipient safety issues.
  - Appropriateness of the pharmaceutical form: Ensure formulations suitable for children, or appropriately adapted to the relevant age groups. E.g., request of alternative dosage forms to be developed to single unit solid dosage forms. Requesting sufficient testing of palatability and acceptability in children of the formulation proposed.

  - Dosing flexibility, accuracy of dosing and practical handling: Focus on practical aspects of administration, feasibility of formulation/dosage form to support correct and accurate dosing in view of needed dosing flexibility, inappropriate manipulation of adult dosage forms and presentations.

- From February 2008 to November 2010, the PIPs were referred to the FWG by Paediatric coordinator or PDCO member on a case-by-case basis. Since Nov 2010, a screening of all PIPs is performed by EMA Quality team, identifying PIPs to be discussed by the FWG, currently applying a more systematic approach.
- Quantitative data: Number of PIPs reviewed by the PDCO FWG:
  - In 2008, from March to December, the FWG discussed 62 PIP applications.
  - In 2009, the FWG assessed 84 PIP applications, 43% of the total number of validated PIP applications (84/195) during this year.
  - 115 and 152 PIPs were discussed by the PDCO FWG, in 2010 and 2011 respectively.
  - Each product has been counted in the year when the last discussion occurred for this product. As each product is generally discussed several times, the figures do not exactly reflect overall activity, however they show the trend of an increased involvement of the PDCO FWG, reviewing systematically all the PIPs raising some quality issues since November 2010.
- Adoption by the PDCO, upon proposal of the PDCO FWG, of standard wording for paediatric formulations key binding elements in PIP Opinions, to better reflect the PDCO's requirements in opinions and avoid the general wording "development of an age-appropriate formulation".
- Implementation of quality questions in the Part A of the PIP application form, to be filled by applicants, to ensure the needed information is provided at the time of the PIP submission, especially the composition of proposed formulations, with qualitative and quantitative data on excipients (http://bit.ly/A6wg0j).
- Implementation of FWG comments/minutes in the EMA Paediatric database, to capture the above data and allow future statistics on paediatric formulations (data entered retrospectively until August 2011 and prospectively since September 2011).
- Support PDCO in the collaboration with other committees by providing recommendations upon specific requests (e.g. PhVWP: medication error issues).
- Annual face-to-face meetings to discuss general issues on paediatric formulations (e.g. state of the art knowledge on paediatric safety of specific excipients).
- 2 workshops for National Assessors on paediatric formulations, in 2010 and 2011, to share the experience with PIP assessment, increase the awareness and understanding of paediatric-specific issues in the development of paediatric formulations and enhance collaboration within the European network. The material of the two workshops has been published on EMA external website (http://bit.ly/HXOoSU and http://bit.ly/I7hbFX)
- Participation in the drafting group of EMA Draft guideline on the pharmaceutical development of medicines for paediatric use (EMA/ CHMP/QWP/180157/2011), published on EMA website in September 2011 (public consultation phase ended December 2011).
- Participation in the drafting group of the revision of European Commission guideline on excipients in the label and package leaflet for medicinal products for human use.

- Comments provided on several guidelines related to paediatric formulations, published by WHO, national agencies or associations.
- Collaboration with European Paediatric Formulation Initiative (EuPFI) through participation to their congresses and a project on acceptability/palatability testing guidance; collaboration with FDA and WHO.
- Overall, the work of the PDCO FWG has raised awareness and deepen the knowledge of the issues specific to the development of paediatric formulations, both among applicants (through the comments on PIP applications) and among the EMA network, such as National Competent Authorities through various workshops or other EMA committees. The participation of experts from National Competent Authorities, hospital and academia in the PDCO FWG meetings is also a bilateral exchange, during which they bring expertise to enrich the global knowledge.

Action plan in the near future

- To continue to support the PDCO by providing recommendations for PIPs, and when needed recommendations to support PDCO's interactions with other committees.
- To maintain a consistent approach and agree on assessment standards that can be applied in evaluation of PIPs.
- To continue participation in the drafting groups of the guideline on "Pharmaceutical Development of Medicines for Paediatric Use" and the revision of the Commission guideline on Excipients in the label and package leaflet of medicinal products for human use.
- To continue collaboration with other stakeholders with an interest in paediatric formulations and forms.
- Develop guidance on acceptability/palatability testing of paediatric formulations (project initiated end of 2010) with input from the European Paediatric Formulation Initiative(EuPFI) and GRIP (Global Research in Paediatrics - Network of excellence) .
- In December 2011, the Committee and its Formulation Working Group were informed that, via the Reagan-Udall Foundation, the FDA is working on a proposal to develop a validated approach to assessing "acceptability/suitability" of formulations in children of different ages. The PDCO FWG may also be involved in this project as part of the paediatric cluster.

22. Non-clinical expert working group

Role

The Non-clinical Working Group (NcWG) was established in November 2008 to complement the Paediatric Committee's (PDCO) work with specialised non-clinical expertise. The NcWG guarantees a high quality consistent approach in the monthly review process of the non-clincal section of paediatric investigation plans (PIPs). Recommendations are made to the PDCO either before adoption of the Request for Modification or the opinion. The recommendations clearly state the respective concern and consequential proposed request and are reflected in the summary report and/or opinion, if endorsed by the PDCO.

Composition

The NcWG is currently composed of 15 non-clinical experts from the PDCO, the EMA Safety Working Party (SWP) and additional members from medicines regulatory authorities in European Union Member States. Two representatives from the United States Food and Drug Administration (FDA) also attend the meetings by teleconference as observers.

Main achievements

Since November 2008, 379 PIPs have been reviewed, which is approximately 69% of total PIPs received (only counting a product once and not including waivers, Figure 7, blue bars) and 117 PIPs have been re-discussed (Figure 7, green bars) when the applicants' responses to the Request for Modification were received and warranted further discussion.

The PDCO generally endorsed the recommendations of the NcWG. All 88 PDCO Opinions adopted between March 2011 and December 2011 were compared to the respective initial application with regards to their pre-clinical strategy and showed the following:

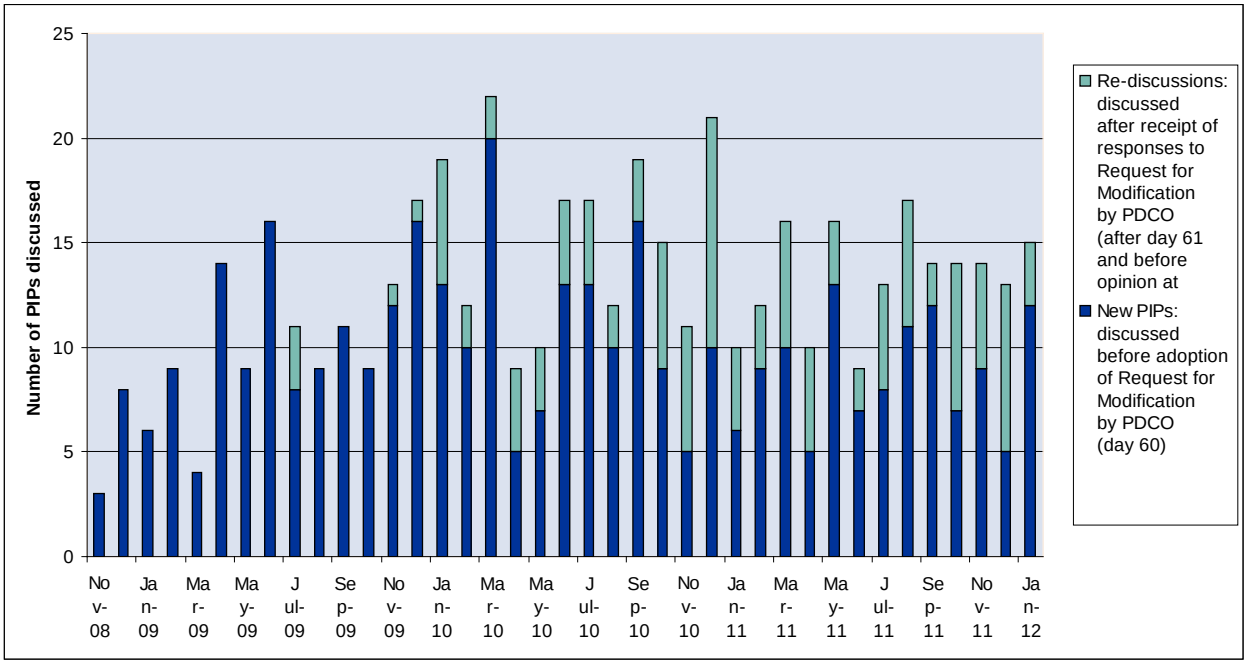
- Juvenile animal studies were present in 19% of the applications for PIPs (17 applications with at least one juvenile study; 30 juvenile studies in total across these 17 applications).
- Juvenile animal studies were required in 25% of the PDCO opinions on PIPs (22 opinions with at least one juvenile study; 37 juvenile studies in total). This means that additional juvenile animal studies were requested by the NcWG/PDCO in about 6% of all proposed PIPs.

A review of all 97 PIPs discussed by the NcWG between November 2008 and May 2010 was recently published (Carleer and Karres, 2011). According to this review, the young age of the paediatric target population was one of the major drivers for requesting juvenile animal studies. In about 14% of the reviewed PIPs, however, the NcWG requested either justifications for, or amendments of the designs of juvenile animal studies proposed by the applicants.

The review also showed that the number of juvenile animal studies required in PDCO opinions was less than the sum of the number of juvenile studies initially proposed by the applicant and of those requested by the NcWG/PDCO in the Request for Modification of the PIP. This reduction of eventually required juvenile animal studies compared to those discussed at any stage of the PIP evaluation, was mainly due to additional data or justifications provided by applicants during the evaluation, such as in the response to the Request for Modification.

It was noted that the PIP applications often lacked information relevant to the non-clinical evaluation.

Figure 7: Frequency of discussions of PIP applications



Review of results of required juvenile animal studies

A preliminary review was performed of reports of 5 completed juvenile animal studies that were required in PDCO opinions for medicines from 4 different classes of oncology products. The review revealed increased sensitivity and unexpected toxicity in 3 of the investigated medicinal products.

Dissemination and public-facing activities

Members of the NcWG and the EMA participated to three international conferences regarding pre-clinical safety aspects for the development of medicinal products used in the paediatric population, organised a training on the need of juvenile animal studies for National Assessors and published two articles describing current experience with requirements for juvenile animal studies in PIPs (Carleer & Karres 2011; Silva-Lima et al. 2010). Furthermore, the NcWG provided comments on the Japanese guideline on non-clinical support for paediatric drug development.

Interactions with the Safety Working Party/CHMP

- When safety concerns regarding the paediatric use of a specific class of medicinal products or excipients were identified by the NcWG, a common approach was decided in collaboration with the Safety Working Party (SWP). Specific examples from the past 2 years are: tolerable daily intake values for the presence of di(2-ethylhexyl) phthalate, benzyl butyl phthalate and dibutyl phthalate within medicinal products; maximal tolerable doses of aluminium hydroxide contained in allergen products; intravenous use of polysorbate 80 in neonates; safety of pegylated drug products for the paediatric population.
- Currently the guideline on Excipients in the Labelling and Package Leaflet (European Commission, 2003) is for revision and the NcWG together with the Formulation Working Group (FWG) of the PDCO and the SWP will contribute to the review of 8 prioritised excipients with potential paediatric issues: (dextran/) cyclodextrins, ethanol, polyethyleneglycol, propyleneglycol (and esters), polysorbates, benzyl alcohol, sorbitol (and other poorly absorbed sweeteners), aspartame.

Conclusions

The NcWG provides a high-quality, consistent approach to the application of the EMA guideline on the need for juvenile animal studies (EMA 2008) and thereby complements the work of the PDCO. The case-by-case evaluation process to determine the need for juvenile animal studies contributes majorly to the protection of the pediatric population during clinical trials and prevents the conduct of unnecessary juvenile animal studies.

Young age of children exposed to the investigated medicinal product was one of the main reasons for requesting juvenile animal studies owing to potentially increased sensitivity toward organ toxicity as several organs or systems of newborns and infants are not fully developed and are maturing postnatally.

The occurrence of increased sensitivity and unexpected organ toxicity in juvenile animals as seen in a preliminary evaluation of completed juvenile animal study reports from PIPs (described above) and as described previously (Bailey and Marien, 2009; Carleer and Karres, 2011) emphasises the general importance of conducting juvenile animal studies. The main values of the results from juvenile animal studies are their contribution to dose predictions in children, their use for risk minimization and for the identification of safety parameters in the pediatric clinical trials to monitor and detect early safety signals.

The collaboration with the FDA (and, occasionally, with the Japanese PMDA/MHLW) increases consistency in pre-clinical safety requirements for the development of medicinal products used in the paediatric population at the international level.

A need was identified for applicants to provide better scientifically-based justifications, when no juvenile animal studies are proposed in the initial PIP submission.

Action plan for the near future

- Continue to support PDCO by providing recommendations for PIPs, and when needed recommendations to support PDCO's interactions with other committees/agencies.
- Continuation of the review of use of juvenile animal studies in different therapeutic areas and product classes.
- Evaluation of the impact of the Paediatric Regulation on the SmPC labelling regarding juvenile animal studies.
- Continuation of the collaboration with the American FDA and the Japanese PMDA/MHLW agencies.

Meeting contributions

- Workshop on "The Value of Juvenile Animal Studies" in Washington, DC. Organised by ILSI Health and Environmental Sciences Institute/Developmental and Reproductive Toxicology Technical Committee (2010).
- Workshop for National Assessors on paediatric formulations, London (2011).
- Biotherapy Development Association (BDA) workshop in collaboration with ITCC, ENCCA and EMA, London. "Innovative Oncology Drug Development for children and adolescents in Europe: Current Status and Where to Go?" (2011).

Meeting organisation

- Workshop organised by EMA for National Assessors on the need of juvenile animal studies for medicinal products used in the paediatric population (2009), to increase their knowledge on the topic and collaboration.

23. Detailed inventory of all medicinal products authorised for paediatric use since its entry into force

Article 50 (2) of the Paediatric Regulation states that *"This [report] shall include in particular a detailed inventory of all medicinal products authorised for paediatric use since its entry into force."*

The inventory includes both medicines that received the initial marketing authorisation since 26 January 2007 and medicines for which the already granted authorisation was varied since 26 January 2007 to include a new paediatric indication. The data for the inventory were collected as part of the survey among Members States used for this report, which have been detailed and aggregated in four sections the Annex II of this report. The summary data are also presented in the section "5. More medicines available for children in the EU" of this report.

Taken together, the following sections form the inventory of all medicinal products authorised for paediatric use since its entry into force:

23.1. Centrally authorised medicines

23.1.1. Initial marketing authorisation (MA) including a paediatric indication

- Line listing in Annex II, section 4.1

For this section, only medicinal products were considered when a paediatric indication was granted as part of the initial MA. Thirty four (34) new medicinal products have been centrally authorised since 26 January 2007 with a paediatric indication at the time of initial MA. Out of these 34 medicinal products, 7 were authorised for a use only in the paediatric population, whereas the remaining 27 medicinal products were authorised for use in adults and in children. For 10 out of the 34 medicinal products, the requirements of the Paediatric Regulation needed to be fulfilled, meaning the corresponding PIP had not been completed.

23.1.2. Extension of therapeutic indication to include the paediatric population

- Line listing in Annex II, section 4.2

The therapeutic indications of 33 centrally authorised medicinal products was extended or amended to include a part or subsets of the paediatric population. 38 changes to the authorised indications were adopted to include a part or subsets of the paediatric population for these 33 centrally authorised medicinal products (several products had more than 1 change to their indications affecting the paediatric population).

23.2. Nationally authorised medicines

23.2.1. Initial marketing authorisation (MA) including a paediatric indication

- Line listing in Annex II, section 7.1

Overall 12 Member States provided data on this question, about 300 data entries covering more than 80 active substances and covering the period from 2006 to 2011 (more than 180 data entries 2011,

less than 35 each for the preceding years). The data provided have been summarised across Member States and presentations by using the English INN for the active substance(s).

The data included medicines that were already authorised in some EU Member States, but became available for use in children through new authorisations in further, new Member States.

The data provided were scrutinised for new medicinal products with new active substances. There were 3 such medicines that could be identified (name of medicinal product): Numeta and associated names, Celtura, Panenza.

The legal basis, under which the medicinal products were authorised, was not requested to be reported, so that no distinction can be made between new medicines linked or not linked to the Paediatric Regulation. Some of the data entries may be for generic medicines, which do not fall under the Paediatric Regulation and thus are not part of this report.

23.2.2. Extension of therapeutic indication to include the paediatric population

- Line listing in Annex II, section 7.2

In total 11 Member States reported a new indication authorisation of a use in the paediatric population for the medicinal products concerned by a total of 33 active substances, none of which is considered a new active substance since coming into force of the Paediatric Regulation. The authorised paediatric indication is reflected in sections 4.1 and / or 4.2 of the SmPC (Table 17 and Table 18 in Annex II, respectively).

Out of the 33 active substances, 8 underwent an Article 29 referral procedure (section 5.2. in the core report) or that have been captured in Article 45 assessments (section 6.1. in the core report).

8 July 2012
EMA/177675/2012

Annex II Cumulative data 2007-2011

This is Annex II to the 5-year Report to the European Commission, the general report on the experience acquired as a result of the application of the Paediatric Regulation. The report does not include data for generic, biosimilar, hybrid, homeopathic, traditional herbal and well-established medicinal products - which are excluded from the scope of the mandatory development - unless otherwise mentioned. Recitals and Articles refer to the Paediatric Regulation, if not otherwise stated.

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7040
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. PDCO opinions on compliance

Summary:

- The PDCO adopted opinions confirming the compliance of the completed studies with 29 agreed PIPs (excluding duplicates).
- Number of PDCO compliance opinions per year: 3 (2008), 9 (2009), 9 (2010) and 8(2011).
- There was 1 adopted PDCO opinions that did not confirm compliance. Compliance could later be confirmed after a modification of the agreed PIP.
- The opinions on compliance are mentioned and summarised in the PDCO monthly reports (http://bit.ly/xGFZEw).
- No Member State reported to have issue an opinion on compliance with an agreed PIP.

Table 1: Opinions on compliance adopted by the PDCO until 31 December 2011

No.	Active substance(s)	Trade name if available	Condition(s) for paediatric use	Date of PDCO compliance opinion	Further outcome / section
1	Abatacept	Orencia		29/05/2009	

No.	Active substance(s)	Trade name if available	Condition(s) for paediatric use	Date of PDCO compliance opinion	Further outcome / section
2	Alanine, Arginine, Aspartic acid, Cysteine/Cystine, Glutamic acid, Glycine, Histidine, Isoleucine, Leucine, Lysine monohydrate, Methionine, Ornithine hydrochloride, Phenylalanine, Proline, Serine, Taurine, Threonine, Tryptophan, Tyrosine, Valine, Sodium chloride, Potassium acetate, Magnesium acetate, tetrahydrate, Calcium chloride, Sodium glycerophosphate, Glucose, Olive oil, refined, Soya-bean oil, refined	Numeta		16/10/2009	
3	Anastrozole	Arimidex and associated names		03/04/2009	
4	Atorvastatin calcium (trihydrate)	Sortis and associated names		13/11/2009	
5	Azelastine hydrochloride / fluticasone propionate			17/06/2011	
6	Caspofungin acetate	Cancidas		04/06/2008	
7	Clopidogrel	Plavix and associated names		10/12/2010	Failed indication
8	Colesevelam hydrochloride	Cholestagel		24/07/2009	
9	Darunavir (as ethanolate)	Prezista		09/12/2011	
10	Esomeprazole sodium / Esomeprazole magnesium trihydrate	Nexium and associated names		16/07/2010	
11	Etanercept	Enbrel		09/12/2011	
12	Human Papillomavirus type 6 L1 protein / Human Papillomavirus type 11 L1 protein / Human Papillomavirus type 16 L1 protein / Human Papillomavirus type 18 L1 protein	Gardasil		16/04/2010	
13	Infliximab	Remicade		09/09/2011	New indication authorised
14	Insulin glargine (EMEA-C-000387-PIP01-08, EMEA-C-000396-PIP01-08)	Optisulin, Lantus		11/11/2011	
15	Latanoprost	Xalatan		19/03/2010	

No.	Active substance(s)	Trade name if available	Condition(s) for paediatric use	Date of PDCO compliance opinion	Further outcome / section
16	Losartan potassium	Cozaar and associated names		06/02/2009	
17	Meningococcal group C oligosaccharide Conjugated to Corynebacterium diphteriae CRM197 protein (MenC-CRM)/Meningococcal group A oligosaccharide Conjugated to Corynebacterium diphteriae CRM197 protein (MenA-CRM)/Meningococcal group Y oligosaccharide Conjugated to Corynebacterium diphteriae CRM197 protein (MenY-CRM)/Meningococcal group W-135 oligosaccharide Conjugated to Corynebacterium diphteriae CRM197 protein (MenW-CRM)	Menveo		20/05/2011	
18	Midazolam (as hydrochloride)	Buccolam		06/08/2010	
19	Montelukast	Singulair		15/01/2010	Failed indication
20	Nevirapine	Viramune		06/08/2010	
21	Nomegestrol / [17-beta] estradiol	Ioa, Zoely		21/05/2010	
22	Peginterferon alfa-2b (EMEA-C-000071-PIP01-07, EMEA-C-000384-PIP01-08)	Viraferonpeg		17/10/2008	
23	Purified diphtheria toxoid, Purified tetanus toxoid, Five component acellular pertussis [Purified Pertussis Toxoid (PT), Purified Filamentous Haemagglutinin (FHA), Purified Fimbriae Types 2 and 3 (FIM) and Purified Pertactin (PRN)], Inactivated poliomyelitis vaccine (Vero) – Type 1 (Mahoney), Type 2 (MEF-1) and Type 3 (Saukett), Purified polyribosylribitol phosphate capsular polysaccharide of Haemophilus influenzae type b covalently bound to Tetanus protein (PRP-T)	Pediacel		18/09/2009	
24	Ribavirin	Rebetol		17/10/2008	

No.	Active substance(s)	Trade name if available	Condition(s) for paediatric use	Date of PDCO compliance opinion	Further outcome / section
25	Rizatriptan (benzoate)	Maxalt and associated names		09/09/2011	Failed indication
26	Rotavirus type P1A[8]/rotavirus type G3/rotavirus type G1/rotavirus type G4/rotavirus type G2	Rotateq		15/07/2011	
27	Tretinoin/clindamycin phosphate	Ziana		10/12/2010	
28	Valsartan	Diovan		21/08/2009	
29	Zoledronic acid	Zometa		21/08/2009	Failed indication

2. Statements on compliance of studies with agreed PIP included in marketing authorisations

Summary:

- The statement of compliance as mentioned in Article 28 (3) of the Paediatric Regulation allows to identify:
  - that a marketing authorisation (MA) or a variation application complied with all the measures contained in the agreed completed paediatric investigation plan and
  - that the SmPC reflects the results of studies conducted in compliance with that agreed paediatric investigation plan.
- In total, a statement of compliance was included in the initial marketing authorisation of 1 new medicinal product (1 active substance combination) authorised through national / decentral / mutual recognition procedures and in the initial marketing authorisations of 2 medicinal products authorised centrally (2 active substances).
- A statement of compliance was added in a variation of the pre-existing marketing authorisation of medicinal products for 18 active substances.
- For all 3 active substances covered by newly authorised medicines, a paediatric use was authorised at the time initial marketing authorisation.
- Overall 4 medicinal products with a statement of compliance included into their marketing authorisations, the results of the studies conducted as per the completed PIP did not lead to the targeted paediatric indication (see sections 4.7. and 7.7. for the full list of products).

2.1. Centrally authorised medicinal products with compliance statement in MA

Table 2: Inclusion of compliance statement in the European Commission decision granting marketing authorisation

No.	Active substance (INN)	Medicinal product	Marketing authorisation holder	Initial Marketing Authorisation or variation?	Any paediatric use targeted in PIP authorised?	Date of the EC Decision including the compliance statement
1	Caspofungin	Cancidas	Merck Sharp and Dohme	Variation	Yes	26/11/2008
2	Peginterferon alfa-2b	PegIntron, ViraferonPeg	Schering-Plough Europe	Variation	Yes	11/11/2009 12/11/2009
3	Ribavirin	Rebetol	Schering-Plough Europe	Variation	Yes	11/11/2009
4	Abatacept	Orencia	Bristol-Myers Squibb Pharma EEIG	Variation	Yes	20/01/2010
5	Zoledronic acid	Zometa	Novartis Europharm Ltd	Variation	No	25/01/2010
6	Clopidogrel	Plavix and associated names	Sanofi BMS	Variation	No	27/05/2011
7	Colesevelam	Cholestagel	Genzyme	Variation	No	10/08/2011
8	Midazolam	Buccolam	Viropharma SPRL	Initial MA	Yes	05/09/2011
9	Nevirapine	Viramune	Boehringer	Variation	Yes	16/09/2011
10	HPV vaccine	Gardasil	Sanofi Pasteur	Variation	Yes	16/11/2011
11	Nomegestrol / estradiol	Ioa,* Zoely*	N.V. Organon, Merck Serono Europe	Initial MA	Yes	16/11/2011, 27/07/2011

* Marketing authorisations being updated to include the compliance statement. MA = Marketing Authorisation

2.2. Medicinal products authorised through national / decentral / mutual recognition procedures, including those subject to Article 29 of the Paediatric Regulation with compliance statement in MA

Summary:

- For 5 medicinal products out of 10, the compliance statement was added to the MA not as the result of a referral procedure subject to Article 29 of the Paediatric Regulation. Out of these 5 medicinal products, 4 had their compliance statement added in 2011 (see the 10 products in table 3 below).
- Overall, the compliance statement related to Article 36 (1) of the Paediatric Regulation was added for 5 medicinal products (see the 5 products sections 4.7 and 7.7). There were no compliance statements introduced in marketing authorisations in 2009 in the following countries: Latvia, Lithuania, Luxembourg, Malta, Slovakia.

Table 3: Inclusion of compliance statement in the marketing authorisations of a newly authorised medicine

No.	Active substance (INN)	Medicinal product	Any paediatric use targeted by PIP authorised?	Marketing authorisation holder	Year of marketing authorisation including the compliance statement
1	Alanine, arginine, aspartic acid, calcium, cysteine, glucose, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, magnesium, methionine, olive oil, ornithine, phenylalanine, potassium, proline, serine, sodium, soybean oil, taurine, threonine, tryptophan, tyrosine, valine	Numeta and associated names	Yes	Baxter	2011

Table 4: Inclusion of compliance statement in marketing authorisations of an already authorised medicinal product

No.	Active substance (INN)	Medicinal product	Marketing authorisation holder	Any paediatric use targeted in PIP authorised?	Member States reporting inclusion	Year of variation including the compliance statement*
1	Anastrazole*	Arimidex	AstraZeneca AB	No	Austria, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, Germany, Hungary, Ireland, Italy, Portugal, Slovenia, Sweden, The Netherlands, United Kingdom	2009-2010
2	Atorvastatin*	Sortis and associated names	Pfizer	Yes	Austria, Cyprus, Czech Republic, Estonia, Finland, Germany, Greece, Hungary, Italy, Portugal,	2010

No.	Active substance (INN)	Medicinal product	Marketing authorisation holder	Any paediatric use targeted in PIP authorised?	Member States reporting inclusion	Year of variation including the compliance statement*
					Sweden, United Kingdom	
3	DTP Polio HiB vaccine	Pediacel	Sanofi Pasteur	Yes	France	2011
4	Esomeprazole sodium / esomeprazole magnesium	Nexium and associated names	Astra Zeneca AB	Yes	Ireland, Romania, United Kingdom	2011
5	Latanoprost*	Xalatan and associated names	Pfizer	Yes	Austria, Czech Republic, Denmark, Estonia, Finland, Hungary, Malta, Portugal, Romania, Sweden, United Kingdom	2010-2011
6	Losartan	Cosaar and associated names	Merck Sharp and Dohme	Yes	Austria, Denmark, Estonia, Finland, Germany, Ireland, Italy, Romania, Slovenia, Sweden, United Kingdom	2008-2009
7	Montelukast	Singulair	MSD	No	Austria, Cyprus, Czech Republic, Denmark, Finland, Portugal, Sweden, United Kingdom	2010-2011
8	Rizatriptan	Maxalt and associated names	Merck Sharpe and Dohme	No	Austria, Cyprus, Czech Republic, Denmark, Finland, Lithuania, Malta, Poland, Portugal, Slovenia, Sweden, United Kingdom	2011
9	Valsartan*	Diovan and	Novartis	Yes	Austria, Cyprus,	2009-2010

No.	Active substance (INN)	Medicinal product	Marketing authorisation holder	Any paediatric use targeted in PIP authorised?	Member States reporting inclusion	Year of variation including the compliance statement*
		associated names			Czech Republic, Denmark, Estonia, Finland, Hungary, Italy, Latvia, Malta, Portugal, Sweden, United Kingdom	

* Indicates that the compliance statement was included after a procedure subject to Article 29 of the Paediatric Regulation (see section 5)

3. Supplementary protection certificate extension (6 months) granted by National Patent Offices

Overview of 6-month extensions of supplementary protection certificates granted in relation to Article 36(1) of the Paediatric Regulation, by medicinal product and by year of granting of the extension. There were no extensions of supplementary protection certificate (SPC) in relation to Article 36(1) of the Paediatric Regulation before 2009.

Summary:

- For 11 medicinal products, an extension of the SPC of the medicine was granted in different Member States between 2009 and 2011 (See table %). Of note, one extension of SPC was reported for one medicinal product in 2012.
- In 16 Member States, the NPO granted an extension of the SPC of at least one medicine
- Overall, on the period covered, 105 national SPCs were granted an extension.

Table 5: List of medicinal products and companies that have benefitted from the 6-month extension of the supplementary protection certificate (SPC)

No.	INN of medicine to which patent applies	Marketing authorisation holder	Member State's NPO granting SPC extension (year)	Member State with SPC extension pending (in year)	No application for SPC extension (yet) in Member State (if not confidential)	Member State in which product has no SPC or patent qualifying for an SPC (if not confidential)
1	Abatacept (Orencia)	Bristol-Myers Squibb Pharma	Austria (year not reported possibly 2011) Denmark (21	Bulgaria (2011) Greece (2010) Lithuania	Hungary Italy (SPC granted)	Romania (no SPC) Slovak Republic

No.	INN of medicine to which patent applies	Marketing authorisation on holder	Member State's NPO granting SPC extension (year)	Member State with SPC extension pending (in year)	No application for SPC extension (yet) in Member State (if not confidential)	Member State in which product has no SPC or patent qualifying for an SPC (if not confidential)
		EEIG	June 2010) Estonia (17 October 2011) Finland (13 September 2011) France (10 December 2010) Germany (16 August 2010) Ireland (30 June 2010) Luxembourg (23 December 2010) The Netherlands (31 August 2010) Portugal (2 November 2010) Slovenia (16 November 2011) Sweden (21 November 2011) United Kingdom (6 January 2011)	(2011) Luxembourg (2011) Romania (2011) Spain (2010)		
2	Anastrazole (Arimidex and associated names)	AstraZeneca AB	Austria (2010) Belgium (2010) Denmark (2010 Finland (2 March 2010)	Romania (2010, 2011; *SPC granted after appeal*)	Greece Portugal Spain	Bulgaria Greece Hungary Portugal Slovak Republic Slovenia *(no*

No.	INN of medicine to which patent applies	Marketing authorisation on holder	Member State's NPO granting SPC extension (year)	Member State with SPC extension pending (in year)	No application for SPC extension (yet) in Member State (if not confidential)	Member State in which product has no SPC or patent qualifying for an SPC (if not confidential)
			France (11 June 2010) Germany (19 July 2010) Ireland (29 June 2010) Italy (16 March 2010) Luxembourg (27 July 2010) The Netherlands (1 April 2010) Sweden (27 April 2010) United Kingdom (10 June 2010)			*SPC)*
3	Atorvastatin (Sortis and associated names)	Pfizer	Austria (year not reported, possibly 2011) Denmark (02 May 2011) Germany (11 August 2011) Ireland (28 June 2011) Italy (17 May 2011) Luxembourg (27 June 2011) Sweden (14 April 2011) The Netherlands (12 April 2011) United	France (2010)	Denmark Finland Greece Ireland Portugal Romania	Bulgaria *(appeal procedure after decision for termination of the procedure for SPC granting)* Germany Greece Hungary Luxembourg Portugal Romania *(no SPC)* Slovak Republic Slovenia *(no SPC)* Spain *(SPC denied)*

No.	INN of medicine to which patent applies	Marketing authorisation on holder	Member State's NPO granting SPC extension (year)	Member State with SPC extension pending (in year)	No application for SPC extension (yet) in Member State (if not confidential)	Member State in which product has no SPC or patent qualifying for an SPC (if not confidential)
			Kingdom (23 June 2011)			
4	Caspofungin (Cancidas)	Merck Sharp and Dohme	Austria (31 May 2010) Belgium (21 December 2010) Finland (14 September 2011) Greece (24 November 2010) Italy (13 July 2010) Portugal (12 March 2010) Slovenia (18 May 2010) Denmark (2009) France (2009) Germany (2009) Ireland (2009) The Netherlands (2009) Sweden (2009) United Kingdom (24 August 2009)	Bulgaria (2010) Czech Republic (2010, 2011) Hungary (2010, 2011) Poland (2011) Romania (2010, 2011) Slovak Republic (2010, 2011) Spain (2010)		Luxembourg
5	Clopidogrel (Plavix and associated names)	Sanofi BMS	Denmark (23 January 2012) Finland (9 November 2011)	Ireland (2011) Italy (2011) The Netherlands (2011)		

No.	INN of medicine to which patent applies	Marketing authorisation holder	Member State's NPO granting SPC extension (year)	Member State with SPC extension pending (in year)	No application for SPC extension (yet) in Member State (if not confidential)	Member State in which product has no SPC or patent qualifying for an SPC (if not confidential)
			Germany (30 November 2011) Portugal (8 November 2011) Sweden (13 October 2011)	United Kingdom (2011)		
6	Latanoprost (Xalatan and associated names)	Pfizer	Austria (year not reported, possibly 2011) Denmark (07 March 2011) Finland (12 May 2011) Germany (30 March 2011) Ireland (1 March 2011) Italy (20 February 2011) Luxembourg (15 July 2011) Portugal (21 January 2011) Sweden (17 March 2011) The Netherlands (27 January 2011) United Kingdom (10 May 2011)	Spain (2010)	France Finland Greece Ireland Romania	Bulgaria *(SPC refused)* Germany Greece Hungary Romania *(no SPC)* Slovak Republic Slovenia *(no SPC)*
7	Losartan (Cozaar and associated	Merck Sharp & Dohme BV	Austria (12 February 2010) The	Cyprus (2010)	Greece Portugal Romania Spain	Bulgaria Greece Hungary Portugal

No.	INN of medicine to which patent applies	Marketing authorisation holder	Member State's NPO granting SPC extension (year)	Member State with SPC extension pending (in year)	No application for SPC extension (yet) in Member State (if not confidential)	Member State in which product has no SPC or patent qualifying for an SPC (if not confidential)
	names)		Netherlands (2009) Germany(2009) Denmark (2009) Finland (2009) France (2009) Ireland (2009) Italy (2009) Sweden (2009) United Kingdom (2009) Luxembourg (2009)			Slovak Republic Slovenia *(no SPC)*
8	Montelukast (Singulair)	Merck Sharp & Dohme	Denmark (23 January 2012) Ireland (28 November 2011) Slovenia (16 November 2011) Sweden (15 September 2011) The Netherlands (21 September 2011) United Kingdom (03 January 2012)	Germany (2011) Italy (2011) Luxembourg (2011) The Netherlands (2011)		
9	Nevirapine (Viramune)	Boehringer	Denmark (23 January 2012) Portugal (2 December	Italy (2011) Luxembourg (2011)		

No.	INN of medicine to which patent applies	Marketing authorisation holder	Member State's NPO granting SPC extension (year)	Member State with SPC extension pending (in year)	No application for SPC extension (yet) in Member State (if not confidential)	Member State in which product has no SPC or patent qualifying for an SPC (if not confidential)
			2011) Sweden (16 November 2011)			
10	Rizatriptan (benzoate) (Maxalt and associated names)	Merck Sharp & Dohme		Portugal (2012)		
11	Valsartan (Diovan and associated names)	Novartis Pharma AG	Austria (10 December 2010) Denmark (1 November 2010) Finland (22 October 2010) France (10 December 2010) Germany (13 January 2011) Ireland (22 December 2010) Italy (05 November 2010) Luxembourg (23 December 2010) The Netherlands (7 October 2010) Portugal (16 December 2010) Sweden (30	Spain (2010)	Greece Hungary Romania Slovenia	Bulgaria Greece Romania (no SPC) Slovak Republic

No.	INN of medicine to which patent applies	Marketing authorisation holder	Member State's NPO granting SPC extension (year)	Member State with SPC extension pending (in year)	No application for SPC extension (yet) in Member State (if not confidential)	Member State in which product has no SPC or patent qualifying for an SPC (if not confidential)
			September 2010) United Kingdom (11 January 2011)			
12	Zoledronic acid (Zometa and associated names)	Novartis	Austria (year not reported possibly 2011) Denmark (6 April 2010) France (11 June 2010) Finland (14 September 2011) Germany (27 May 2010) Ireland (28 June 2010) Italy (13 July 2010) Luxembourg (22 December 2010) The Netherlands (3 March 2010) Portugal (15 March 2010) Slovenia (19 March 2010) Sweden (27 April 2010) United Kingdom (30 June 2010)	Cyprus (2010) Greece (2010) Hungary (2010, 2011) Romania (2010, 2011) Spain (2010)		Bulgaria Slovak Republic

NPO = National Patent Office

4. Centrally authorised medicinal products

4.1. Initial marketing authorisation (MA) including a paediatric indication

Summary:

- For this section, only medicinal products were considered when a paediatric indication was granted as part of the initial MA.
- Thirty four (34) new medicinal products have been centrally authorised since 26 January 2007 with a paediatric indication at the time of initial MA.
- Out of these 34 medicinal products, 7 were authorised for a use only in the paediatric population, whereas the remaining 27 medicinal products were authorised for use in adults and in children.
- For 10 out of the 34 medicinal products, the requirements of the Paediatric Regulation needed to be fulfilled, meaning the corresponding PIP had not been completed.

Table 6: Medicinal Products with initial marketing authorisation including a paediatric indication

Year of European Commission Decision	No. in year	Requirement to fulfil Paediatric Regulation at first authorisation?	Indication is paediatric-only or "mixed" (adult and paediatric)?	Active substance(s)	Trade name
2007	1	No	Mixed	Retapamulin	Altargo
2007	2	No	Mixed	Nelarabine	Atriance
2007	3	No	Mixed	Human papillomavirus vaccine [types 16, 18]	Cervarix
2007	4	No	Mixed	Hydroxocobalamin	Cyanotik
2007	5	No	Mixed	Idursulfase	Elaprase
2007	6	No	Mixed	Gadoversetamide	Optimark
2007	7	No	Mixed	Betaine anhydrous	Cystadane
2007	8	No	Paediatric-only	Stiripentol	Diacomit
2007	9	No	Paediatric-only	Mecasermin	Increlex
2007	10	No	Mixed	Rufinamide	Inovelon
2007	11	No	Mixed	Hydroxycarbamide	Siklos
2007	12	No	Mixed	Human normal immunoglobulin (ivig)	Flebogamma DIF
2008	1	No	Mixed	Fluticasone furoate	Avamys
2008	2	No	Mixed	Human normal immunoglobulin	Privigen
2008	3	No	Mixed	Lacosamide	Vimpat
2008	4	No	Mixed	Micafungin	Mycamine
2008	5	No	Mixed	Sapropterin	Kuvan
2008	6	No	Mixed	Sugammadex	Bridion

Year of European Commission Decision	No. in year	Requirement to fulfil Paediatric Regulation at first authorisation?	Indication is paediatric-only or "mixed" (adult and paediatric)?	Active substance(s)	Trade name
2009	1	No	Paediatric-only	Tocofersonal d-alpha tocopheryl polyethylene glycol succinate	Vedrop
2009	2	No	Mixed	Mifamurtide	Mepact
2009	3	No	Mixed	Rilonacept	Rilonacept Regeneron
2009	4	No	Mixed	Tacrolimus	Modigraf
2009	5	No	Paediatric-only	Pneumoccocal polysaccharide conjugate vaccine (absorbed)	Synflorix
2009	6	Yes	Mixed	Canakinumab	Ilaris (PIP not yet completed)
2009	7	Yes	Paediatric-only	Pneumoccocal polysaccharide conjugate vaccine (13-valent, absorbed)	Prevenar 13 (PIP not yet completed)
2010	1	Yes	Mixed	Meningococcal group a, c, w135 and y conjugate vaccine	Menveo (PIP completed)
2010	2	Yes	Mixed	Velaglucerase alfa	Vpriv (PIP not yet completed)
2011	1	Yes*	Paediatric-only	Influenza vaccine (live attenuated, nasal)	Fluenz (Waiver)
2011	2	Yes	Mixed	C1 inhibitor, human	Cinryze (PIP not yet completed)
2011	3	Yes	Mixed	Dihydroartemisinin / piperaquine phosphate	Eurartesim (PIP not yet completed)
2011	4	Yes (PUMA)	Paediatric-only	Midazolam	Buccolam (PIP completed)
2011	5	Yes**	Mixed	Everolimus	Votubia (PIP not yet

Year of European Commission Decision	No. in year	Requirement to fulfil Paediatric Regulation at first authorisation?	Indication is paediatric-only or "mixed" (adult and paediatric)?	Active substance(s)	Trade name
					completed)
2011	6	Yes**	Mixed	Tobramycin	Tobi Podhaler (PIP not yet completed)
2011	7	Yes	Mixed	Nomegestrol / estradiol	Ioa, Zoely(PIP completed)

* The PDCO opinion had granted a waiver for the full paediatric population. ** This was a new marketing authorisation for an orphan designated condition of a medicinal product that was already authorised in the EU for non-orphan designated condition(s). PUMA = Paediatric use marketing authorisation

4.2. Extension of therapeutic indication to include the paediatric population

- The therapeutic indications of 33 centrally authorised medicinal products was extended or amended to include part or subsets of the paediatric population.
- 38 changes to the authorised indications were adopted to include part or subsets of the paediatric population for these 33 centrally authorised medicinal products (several products had more than 1 change to their indications affecting the paediatric population).

Table 7: List of centrally authorised medicinal products for which the therapeutic indication was extended or amended to the paediatric population

Trade name	Active substance (INN)Inn	Date of EU DC	Subject of extension	MAH	Requirement to fulfil Article 8 of Paediatric Regulation Yes/No
Keppra	Levetiracetam	04/01/2007	Extension of the indication to include adjunctive therapy in the treatment of primary generalised tonic-clonic (PGTC) seizures in adults and adolescents from 12 years of age with idiopathic generalized epilep	UCB Pharma SA	No
Prevenar	Pneumococcal saccharide conjugated vaccine, adsorbed	09/03/2007	Extension of the indication to include new information on efficacy against disease caused by Streptococcus pneumoniae serotypes 4, 6B, 9V, 14, 18C, 19F and 23F in otitis media.	Wyeth Lederle Vaccines S.A.	No

Trade name	Active substance (INN)Inn	Date of EU DC	Subject of extension	MAH	Requirement to fulfil Article 8 of Paediatric Regulation Yes/No
Prevenar	Pneumococcal saccharide conjugated vaccine, adsorbed	02/04/2007	Extension of indication from active immunisation against bacteraemic pneumonia to active immunisation against pneumonia.	Wyeth Lederle Vaccines S.A.	No
Remicade	Infliximab	30/05/2007	Extension of indication to include treatment of severe active Crohn's disease in children aged 6 to 17 years.	Janssen Biologics B.V.	No
Aranesp	Darbepoetin alfa	30/08/2007	Extension of indication for CRF patients, which currently restricts the use of Nespo to paediatric subjects >/= 11 years of age	Amgen Europe B.V.	No
Telzir	Fosamprenavir	13/09/2007	Extension of indication of Telzir in combination with ritonavir for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults in combination with other antiretroviral medicinal products to include paediatric populations.	ViiV Healthcare UK Limited	No
Combivir	Lamivudine / zidovudine	13/11/2007	Extension of indication to include paediatric patients and replacement of film coated tablets by scored film coated tablets.	ViiV Healthcare UK Limited	No
Aerius	Desloratadine	31/03/2008	Extension of indication from 'chronic idiopathic urticaria' to 'urticaria'.	Merck Sharp & Dohme Ltd.	No
Apidra	Insulin glulisine	20/06/2008	Extension of indication to include 6 years old and older children based on the results of 2 paediatric studies.	Sanofi-aventis Deutschland GmbH	No
Gardasil	Human papilloma virus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)	10/07/2008	Extension of indication to include the prevention of high-grade vaginal dysplastic lesions (VaIN 2/3).	Sanofi Pasteur MSD, SNC	No

Trade name	Active substance (INN)Inn	Date of EU DC	Subject of extension	MAH	Requirement to fulfil Article 8 of Paediatric Regulation Yes/No
Humira	Adalimumab	25/08/2008	Extension of indication to include treatment of active polyarticular juvenile idiopathic arthritis in adolescents from 13 to 17 years of age.	Abbott Laboratories Ltd.	No
Cancidas	Caspofungin	26/11/2008	Extension of the indication to include the paediatric population.	Merck Sharp & Dohme Ltd.	No
Enbrel	Etanercept	22/12/2008	Extension of indication to include the treatment of chronic severe plaque psoriasis in children and adolescents from the age of 8 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.	Pfizer Ltd.	No
Zavesca	Miglustat	26/01/2009	Extension of indication to include the treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease.	Actelion Registration Ltd.	No
Protopic	Tacrolimus	26/02/2009	Extension of indication to 'maintenance treatment' further to completion of one study in adult patients and one in paediatric patients.	Astellas Pharma Europe B.V.	No
Aptivus	Tipranavir	23/06/2009	Extension of indication to include the treatment of HIV-1 infection in highly pre-treated adolescents 12 years of age or older with virus resistant to multiple protease inhibitors.	Boehringer Ingelheim International GmbH	No
Xolair	Omalizumab	27/07/2009	Extension of indication to children from 6 to <12 years of age as add-on therapy to improve allergic asthma control.	Novartis Europharm Ltd.	No
Abilify	Aripiprazole	21/08/2009	Extension of indication to include treatment of schizophrenia in adolescents 15 years and older.	Otsuka Pharmaceutical Europe Ltd.	No
Keppra	Levetiracetam	02/09/2009	Extension of indication to include the adjunctive treatment of partial seizures with or without secondary generalisation in children from 1 month to <4 years old.	UCB Pharma SA	No

Trade name	Active substance (INN)Inn	Date of EU DC	Subject of extension	MAH	Requirement to fulfil Article 8 of Paediatric Regulation Yes/No
PegIntron	Peginterferon alfa-2b	11/11/2009	Extension of indication of the combination therapy peginterferon alfa-2b and ribavirin to include treatment of the paediatric population.	Schering-Plough Europe	Yes
Rebetol	Ribavirin	11/11/2009	Extension of indication of the combination therapy peginterferon alfa-2b and ribavirin to include treatment of the paediatric population.	Schering-Plough Europe	Yes
Orencia	Abatacept	20/01/2010	Extension of indication to include the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis in paediatric patients 6 years of age and older who have had an insufficient response to other DMARDs including at least one TNF inhibitor.	Bristol-Myers Squibb Pharma EEIG	Yes
Reyataz	Atazanavir sulphate	05/07/2010	Extension of indication for Reyataz capsules to include the treatment of HIV-infected children and adolescents above the age of 6 in combination with other antiretroviral medicinal products.	Bristol-Myers Squibb Pharma EEIG	No
M-M-RVAXPRO	Measles, mumps and rubella vaccine (live)	06/09/2010	Extension of indication to include administration to healthy children from 9 months of age.	Sanofi Pasteur MSD, SNC	No
Inomax	Nitric oxide	17/03/2011	Extension of indication to include the treatment of pulmonary hypertension peri- and post heart surgery in children.	INO Therapeutics AB	Yes
Humira	Adalimumab	18/03/2011	Extension of indication to include treatment of active polyarticular juvenile idiopathic arthritis in the paediatric population aged from 4 to 12 years.	Abbott Laboratories Ltd.	Yes
Viread	Tenofovir disoproxil fumarate	24/03/2011	Amendment of indication based on the 48-week results of a safety and efficacy study GS-US-104-0321 in treatment-experienced adolescents aged 12 to 18 years old.	Gilead Sciences International Ltd.	Yes

Trade name	Active substance (INN)Inn	Date of EU DC	Subject of extension	MAH	Requirement to fulfil Article 8 of Paediatric Regulation Yes/No
Invega	Paliperidone	08/04/2011	Extension of indication to include treatment of psychotic or manic symptoms of schizoaffective disorder.	Janssen-Cilag International N.V.	Yes
Revatio	Sildenafil	02/05/2011	Extension of indication in paediatric patients aged 1 year to 17 years old with pulmonary arterial hypertension.	Pfizer Ltd.	Yes
Kiovig	Human normal immunoglobulin (ivig)	27/07/2011	Extension of indication to include treatment of multifocal motor neuropathy (MMN). Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation (HSCT) in adults and children.	Baxter AG	Yes
Roactemra	Tocilizumab	01/08/2011	Extension of indication to include treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids.	Roche Registration Ltd.	Yes
Synflorix	Pneumococcal polysaccharide conjugate vaccine (adsorbed)	05/08/2011	Extension of indication to increase the upper age limit of infants and children from 2 years to 5 years.	GlaxoSmith Kline Biologicals S.A.	Yes
Enbrel	Etanercept	24/08/2011	Extension of indication to include lower age range for polyarticular juvenile idiopathic arthritis (JIA) "from the age of 4 years" to "from the age of 2 years".	Pfizer Ltd.	Yes
Enbrel	Etanercept	24/08/2011	Extension of indication to include lower age range for paediatric plaque psoriasis from "from the age of 8 years" to "from the age of 6 years".	Pfizer Ltd.	Yes

Trade name	Active substance (INN)Inn	Date of EU DC	Subject of extension	MAH	Requirement to fulfil Article 8 of Paediatric Regulation Yes/No
Levemir	Insulin detemir	24/10/2011	Extension of indication as add-on therapy to liraglutide treatment.	Novo Nordisk A/S	Yes
Levemir	Insulin detemir	24/10/2011	Extension of indication to children aged 2-5 years	Novo Nordisk A/S	Yes
Soliris	Eculizumab	24/11/2011	Extension of indication to include atypical haemolytic uremic syndrome (aHUS). Additional vaccination and antibiotic prophylaxis recommendation have also been added in section 4.2 for treatment of aHUS in adults and children.	Alexion Europe SAS	Yes
Cervarix	Human papilloma virus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed)	05/12/2011	Extension of indication to children from 9 years.	GlaxoSmith Kline Biologicals S.A.	Yes

4.3. New route of administration or new pharmaceutical form for paediatric use

- 14 Centrally authorised products had either a new pharmaceutical form (10/14) and/or a new route of administration (1/14) or a new strength (3/14) authorised that has paediatric interest. It should be noted that even though there is an interest for the paediatric population, the addition of a new strength does not fall under the Article 8 of the Paediatric Regulation.

Table 8: List of paediatric relevant line extensions (addition of new route of administration, a new pharmaceutical form or new strengh) for centrally authorised medicinal products

Trade name	**Active substance (INN)**	**Date of EU CD**	**Subject of line extension**	**Paediatric interest**	**Marketing authorisation holder**	**Requirement to fulfil Article 8 of Paediatric Regulation?**
Aerius	desloratadine	23/04/2007	Addition of new pharmaceutical form: orodispersible tablets, 2.5 mg and 5 mg		Merck Sharp & Dohme Ltd.	No
BeneFIX	nonacog alfa	30/07/2007	Addition of new pharmaceutical form: powder and solvent for solution for injection, 250 IU, 500 IU, 1000 IU		Pfizer Ltd.	No
Ferriprox	deferiprone	19/11/2007	Addition of new pharmaceutical form: oral solution 100 mg/ml.	Already authorised in children	Apotex Europe B.V.	No
Rotarix	rotavirus vaccine, live	01/09/2008	Addition of new pharmaceutical form: oral suspension ("liquid formulation").	Already authorised in children	GlaxoSmithKline Biologicals S.A.	No
Temodal	temozolomide	17/02/2009	Addition of new pharmaceutical form: powder for solution for infusion	Paediatric statement clarifies in 4.1 the use of the products in children from 3 years onwards	Schering-Piough Europe	No
Aptivus	tipranavir	23/06/2009	Addition of new pharmaceutical form: oral solution		Boehringer Ingelheim International GmbH	No
Apidra	insulin glulisine	14/01/2010	Addition of new route of administration: intravenous use.	Already authorised	Sanofi-aventis Deutschland GmbH	No
Norvir	ritonavir	25/01/2010	New strength: 100 mg film coated tablet	Already authorised in children	Abbott Laboratories Ltd.	No
INOmax	nitric oxide	18/03/2011	Addition of new strength: 800 ppm	New strengh adopted in parallel of a new indication		Yes

Trade name	Active substance (INN)	Date of EU CD	Subject of line extension	Paediatric interest	Marketing authorisation holder	Requirement to fulfil Article 8 of Paediatric Regulation?
				Pulmonary hypertension associated with heart surgery (II/19) for adults and children (see section 4.2 of the report)		
ReFacto AF	morocto cog alfa	06/05 /2011	To apply for a Addition of new pharmaceutical form 3000 IU.	Product already authorised in children prior to this procedure.		No
ReFacto AF	morocto cog alfa	06/05 /2011	Addition of new pharmaceutical form: 500, 1000 and 2000 IU powder and solvent for solution for injection in pre-filled syringe.	Product already authorised in children prior to this procedure.		No
Myclausen	mycophenolate mofetil	16/09 /2011	Addition of a new pharmaceutical form and strength 250 mg hard capsules (two presentations)	Product already authorised in children. New lower dosage. Strengh not linked to PIP		No
Viramune	nevirapine	16/09 /2011	Addition of new strengths: 50 mg, 100 mg and 400 mg + a new pharmaceutical form: Prolonged-release tablet	For adults + ado and children from > 3 years onwards		Yes
Inovelon	rufinamide	21/11 /2011	New pharmaceutical form: 40 mg/ml, oral suspension.			Yes
Tamiflu	oseltamivir	28/11 /2011	Addition of the new strength: 6 mg/ml, powder for oral suspension	New paediatric. strengtgh so no linked to PIP		No

4.4. Variation to include statement on waiver or deferral in the SmPC

Summary:

- In total, the SmPCs of 59 centrally authorised medicinal products have been updated to include statement on waiver or deferral on the SmPC.
- The SmPCs of 33/59 centrally authorised medicinal products have been updated in section 5.1 to state that a full waiver has been granted.
- The SmPCs of 26/59 centrally authorised medicinal products have been updated to state that there is an ongoing PIP and that the submission of results of paediatric studies has been deferred
- For 10/59 centrally authorised medicinal products, the SmPC was updated after the product had been authorised (variation) and for 49/59, the statement was included in the SmPC at time of Marketing Authorisation.
- The EMA Report to the European Commission (2010) had identified 5 centrally authorised medicinal products, for which the statement on deferral and / or waiver had been inadvertently omitted. Since, the statement could be added in variations for 3 medicines (the marketing authorisation was withdrawn for the 2 other medicines).

Table 9: Variation procedures for centrally authorised medicines in which, inter alia, a statement on a deferral and / or a waiver was added to the SmPC

Invented name	**INN**	**Marketing authorisation holder**	**Full waiver**	**Deferral**	**Marketing Authorisation (MA) / Variation (V)**	**Date of EC Decision**
Exforge and associated names	Amlodipine besylate/ valsartan/ hydrochloro-thiazide	Novartis Europharm Ltd	X		MA	16/10/2009
Onbrez Breezhaler and associated names	Indacaterol maleate	Novartis Europharm Ltd	X		MA	30/11/2009
Orencia	Abatacept	Bristol Myers Squibb Pharma EEIG	X		V	20/01/2010
Elonva	Corifollitropin	N. V. Organon		x	MA	25/01/2010
Silodyx/ Urorec	Silodosin	Recordati Ireland Ltd.	x		MA	29/01/2010
Revolade	Eltrombopag	GlaxoSmithKline Trading Services Ltd		x	MA	11/03/2010
Duocover	Clopidogrel/ acetylsalicylic acid	Bristol-Myers Squibb Pharma EEIG	x		MA	15/03/2010
Duoplavin	Clopidogrel/ acetylsalicylic acid	Sanofi Pharma Bristol-Myers Squibb SNC	x		MA	15/03/2010
Menveo	Meningococcal	Novartis Vaccines		x	MA	15/03/2010

Invented name	INN	Marketing authorisation holder	Full waiver	Deferral	Marketing Authorisation (MA) / Variation (V)	Date of EC Decision
	group a, c, w-135 and y conjugate vaccine	and Diagnostics SRL				
Ristaben	Sitagliptin	Merck Sharp & Dohme Ltd		x	MA	15/03/2010
Ristfor	Sitagliptin / metformin hydrochloride	Merck Sharp & Dohme Ltd	x		MA	15/03/2010
Arzerra	Ofatumumab	Glaxo Group Ltd	x		MA	19/04/2010
Prolia	Denosumab	Amgen Europe B.V.	x		MA	26/05/2010
Votrient	Pazopanib	Glaxo Group Ltd	x		MA	14/06/2010
Daxas	Roflumilast	Nycomed GmbH	x		MA	05/07/2010
Ozurdex	Dexamethasone	Allergan Pharmaceuticals Ireland	X		MA	27/07/2010
Byetta	Exenatide	Eli Lilly Nederland B.		x	V	06/08/2010
Vpriv	Velaglucerase alfa	Shire Pharmaceuticals Ireland Ltd	x	x	MA	26/08/2010
Brinavess	Vernakalant hydrochloride	Merck Sharp & Dohme Ltd.	x		MA	01/09/2010
Sycrest	Asenapine	N.V. Organon		x	MA	01/09/2010
Raspican	Regadenoson	Gilead Sciences International Ltd.		x	MA	06/09/2010
Twynsta	Telmisartan / amlodipine	Boehringer Ingelheim International GmbH	x		MA	07/10/2010
Ruconest	Conestat alfa	Pharming Group N.V.		x	MA	28/10/2010
Sutent	Sunitinib	Pfizer Ltd	x	x	V	29/11/2010
Brilique/ Possia	Ticagrelor	Astra-Zeneca AB	x		MA	03/12/2010
Sprycel	Dasatinib	Bristol Myers Squibb EEIG		x	V	06/12/2010
Invega	Paliperidone	Janssen-Cilag International NV	x		V	13/12/2010
Baraclude	Entecavir	BRISTOL-MYERS SQUIBB PHARMA EEIG		x	V	16/12/2010
Tasigna	Nilotinib	Novartis		X	V	20/12/2010

Invented name	INN	Marketing authorisation holder	Full waiver	Deferral	Marketing Authorisation (MA) / Variation (V)	Date of EC Decision
		Europharm Ltd				
Fluenz	influenza vaccine (live attenuated, nasal)	MedImmune, LLC	X		MA	27/01/2011
Esbriet	pirfenidone	InterMune Europe Ltd	X		MA	28/02/2011
Xiapex	collagenase clostridium histolyticum	Pfizer Limited	X		MA	28/02/2011
Pumarix	pandemic influenza vaccine (h5n1) (split virion, inactivated, adjuvanted)	GlaxoSmithKline Biologicals s.a.		X	MA	04/03/2011
Teysuno	tegafur / gimeracil / oteracil	Taiho Pharma Europe, Limited	X		MA	14/03/2011
Gilenya	fingolimod	Novartis Europharm Limited		X	MA	17/03/2011
Halaven	eribulin	Eisai Europe Ltd	X		MA	17/03/2011
Jevtana	cabazitaxel	Sanofi-aventis	X		MA	17/03/2011
Viread	Tenofovir disoproxil fumarate	Gilead Sciences International Ltd.		x	V	24/03/2011
Trobalt	retigabine		X	X	MA	28/03/2011
Eliquis	apixaban	Bristol-Myers Squibb/Pfizer EEIG, Bristol-Myers Squibb House		X	MA	18/05/2011
Yellox	bromfenac	Croma Pharma GmbH	X		MA	18/05/2011
Cinryze	c1 inhibitor, human	ViroPharma SPRL		X	MA	15/06/2011
Nulojix	belatacept	Bristol-Myers Squibb Pharma EEIG		X	MA	17/06/2011
Benlysta	belimumab	Glaxo Group Limited		X	MA	13/07/2011
Yervoy	ipilimumab	Bristol-Myers Squibb Pharma EEIG	X		MA	13/07/2011
Victrelis	boceprevir	Merck Sharp & Dohme Ltd		X	MA	18/07/2011
Fampyra	fampridine	Biogen Idec	X		MA	20/07/2011

Invented name	INN	Marketing authorisation holder	Full waiver	Deferral	Marketing Authorisation (MA) / Variation (V)	Date of EC Decision
		Limited				
Trajenta	linagliptin	Boehringer Ingelheim International GmbH		X	MA	24/08/2011
Vibativ	telavancin	Astellas Pharma Europe B.V.		X	MA	02/09/2011
Zytiga	abiraterone	Janssen-Cilag International NV	X		MA	05/09/2011
Incivo	telaprevir	Janssen Cilag International NV		X	MA	19/09/2011
Vectibix	Panitumumab	Amgen Europe B.V.	x		V	10/11/2011
Vyndaqel	tafamidis	Pfizer Specialty UK Limited	X		MA	16/11/2011
Edurant	rilpivirine	Janssen-Cilag International NV		X	MA	28/11/2011
Eviplera	emtricitabine / rilpivirine / tenofovir disoproxil	Gilead Sciences International Limited		X	MA	28/11/2011
Dificlir	fidaxomicin	FGK Representative Service GmbH		X	MA	05/12/2011
Ipreziv	azilsartan medoxomil	Takeda Global Research and Development Centre (Europe) Ltd		X	MA	07/12/2011
Mabthera	Rituximab	Roche Registration Ltd.	X		V	14/12/2011
Nevanac	Nepafenac	Alcon Laboratories (UK) Ltd.	X		V	22/12/2011

4.5. Variation to include paediatric dosing information or recommendations (section 4.2 of SmPC)

- In total, the SmPCs of 63 centrally authorised medicinal products have been updated to include or amend paediatric dosing information or recommendations.
- 79 changes to the authorised section 4.2 of SmPCs were adopted to include include or amend paediatric dosing information or recommendations of these 63 centrally authorised medicinal products (several products had more than 1 change to their SmPC affecting the paediatric docing information or recommendations).

Table 10: List of variations that resulted in addition or amendment of paediatric dosage recommendations (no other paediatric relevant change in the SmPC is considered in this table).

Tradename	Inn	CD	Scope of the change	MAH
Fabrazyme	Agalsidase beta	24/01/ 2007	Based on the evaluation of Specific Obligation 2 (paediatric clinical study AGAL-016-01), the Marketing Authorisation Holder has applied for an update of sections 4.2, 4.8, 5.1 and 5.2 of the Summary of Product Characteristics. Section 3 of the Packa	Genzyme Europe B.V.
Ferriprox	Deferiprone	26/01/ 2007	Update of the information pertaining to chronic overdose and the risk of neurological disorders (sections 4.2, 4.4, 4.8 and 4.9) following the assessment of the 13th PSUR, and strengthening the wording on neutropenia and agranulocytosis and the monit	Apotex Europe B.V.
Betaferon	Interferon beta-1b	29/03/ 2007	Update of section 4.2 of the SPC regarding the use of Betaferon in paediatrics, as recommended by the CHMP. The Package Leaflet was amended accordingly. In addition a mistake was corrected in section 5.1 of the SPC. Furthermore, the product informati	Bayer Pharma AG
Emtriva	Emtricitabine	25/04/ 2007	Update of sections 4.2 and 5.2 of the SmPC to reflect results of a study evaluating the pharmacokinetics and safety of emtricitabine in neonates and young infants over the first 3 months of life, at CHMP request further	Gilead Sciences International Ltd.
Azopt	Brinzolamide	13/06/ 2007	Update of SmPC to include information on the paediatric data on Azopt. Amendments have been made to sections 4.2, 4.4, 4.8 and 5.1 of the SPC and to the Package Leaflet as appropriate.	Alcon Laboratories (UK) Ltd.
Ceprotin	Protein c	10/08/ 2007	Update sections 4.2 and 5.1 of the SmPC to include information on dosing in paediatric patients. Section 4.8 of the SmPC was also updated in order to clarify the assignment of related adverse drug reactions. F	Baxter AG

Tradename	Inn	CD	Scope of the change	MAH
Fasturtec	Rasburicase	10/08/ 2007	Update sections 4.2 and 5.1 of the SmPC with paediatric data. The Package Leaflet has also been updated accordingly. The MAH has also taken the opportunity to update the annexes according to the latest QRD template (version 7.2)	Sanofi-aventis
Tritanrix HepB	Diphtheria (d), tetanus (t), pertussis (whole cell) (pw) and hepatitis b (rdna) (hbv) vaccine (adsorbed)	10/08/ 2007	Update section 5.1 of the SmPC to include information about the immune response induced by the 6, 10, 14-week schedule further to the assessment of the renewal. Section 4.2 "Posology	GlaxoSmithKline Biologicals S.A.
NovoSeven	Eptacog alfa (activated)	03/09/ 2007	Update of section 5.2 of the SmPC based on the results from two pharmacokinetic studies. Consequently, the MAH proposed to update section 4.2 of the SPC with regards to dosing information	Novo Nordisk A/S
Lamivudine ViiV	Lamivudine	20/09/ 2007	Update of SmPC To update sections 3, 4.2 and 5.2 of the SPC to replace film coated tablets by scored film coated tablets for use by paediatric patients.	ViiV Healthcare UK Limited
Epivir	Lamivudine	30/10/ 2007	Update sections 3, 4.2 and 5.2 of the SmPC to replace film coated tablets by scored film coated tablets for use by paediatric patients.	ViiV Healthcare UK Limited
Ziagen	Abacavir sulfate	20/11/ 2007	Update sections 3 and 4 of the SmPC to replace film coated tablets by scored film coated tablets for use by paediatric patients.	ViiV Healthcare UK Limited
RotaTeq	Rotavirus vaccine, live, oral	14/12/ 2007	Update of sections 4., 4.4 and 5.1 of the SmPC regarding administration of Rotateq to prematurely born infan	Sanofi Pasteur MSD, SNC
NovoMix	Insulin aspart	18/12/ 2007	Update of sections 4.2, 5.1 and 5.2 of the SmPC to include information about paediatric use.	Novo Nordisk A/S
Prevenar	Pneumococcal saccharide conjugated vaccine,	06/02/ 2008	Update of sections 4.2, 4.4 and 5.1 with immunogenicity and effectiveness data on the 3 dose immunisation schedule.	Wyeth Lederle Vaccines S.A.

Tradename	Inn	CD	Scope of the change	MAH
	adsorbed			
Avastin	Bevacizumab	26/02/2008	Update of SmPC following the fulfilment of follow-up measures: Section 4.2. and Section 5.2 were revised following the results of a PK study in a limited number of paediatric patients.	Roche Registration Ltd.
Optisulin	Insulin glargine	31/03/2008	Update of section 4.2 of the SmPC to add a more flexible dosing scheme, i.e. administration once daily at any time but the same time each day.	Sanofi-aventis Deutschland GmbH
Aldara	Imiquimod	07/07/2008	Update of sections 4.2, 5.1 and 5.2 of the SmPC following evaluation of paediatric studies in the treatment of molluscum contagiosum.	Meda AB
NovoMix	Insulin aspart	28/07/2008	Update of sections 4.2 and 5.1 of the SmPC to include information regarding the transfer from biphasic human insulin to biphasic insulin aspart 30.	Novo Nordisk A/S
Infanrix penta	Diphtheria (d), tetanus (t), pertussis (acellular, component) (pa), hepatitis b (rdna) (hbv), poliomyelitis (inactivated) (ipv) vaccine (adsorbed)	13/08/2008	Update of section 4.2 of the SmPC to harmonise the information on booster vaccination with that of Infanrix hexa.	GlaxoSmithKline Biologicals S.A.
Ziagen	Abacavir sulfate	02/09/2008	Update of sections 4.2 and 5.2 of the SmPC relating to administration of crushed tablets with food and liquid.	ViiV Healthcare UK Limited
Epivir	Lamivudine	05/09/2008	Update of sections 4.2 and 5.2 of the SmPC relating to administration of crushed tablets with food and liquid.	ViiV Healthcare UK Limited
Sustiva	Efavirenz	15/09/2008	Update of section 4.2 and 5.2 of the SmPC to incorporate bioequivalence results of the open capsules, further to request of the CHMP made in the context of the evalution	Bristol-Myers Squibb Pharma EEIG

Tradename	Inn	CD	Scope of the change	MAH
			of PSUR 10.	
Combivir	Lamivudine / zidovudine	16/09/ 2008	Update of sections 4.2 and 5.2 of the SmPC relating to administration of crushed tablets with food and liquid.	ViiV Healthcare UK Limited
Infanrix penta	Diphtheria (d), tetanus (t), pertussis (acellular, component) (pa), hepatitis b (rdna) (hbv), poliomyelitis (inactivated) (ipv) vaccine (adsorbed)	30/10/ 2008	Update of sections 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC based on a review of data available from clinical studies or post-marketing surveillance and in line with relevant guidelines.	GlaxoSmithKline Biologicals S.A.
Rapamune	Sirolimus	30/10/ 2008	Update of sections 4. 2, 4.8, 5.1 and 5.2 of the SmPC to include data from completed clinical trials in paediatric patients, as requested by the CHMP in April 2006.	Pfizer Ltd.
Infanrix hexa	Diphtheria (d), tetanus (t), pertussis (acellular, component) (pa), hepatitis b (rdna) (hbv), poliomyelitis (inactivated) (ipv) and haemophilus influenzae type b (hib) conjugate vaccine (adsorbed)	31/10/ 2008	Update of sections 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC based on a review of data available from clinical studies or post-marketing surveillance and in line with relevant guidelines.	GlaxoSmithKline Biologicals S.A.

Tradename	Inn	CD	Scope of the change	MAH
Telzir	Fosamprenavir	22/12/2008	Update of section 4.2 of the SmPC in order to clarify the dosing recommendations in children further to the CHMP conclusion on a clinical follow-up measure.	ViiV Healthcare UK Limited
BYETTA	Exenatide	07/01/2009	Update of sections 4.2 and 5.2 of the SmPC with information regarding pharmacokinetic data in adolescents from study 2993-124 (PK/PD in adolescents).	Eli Lilly Nederland B.V.
Tamiflu	Oseltamivir	26/01/2009	Update of section 4.2 of the SmPC to provide instructions on the extemporaneous preparation of liquid formulations of Tamiflu using the capsule contents.	Roche Registration Ltd.
Onsenal	Celecoxib	17/03/2009	Alignment of SmPC of Onsenal with SmPC of Celebra (version date 14 November 2007) as requested by the CHMP at the time of the opinion on the 4th Annual Re-assessment, with amendment to the sections 4.2.	Pfizer Ltd.
Telzir	Fosamprenavir	25/03/2009	Update of section 4.2, 4.3, 4.4 and 5.2 of the SmPC.	ViiV Healthcare UK Limited
Alisade	Fluticasone furoate	02/06/2009	Update the sections 4.2, 4.4 and 4.8 of the SmPC with safety information following the assessment of the first PSUR.	Glaxo Group Ltd.
Tracleer	Bosentan	01/07/2009	Update of the SmPC with regard to the posology in paediatric patients in section 4.2 of the SPC, further to the results of clinical studies and a review of the literature and post-marketing experience.	Actelion Registration Ltd.
Rotarix	Rotavirus vaccine, live	21/08/2009	Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC regarding safety and immunogenicity of Rotarix when administered to pre-term infants with gestational age of 27 to 36 weeks based on a phase IIIb study.	GlaxoSmithKline Biologicals S.A.
Neulasta	Pegfilgrastim	23/10/2009	Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC to add information for physicians on recommended use in paediatric patients based on a clinical study 990130 and publication.	Amgen Europe B.V.

Tradename	Inn	CD	Scope of the change	MAH
Tamiflu	Oseltamivir	23/10/ 2009	Update of sections 4.2 of the SmPC to provide instructions to prepare home and pharmacy extemporaneous formulations from Tamiflu 30, 45 and 75mg capsules.	Roche Registration Ltd.
Ketek	Telithromycin	04/11/ 2009	Update of of sections 4.2 and 5.2 of the SmPC following CHMP request further to the evaluation of paediatric data in accordance with article 46 of the paediatric regulation.	Aventis Pharma S.A.
Exjade	Deferasirox	23/11/ 2009	Update of Section 4.2 of the SmPC to extend the recommended dose range for maintenance therapy to a maximum of 40 mg/kg/day. Consequently the section 4.4 is amended.	Novartis Europharm Ltd.
Focetria	Pandemic influenza vaccine (surface antigen, inactivated, adjuvanted) a/california/7/ 2009 (h1n1)v like strain (x-181)	27/11/ 2009	Update of sections 4.2, 4.8 and 5.1 of the SmPC to reflect the currently immunogenicity and safety clinical trial data available in children and adolescents, as requested by the CHMP.	Novartis Vaccines and Diagnostics S.r.l.
Pandemrix	Pandemic influenza vaccine (h1n1) (split virion, inactivated, adjuvanted) a/california/7/ 2009 (h1n1)v like strain (x-179a)	27/11/ 2009	Update of SmPC, Annex II and Package Leaflet To update sections 4.2, 4.4, 4.8 and 5.1 of the SmPC, and Annex IIC to reflect newly available results from clinical study D-PAN-H1N1-009.	GlaxoSmithKline Biologicals S.A.
Pandemrix	Pandemic influenza vaccine (h1n1) (split virion, inactivated, adjuvanted) a/california/7/ 2009 (h1n1)v like strain (x-179a)	09/12/ 2009	Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC to reflect new safety and efficacy data post dose 2 (half adult dose) from a study in children aged 6 to 35 months (D-Pan-H1N1-009).	GlaxoSmithKline Biologicals S.A.

Tradename	Inn	CD	Scope of the change	MAH
Pandemrix	Pandemic influenza vaccine (h1n1) (split virion, inactivated, adjuvanted) a/california/7/ 2009 (h1n1)v like strain (x-179a)	22/12/ 2009	Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC to reflect post dose 2 safety and immunogenicity results from a phase III study.	GlaxoSmithKline Biologicals S.A.
Focetria	Pandemic influenza vaccine (surface antigen, inactivated, adjuvanted) a/california/7/ 2009 (h1n1)v like strain (x-181)	23/12/ 2009	Update of sections 4.2, 4.8 and 5.1 of the SmPC regarding administration of Focetria to children of 3 to 8 years of age based on results of a study in children as requested by the CHMP. Section 4.8 was also updated.	Novartis Vaccines and Diagnostics S.r.l.
Tamiflu	Oseltamivir	20/01/ 2010	Update of sections 4.2 and 4.4 of the SmPC to add information on the use of Tamiflu in premature infants.	Roche Registration Ltd.
Viracept	Nelfinavir	20/01/ 2010	Update of sections 4.2, 4.5 and 5.2 of the SmPC following the CHMP's assessment of PSUR 13 on 21 August 2008.	Roche Registration Ltd.
Xolair	Omalizumab	25/01/ 2010	Update of section 4.2 of the SmPC to amend the current dosing table to include patients with baseline IgE concentrations of up to 1500 IU/mL.	Novartis Europharm Ltd.
Tamiflu	Oseltamivir	15/03/ 2010	Update of sections 4.2, 4.4, 4.8, 5.1 and 5.3 of the SmPC with information on the prophylaxis of immunocompromised patients and safety information for the seasonal prophylaxis of children from 1 to 12 years of age.	Roche Registration Ltd.
Norvir	Ritonavir	23/03/ 2010	Update of section 4.2 of the SmPC following the annual review of relevant information on ritonavir-boosted protease inhibitors in line with follow-up measure 033.	Abbott Laboratories Ltd.

Tradename	Inn	CD	Scope of the change	MAH
Kaletra	Lopinavir / ritonavir	30/03/ 2010	Update of sections 4.2, 4.5, 4.8 and 5.1 of the SmPC of the Kaletra film-coated tablets (200/50 mg and 100/25 mg) based on the Phase III study M06-80.	Abbott Laboratories Ltd.
Focetria	Pandemic influenza vaccine (surface antigen, inactivated, adjuvanted) a/california/7/ 2009 (h1n1)v like strain (x-181)	27/04/ 2010	Update of section 4.2, 4.5, 4.8 and 5.1 of the SmPC to include safety and immunogenicity information following assessment of the H1N1 data available with Focetria in children, adults and the elderly.	Novartis Vaccines and Diagnostics S.r.l.
Mirapexin	Pramipexole	01/07/ 2010	Update of section 5.1 of the SmPC to include results from study 248.644, in line with article 46 of the paediatric legislation. In addition, the description of the paediatric population in section 4.2 and 5.1	Boehringer Ingelheim International GmbH
Celvapan	Pandemic influenza vaccine (h1n1) (whole virion, inactivated, prepared in cell culture)	05/07/ 2010	Update of sections 4.2 and 5.1 of the SmPC based on clinical study results (study 920903) with Celvapan containing 7.5µg H1N1 antigen of the A/H1N1/California/07/2009 influenza virus in infants, children and adolescent aged 6 months to 17 years.	Baxter AG
Cervarix	Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed)	06/08/ 2010	Update of section 4.2 with regards to flexibility in dosing schedule of the third vaccination on the basis of results from study HPV-044.	GlaxoSmithKline Biologicals S.A.
Focetria	Pandemic influenza vaccine (surface antigen, inactivated, adjuvanted) a/california/7/ 2009 (h1n1)v like strain (x-181)	12/08/ 2010	Update of sections 4.2, 4.8 and 5.1 of the summary of product characteristics regarding administration of Focetria to children of 12 to 35 months of age based on results of study V111_3 in children. Furthermore, posology recommendation in children is	Novartis Vaccines and Diagnostics S.r.l.

Tradename	Inn	CD	Scope of the change	MAH
Abilify	Aripiprazole	05/11/2010	Update of sections 4.2 and 5.1 of the SPC to include information related to studies CN138-178, CN138-179, and CN138-180 conducted in patients (6-17 years) with irritability associated with autistic disorder (IAD) following CHMP conclusions on article	Otsuka Pharmaceutical Europe Ltd.
Twinrix Paediatric	Hepatitis a (inactivated) and hepatitis b(rdna) (hab) vaccine (adsorbed)	05/11/2010	To update section 4.2 "Posology and method of administration" and section 5.1 "Pharmacodynamic properties"of the Twinrix Paediatric SmPC with data coming from two long-term immune persistence studies: HAB-137 and HAB-157 which were conducted in child	GlaxoSmithKline Biologicals S.A.
Ambirix	Hepatitis a (inactivated) and hepatitis b(rdna) (hab) vaccine (adsorbed)	26/11/2010	Update of SPC sections 4.6, 4.7, 4.8 and 4.9 to reflect the safety and reactogenicity data acquired through PMS data. The MAH took also the opportunity to clarify wording in sections 4.1, 4.2, 5.1 and 6.6. The PL is updated accordingly. The MAH furth	GlaxoSmithKline Biologicals S.A.
Aloxi	Palonosetron hydrochloride	20/12/2010	Update of section 4.2, 5.1 and 5.2 of the SmPC to include information from Aloxi paediatric studies PALO-99-07 and PALO-07-29 following P46 procedure. Furthermore, editorial changes have been made in sections 8, 9 and 10 of the SmPC, Annex II and Pac	Helsinn Birex Pharmaceuticals Ltd.
INOmax	Nitric oxide	21/01/2011	Update of sections 4.2, 4.4 and 5.1 of the SmPC to include efficacy and safety data from study INOT27, as requested by the CHMP.	INO Therapeutics AB
Torisel	Temsirolimus	24/01/2011	Update of SmPC sections 4.2, 4.4, 4.8, 5.1 and 5.2 with information based on the results of a Phase I/II safety and exploratory PK study in paediatric subjects with relapsed/refractory solid tumours in line with FUM 007.	Pfizer Ltd.
Protopic	Tacrolimus	21/02/2011	Update of sections 4.4, 4.5 and 5.1 of the SmPC with information related to the impact of the use of tacrolimus ointment on the immunocompetence in paediatric population.	Astellas Pharma Europe B.V.
Erbitux	Cetuximab	18/04/2011	Update of SmPC sections 4.2, 4.4, and 5.2 with information from paediatric PK study.	Merck KGaA

Tradename	Inn	CD	Scope of the change	MAH
Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvant	Pandemic influenza vaccine (h5n1) (split virion, inactivated, adjuvanted) a/vietnam/1194/2004 nibrg-14	18/04/2011	Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC to reflect new data obtained from study D-Pan H5N1-009, a clinical study is conducted in children aged 3 to 9 years.	GlaxoSmithKline Biologicals S.A.
Prepandrix	Prepandemic influenza vaccine (h5n1) (split virion, inactivated, adjuvanted)	20/04/2011	Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC to reflect new data obtained from study D-Pan H5N1-009, a clinical study is conducted in children aged 3 to 9 years.	GlaxoSmithKline Biologicals S.A.
Plavix	Clopidogrel	27/05/2011	Update of sections 4.2 and 5.1 of clopidogrel SmPC to include new paediatric information.	Sanofi Pharma Bristol-Myers Squibb SNC
Busilvex	Busulfan	26/07/2011	Update of sections 4.2, 4.4 and 4.5 of the SmPC based on the results of a Phase II study assessed with FU2 007.1 regarding information on seizure prophylaxis treatment.	Pierre Fabre Médicament
Remicade	Infliximab	26/07/2011	Update of sections 2, 4.1, 4.2, 4.4, 4.5, 4.6, 4.7, 4.8, 5.1 and 5.2 of the SmPC to align with the SmPC guideline and the QRD template.	Janssen Biologics B.V.
Faslodex	Fulvestrant	27/07/2011	Update of sections 4.2, 4.4, 5.1 and 5.2 the SmPC based on paediatric data from Study D6992C0044 further to the assessment of the paediatric Article 46 follow up measure (P46 022).	AstraZeneca UK Ltd.
Kiovig	Human normal immunoglobulin (ivig)	27/07/2011	Update of section 4.4 of the SmPC to add a statement regarding hyperproteinemia and hyponatremia. Furthermore, changes are proposed to align the SmPC with the revised Core SmPC for IVIg products.	Baxter AG
Tygacil	Tigecycline	24/08/2011	To update sections 4.2, 4.8 and 5.2 of the Tygacil SmPC with paediatric PK and safety information based on the results of paediatric studies 3074K4-2207-WW and 3074A1-110-US, both submitted and assessed in previous procedures	Pfizer Ltd.

Tradename	Inn	CD	Scope of the change	MAH
Tepadina	Thiotepa	26/08/2011	Update of sections 4.2 and 6.6 of the SmPC regarding reconstitution instructions and final target concentration in the solution for infusion and update of section 6.3 of the SmPC to amend shelf life.	ADIENNE S.r.l.
Removab	Catumaxomab	05/09/2011	Update of section 4.2 of the SmPC to reduce the infusion time from 6 hours to 3 hours following the assessment of PSUR 02, substantiated by new additional data.	Fresenius Biotech GmbH
Viracept	Nelfinavir	05/09/2011	Update of section 4.2 of the SmPC and section 3 of the PL to change the TID dosing recommendations for children aged 3-13 years from 25-30 mg/kg to 25-35 mg/kg and include dose recommendations for tablets for children aged 3-13 years weighing less than 18kg.	Roche Registration Ltd.
ROTARIX	Rotavirus vaccine, live	24/10/2011	To update sections 4.4 and 5.1 of the SmPC to include efficacy data from trial Study Rota-028/029/030 in Asia that was extended up to the age of 3 years.	GlaxoSmithKline Biologicals S.A.
EVOLTRA	Clofarabine	21/11/2011	Update of sections 4.2, 4.4 and 5.2 of the SmPC to include a dosing recommendation for paediatric patients with moderate renal impairment further to the request of the CHMP following the assessment of the responses to Specific Obligation 12 (SO2 012.7).	Genzyme Europe B.V.
FABRAZYME	Agalsidase beta	22/11/2011	Update of Section 4.2 of the SmPC to include a statement about the possibility for the patients to be treated by home infusion with Fabrazyme.	Genzyme Europe B.V.
REYATAZ	Atazanavir sulphate	22/11/2011	Update of sections 4.2, 4.6 and 5.2 of the SmPC with pharmacokinetic and safety data from study AI424182 of ATV/RTV administered as part of HAART to HIV infected pregnant women. The PL was updated accordingly.	Bristol-Myers Squibb Pharma EEIG
SYNAGIS	Palivizumab	19/12/2011	Update of sections 4.4 and 4.8 of the SmPC in order to add a warning for anaphylactic shock.	Abbott Laboratories Ltd.

4.6. Variation with paediatric data linked to off label use included into SmPC

- No specific data and no case could be retrieved on this question. The data bases do not allow to pick up such information if it were present. Data on off label use are not tracked by the EMA.

4.7. Variations under Article 36.1.2 – data of completed PIP failed to lead to a paediatric indication

Table 11: Variations assessing paediatric data that were in compliance with a completed, agreed PIP, but not leading to any paediatric indication

Active substance (INN)	Product name	Condition that was targeted but no paediatric use but was authorised	Outcome of CHMP assessment	Date of EC Decision
Zoledronic acid	Zometa	Treatment of osteogenesis imperfecta	The CHMP considered that the overall Benefit-Risk Ratio of Zometa in the applied extension of indications is negative.	25/01/2010
Clopidogrel	Plavix and associated names	Prevention of thromboembolic events	Clopidogrel should not be used in children because of efficacy concerns.	27/05/2011

5. Article 29 Paediatric Regulation referral procedures

This type of procedure may be triggered by a marketing authorisation holder when applying for a new indication, new pharmaceutical form or new route of administration for use in the paediatric population for a product authorised under Directive 2001/83/EC. The Committee for Medicinal Products for Human Use (CHMP) makes a recommendation, and the European Commission issues a decision to all Member States reflecting the measures to take to implement the CHMP recommendation. The following table is based on information published here: http://bit.ly/xNihRe. From this webpage, the CHMP assessment reports can be accessed.

Summary:

- From 2007 to 2011, for 5 active substances in total 8 referral procedures under Article 29 of the Paediatric Regulation were completed: anastrozol, irbesartan, valsartan, atorvastatin and latanoprost. Except for anastrozol, new paediatric indications and new pharmaceutical forms were recommended for the first time.

Table 12: Article 29 Paediatric Regulation referral procedures completed by 2011

No.	Active substance (INN)	Trade name	Associated names if any	Summary of outcome of CHMP assessment	Date of CHMP opinion
1	Anastrozol	Arimidex		Based on the CHMP review of data on safety and efficacy, the CHMP considered that the risk benefit balance of Arimidex 1mg film-coated tablets in the treatment of short stature in pubertal boys with growth hormone deficiency, in combination with exogenous growth	06/11/2009

No.	Active substance (INN)	Trade name	Associated names if any	Summary of outcome of CHMP assessment	Date of CHMP opinion
				hormone, was unfavourable and therefore did not recommend the granting of an extension of the Marketing Authorisation.	
2	Irbesartan	Cozaar	Loortan, Loortan Cardio Start, Cozaar Startpakkle, Cardopal Start, Lorzaar, Lorzaar start, Lorzaar Protect, Pinzaar, Lorzaar Varipharmstart, Lortaan, Neo-Lotan, Losaprex, Cozaar IC, Lortaar IC	Based on the CHMP review of data on quality, the CHMP considered by consensus decision that the risk-benefit balance of Cozaar and associated names in the treatment of • essential hypertension in adults and in children and adolescents 6 - 16 years of age. • renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment • reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG was favourable and therefore recommended the granting of the marketing authorisation.	23/10/2008
3, 4	Valsartan	Diovan	Angiosan, Diovane, Tareg, Cordinate, Provas, Dalzad, Rixil, Kalpress Cardio, Diovan Cardio, Miten Cardio, Valsartan Novartis, Kalpress, Miten	Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Diovan (oral solution 3 mg/ml) in the treatment of hypertension in children and adolescents 6 to 17 years of age is favourable and therefore recommended the granting of the marketing authorisation. A post-approval study of long-term effects in CKD and non-CKD patients needs to be carried out and the efficacy of valsartan in younger age group (having potential impact also to the older children with secondary hypertension) has to be clarified in an additional randomised trial.	15/12/2009
5, 6, 7	Atorvastatin	Sortis	Lipitor, Zarator, Orbeos,	Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-	18/03/2010

No.	Active substance (INN)	Trade name	Associated names if any	Summary of outcome of CHMP assessment	Date of CHMP opinion
			Tahor, Liprimar, Atorvastatin , Atorvastatina, Edovin, Obradon, Xarator, Torvast, Totalip, Texzor, Cardyl, Prevencor	benefit balance of Sortis and associated names chewable tablets 5 mg, 10 mg, 20 mg and 40 mg and film-coated tablets 10 mg, 20 mg, 40 mg and 80 mg as an adjunct to diet for reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides in adolescents and children aged 10 years or older with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (Corresponding to Types IIa and IIb of the Fredrickson classification) when response to diet and other non-pharmacological measures is inadequate was favourable, and therefore recommended the granting of the marketing authorisation.	
8	Latanoprost	Xalatan	Latanoprost Pharmacia & Upjohn; Xalatan 50 mikrogramov/ml kaplijice za oko, raztopina	Based on overall submitted data on safety and efficacy provided by the MAH, the CHMP considered by consensus that the risk-benefit balance of Xalatan and associated names for reduction of elevated intraocular pressure in paediatric patients with elevated intraocular pressure and paediatric glaucoma was favourable and therefore recommended amendments to the marketing authorisations of the medicinal product referred to in Annex I of the Opinion.	22/07/2010

6. Data from Member States

6.1. Scientific advice for paediatric medicine development

Summary:

- Detailed information on Scientific Advices related to paediatric medicine development was provided only from 2010 onwards for the majority of Member States.
- Altogether, 9 Member States reported to have provided 128 such Scientific Advices (49 in 2010 and 79 in 2011). The number of such advices provided ranged from 2 to 65 between Member States.
- Approximately 80 companies benefited from the scientific advice provided by Member States during the years 2010 and 2011.

- The line listings of medicines for which Scientific Advice(s) has been obtained are commercially confidential information and therefore are provided to the European Commission in the confidential Annex III to this report.

Table 13: Overview on number of Scientific Advices (SA) and populations addressed with questions for SA by Member States (only those that provided data) and by year as well as incentives

Year	Member State	I 1. - SA: paediatric only	I 1. - SA: "mixed"	I 2. - Fee waiver for paediatric-only SA?
2011	Austria	0	0	No
2011	Belgium	0	5	No
2011	Cyprus	0	0	No
2011	Czech Republic	0	0	No
2011	Denmark	0	2	No
2011	Estonia	0	0	No
2011	Finland	0	0	ND
2011	France	1	2	Yes
2011	Germany	0	32	No
2011	Hungary	0	0	No
2011	Ireland	0	0	No
2011	Italy	3	1	No
2011	Latvia	NR	NR	No
2011	Lithuania	0	0	ND
	Luxembourg			
2011	Malta	0	0	No
2011	Poland	NR	NR	ND
2011	Portugal	0	0	No
2011	Romania	0	0	No
2011	Slovenia	0	0	No
2011	Spain	1	3	NR
2011	Sweden	3	8	No
2011	The Netherlands	0	0	No
2011	United Kingdom	3	12	Yes
2010	Belgium	0	7	
2010	Germany	0	23	
2010	Sweden	2	7	
2010	United Kingdom	3	7	
2009	Sweden		16	
2008	Sweden		13	
2007	Sweden		22	

"Mixed" = Adult and paediatric population. NR = Not responsible for Scientific Advice. ND = Not documented. NR = Not reported for respective year.

6.2. Support for paediatric medicine development

The national paediatric research incentives were described in detail in the EMA annual report 2010 (http://ec.europa.eu/health/files/paediatrics/2011_report_art50l.pdf).

Table 14: Incentives and support for paediatric medicine development available by Member State (listing only those that provided data)

Member State	**National support for paediatric medicine development?**	**Fee waiver / reduction for paediatric clinical trial application (CTA)?**	**Priority review for paediatric CTA**	**Fee reduction for paediatric MA / variation?**	**Priority review for paediatric MA / variation?**
Austria	No	No	No	No	No
Belgium	Partial	No	No	No	No
Cyprus	No	No	No	No	No
Czech Republic	No	No	No	No	No
Denmark	No	No	No	No	No
Estonia	No	No	No	No	No
Finland	No	No	No	No	No
France	Yes	Yes	No	No	No
Germany	No	No	No	No	No
Hungary	No	No	No	No	No
Ireland	No	No	No	No	No
Italy	Yes	No	No	No	No
Latvia	No	No	No	No	No
Lithuania	No	No	No	No	No
Malta	No	No	No	No	No
Poland	No data available		No	No	No
Portugal	No	No	No	No	No
Romania	No	No	No	No	No
Slovenia	No	Yes	No	No	No
The Netherlands	No	No	No	No	No
Spain	Partial				
Sweden	No	No	No	No	No
United Kingdom	Yes	No	No	Yes	Yes

6.3. Benefits and infringements

Table 15: Data from Member States (listing only those that provided data) related to other benefits offered for paediatric medicines and documenting any known infringements of the obligations and responsibilities under the Paediatric Regulation

Member State	**Benefits for reimburse-ment of paediatric medicines?**	**Marketing authorisation application submission validated without Article 7 or 8 fulfilled?**	**Compliance statem without paediatric data included in SmPC?**	**Authorisation obtained without waiver or deferral statement added to SmPC?**	**Any other situation of benefit or infringement?**
Austria	No	No	No		No
Belgium	No	No	No	No	No
Cyprus	No	No	No	No	No
Czech Republic	No	No	No	No	No
Denmark	No				No
Estonia	No	No	No	No	No
Finland		No	No	No	No
Germany	No	No	No	No	No
Hungary	Yes (1)	No	No	Yes (2)	No
Ireland					Do not know
Italy	No	No	No	No	No
Lithuania	No	No	No	No	No
Malta	No	No	No		
The Netherlands	No	No	No	No	No
Poland	No	No	No	No	No
Portugal	No	No	No		No
Romania	No	No	No	No	
Slovenia	No	No	No	No	No
Sweden	No	No	No	No	No
United Kingdom	Yes (3)	None known	None known	None known	No

(1) Products included in the national Immunisation programme are provided for children by the Hungarian government free of charge.
(2) Statement on waiver not included in marketing authorisations for amlodipin / bisoprolol and bisoprolol / acetylsalicylic acid
(3) Under the Pharmaceutical Price Regulation Scheme, companies may benefit from the variable rate for paediatrics element of the R&D allowance. However, the amount is small (a maximum of 3%) of a company's sales of branded medicines to the NHS and in practice only one or two companies have claimed the paediatrics element. Companies have not benefited materially as the amount was insufficient to generate a price increase for the company or to reduce the amount of excess profits repayable under the PPRS and so NHS list prices were unchanged.

6.4. National competent authorities on the internet

The National compentent authorities (NCAs) in the Member States of the EU, including contact details and links to their websites, are listed here: http://bit.ly/pPT5TD. See Table 16 for Member States' databases on medicines. Information on nationally authorised medicines authorised in relation to the Mutual Recognition procedure are made available here: http://mri.medagencies.org/Human/.

Table 16: Addresses of NCA's publicly accessible databases on medicinal products for human use.

Member State	SmPCs available under address
Austria	http://pharmaweb.ages.at/
Estonia	http://193.40.10.165/register/register.php?keel=eng&inim_vet=inim
Hungary	http://www.ogyi.hu/gyogyszeradatbazis/
Ireland	http://www.imb.ie/EN/Medicines/HumanMedicines/HumanMedicinesListing.aspx
Poland	http://www.urpl.gov.pl/drugs
Slovakia	http://www.zdravila.net/
Spain	http://www.aemps.gob.es/cima/fichasTecnicas.do?metodo=detalleForm
Sweden	http://www.fass.se/

Source: Data provided by Member States.

7. Medicinal products authorised through national / decentral / mutual recognition procedure, including those subject to Article 29 of the Paediatric Regulation

7.1. Initial marketing authorisation (MA) including a paediatric indication

Summary:

- Overall 12 Member States* provided data on this question, about 300 data entries covering more than 80 active substances and covering the period from 2007 to 2011 (more than 180 data entries 2011, less than 35 each for the preceding years). * Austria, Cyprus, Czech Republic, Finland, Hungary, Italy, Poland, Romania, Slovenia, Spain, Sweden, United Kingdom.
- In Table 17, the data provided have been summarised across Member States and presentations by using the English INN for the active substance(s).
- The data included medicines that were already authorised in some EU Member States, but became available for use in children through initial Marketing Authorisations in further, new Member States.
- The data provided were scrutinised for new medicinal products with new active substances. There were 3 such medicines that could be identified (name of medicinal product): Numeta and associated names, Celtura, Panenza. These are represented in section 5.1 of the core report.
- The legal basis, under which the medicinal products were authorised, was not requested to be reported, so that no distinction can be made between new medicines linked or not linked to the Paediatric Regulation. Some of the data entries may be for generic medicines, which do not fall under the Paediatric Regulation and thus are not part of this report. It should be noted that some of the medicinal products mentioned in the table 17 are not newly available on the European market but were reported as new marketing authorisations by Member States as newly accessible on their market.

Table 17 Data on medicines newly nationally authorised since 2007

Active substance (INN)	Medicinal product	Paediatric-only or adult / paediatric use (mixed)?	Marketing authorisation holder	Member State(s)	Year of marketing authorisation
Acetylsalicylic acid and pseudoephedrine hydrochloride	Asprin Complex 500 mg/30 mg granules for oral suspension	Mixed	Bayer d.o.o., Bravničarjeva 13, Ljubljana, Slovenia	Slovenia	2008
Acyclovir and hydrocortisone	Zovirax Plus, Xerclear, 50 mg/g + 10mg/g, Cream	Mixed	GlaxoSmithKline Pharmaceuticals S.A., Medivir AB, Sweden (SME)	Poland, Sweden	2010
Alendronic acid	Neraxer	Not reported	ABIOGEN PHARMA S.p.A.	Italy	2011
Alfacalcidol	Alpha D3 lágy kapszula, Alpha D3 Osteo lágy kapszula	Mixed	Teva Magyarország Zrt.	Hungary	2011
Amikacin	Amikacin B. Braun 5 mg/ml, 10mg/ml oldatos infúzió	Mixed	B.Braun Melsungen AG	Hungary	2011
Alanine, arginine, aspartic acid, calcium, cysteine, glucose, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, magnesium, methionine, olive oil, ornithine, phenylalanine, potassium, proline, serine, sodium, soybean oil, taurine, threonine, tryptophan, tyrosine, valine	Numeta and associated names	Mixed	Baxter Czech spol.s.r.o ,Medias International d.o.o., Leskoškova cesta 9D, Ljubljana, Slovenia, Baxter Hungary Kft, Genzyme Europe B.V., Baxter Oy, Baxter World Trade SA/NV	Czech Republic, Slovenia, Hungary, Finland, Spain	2007, 2010, 2011
Amisulpride	Amisulpride Mylan 400 mg filmtabletta, Amisulpride Mylan 100 mg tabletta,	Mixed	Generics UK Ltd.	Hungary	2011

Active substance (INN)	Medicinal product	Paediatric-only or adult / paediatric use (mixed)?	Marketing authorisation holder	Member State(s)	Year of marketing authorisation
	Amisulpride Mylan 200 mg tabletta				
Amlodipine	Norvadip 5mg, 10 mg tabletta, Amlodipin Bluefish, Amlodipin Vitablans	Mixed	Actavis Group PTC ehf, Bluefish, Vitablans	Hungary	2011
Atomoxetine	Strattera 80 mg, 100 mg capsules, hard	Paediatric-only	Eli Lilly farmacevtska družba, d.o.o., Dunajska 156, 1000 Ljubljana, Slovenia	Slovenia	2009
Atorvastatin	Sortis 5, 10, 20, 40 mg chewable tablets, Atorvastatin STADA filmtabletta, Astator filmtabletta, Atoris filmtabletta, Atorvastatin Miklich filmtabletta, Lipitor 5 mg , 10 mg, 20 mg, 40 mg, purutabletti, Orbeus 5 mg , 10 mg, 20 mg, 40 mg, purutabletti	Mixed	Pfizer Europe MA EEIG, Stada Arzneimittel AG, Miklich Laboratorios S.L., KRKA, Pfizer Oy,	Romania, Hungary, Finland	2010, 2011
Attenuated poliomyelitis virus type 1	Bivalent opv, mono opv1	Not reported	Novartis Vaccines and diagnostics	Italy	2011, 2007
Attenuated poliomyelitis virus type 3	Mono opv3	Not reported	Novartis Vaccines and	Italy	2007

Active substance (INN)	Medicinal product	Paediatric-only or adult / paediatric use (mixed)?	Marketing authorisation holder	Member State(s)	Year of marke-ting authori-sation
			diagnostics		
Azathioprine	Azathioprin Ebewe filmtabletta	Mixed	Ebewe Pharma Ges.m.b.H. Nfg.KG	Hungary	2011
Azithromycin	Azithromycin-Q Pharma 500 mg filmtabletta	Mixed	Q Pharma Kft.	Hungary	2011
Bacillus clausii spora	Normaflore belsőleges szuszpenzió, Normaflore kemény kapszula	Mixed	Sanofi-aventis zrt.	Hungary	2011
Benzalkonium chloride	Dettolmed 2 mg/g cutaneous spray, solution, Tantum Verde, Tantum Verde Forte	Mixed	Reckitt Benckiser (UK) Ltd, Delta 1200, Welton Road, United Kingdom, CSC Pharmaceuticals Handels GmbH	Slovenia, Hungary	2010, 2011
Bilastine	Bilador 20 mg tablets, Lendin 20 mg tbl.	Mixed	Menarini International O.L.S.A., 1, Avenue de la Gare, Luxemburg, Luxembourg, Menarini Intern.Operations Luxembourg S.A.	Slovenia, Hungary	2011
Bisacodyl	Bisacodyl-propharma 5mg gyomornedv-ellenálló tabletta	Mixed	Pro-Pharma '93 Kft	Hungary	2011
Budesonide/ formoterol fumarate dihydrate	Budfor 80 micrograms/ 4.5 micrograms /inhalation, 160 micrograms	Mixed	AstraZeneca AB,	Slovenia	2011

Active substance (INN)	Medicinal product	Paediatric-only or adult / paediatric use (mixed)?	Marketing authorisation holder	Member State(s)	Year of marketing authorisation
	/4.5 micrograms/inhalation and 320 micrograms /4.5 micrograms/inhalation, inhalation powder, Edoflo 80 micrograms/ 4.5 micrograms /inhalation, 160 micrograms /4.5 micrograms/inhalation and 320 micrograms /4.5 micrograms/inhalation, inhalation powder				
C1-esterase inhibitor, human	Berinert 500 units, powder and solvent for solution for injection or infusion	Mixed	CSL Behring GmbH	Slovenia	2009
Calcium carbonate	Rennie Jégmenta rgtbl.	Mixed	Bayer Hungária Kft.	Hungary	2011
Calcium polystyrene sulfonate	Sorbisterit,	Mixed	Fresenius Medical Care	Italy	2010
Cefixime	Cefixim Pfizer 200 mg ftbl.	Mixed	Pfizer Kft.	Hungary	2011
Cefuroxime	Cefuroxim-Kabi por injekcióhoz	Mixed	Freseneus Kabi Hungary Kft.	Hungary	2011
Cetirizine	Cetimax 10 mg ftbl.	Mixed	Vitablans Oy	Hungary	2011
Chlorhexidine	Drill	Not reported	Pierre Fabre Pharma s.r.l.	Italy	2009
Ciprofloxacin	Cexidal, ibixacin, ciprofloxacina baxter	Not reported	Italchimici spa, IBI Giovanni Lorenzini SpA, BAXTER	Italy	2010, 2009, 2008
Cisatracurium	Cisatracurium-Teva 2mg/ml	Mixed	Teva Gyógyszergyár	Hungary	2011

Active substance (INN)	Medicinal product	Paediatric-only or adult / paediatric use (mixed)?	Marketing authorisation holder	Member State(s)	Year of marke-ting authori-sation
	oldatos inj vagy inf, Cisatracurium-Teva 2mg/ml oldatos inj vagy inf		Zrt.		
Cisplatin	Cisplatin Accord 1 mgl/ml konc. Old. Inf-hoz	Mixed	Accord Healthcare Limited	Hungary	2011
Clarithromycin	Clarithromycin Pfizer ftbl., Claritromycin Mylan 500 mg ret. Tbl., Soriclar, Winclar	Mixed	Pfizer Kft., Generics UK Ltd., ABIOGEN PHARMA S.p.A., Istituto Biotecnico Nazionale Savio	Hungary, Italy	2011, 2007
C-vitamin	C-vitamin Patikus Céh filmtabletta	Mixed	Patikus Céh Kft	Hungary	2011
Desloratadine	Esradin 5 mg filmtabletta	Mixed	Pharma-Regist Kft.	Hungary	2011
Desmopressin	MINIRIN 0,1 mg; 0,2 mg tablets	Mixed	PharmaSwiss d.o.o.,Wolfova 1, Ljubljana, Slovenia	Slovenia	2008
Dextromethorphan	Meddex Wick 20mg/15 ml méz izű szirup, Meddex Wick 7,33 mg méz ízű szop.tbl.	Mixed	Wick Pharma, Procter & Gamble GmbH	Hungary	2011
Diphtheria, Tetanus, Pertussis (acellular component) Vaccine	BOOSTRIX suspension for injection	Mixed	GSK d.o.o., Knezov štradon 90, Ljubljana, Slovenia	Slovenia	2008
Diphtheria, Tetanus, Pertussis (acellular component) Vaccine	BOOSTRIX POLIO Suspension for injection in	Mixed	GSK d.o.o., Knezov štradon 90, Ljubljana,	Slovenia	2008

Active substance (INN)	Medicinal product	Paediatric-only or adult / paediatric use (mixed)?	Marketing authorisation holder	Member State(s)	Year of marketing authorisation
	prefilled syringe, BOOSTRIX POLIO suspension for injection		Slovenia		
Diphtheria, Tetanus, Pertussis (acellular component) Vaccine	Adacel suspension for injection	Mixed	Sanofi Pasteur SA,2, Avenue Pont Pasteur, Lyon, France	Slovenia	2010
Diphtheria, Tetanus, Pertussis (acellular component) Vaccine	PEDIACEL suspension for injection in pre-filled syringe	Paediatric	Sanofi Pasteur SA,2, avenue Pont Pasteur, Lyon, France	Slovenia	2011
Diphtheria, Tetanus, Pertussis (acellular component) Vaccine	Pediacel,Suspension for injection in pre-filled syringe (DCP)	Paediatric	Sanofi Pasteur MSD, Belgium	Sweden	2011
Diphtheria, Tetanus, Pertussis (acellular component) Vaccine	Pediacel szuszp. Inj. Előretölt. Fecsk.-ben	Mixed	Sanofi Pasteur SA	Hungary	2011
Diphtheria, Tetanus, Pertussis (acellular component) Vaccine	PEDIACEL, SUSPENSION INYECTABLE EN JERINGA PRECARGADA	Not reported	Sanofi Pasteur MSD, S.A.	Spain	2009
Dorzolamide	Dorzolep 20 mg/ml oldatos szemcsepp	Mixed	Extractum Pharma Zrt.	Hungary	2011
Ebastine	Ebastine teva	Mixed	Teva	Hungary	2011
Esomeprazole	Nexium 10 mg gastro-resistant granules for oral suspension, sachet, Esorin gyomornedv-ellenálló tabletta, Themospes gyomornedv-ellenálló	Mixed	AstraZeneca AB, Specifar S.A., Pharmaceutical Works POLPHARMA SA, Mylan, Teva, AstraZeneca	Poland, Hungary, Italy	2009, 2011

Active substance (INN)	Medicinal product	Paediatric-only or adult / paediatric use (mixed)?	Marketing authorisation holder	Member State(s)	Year of marketing authorisation
	tabletta, Esomeprazole Polpharma por oldatos inf vagy inj, Esomeprazol Mylan, Omyprex, NEXIUM,				
Etoricoxib	Auxib 30/60/90/120 mg filmtabletta	Mixed	MSD Magyarország Kft.	Hungary	2011
Ezetimibe	ABSORCOL, PICOLAX powder for oral solution	Not reported	MSD ITALIA S.R.L., FERRING S.P.A.	Italy	2010, 2011
Fentanyl	Fentanyl Pharmabide 100mikrogr/óra transzd tap, Fentanyl Pharmabide 25mikrogr/óra transzd.tap, Fentanyl Pharmabide 50mikrogr/óra transzd.tap, Fentanyl Pharmabide 75mikrogr/óra transzd.tap	Mixed	Pharmabide Ltd.	Hungary	2011
Ferric carboxymaltose	Iroprem 50 mg iron/ml solution for injection/infusion	Mixed	Vifor France SA 7-13, Boulevard Paul-Emile Victor 92200 Neuilly-sur-Seine, France	Slovenia	2010
Fexofenadine	Allegra junior	Paediatric	sanofi	Hungary	2011
Fluconazole	Femgin 150 mg kemény kapszula,	Mixed	Actavis Group PTC ehf, Bluefish,	Hungary	2011

Active substance (INN)	Medicinal product	Paediatric-only or adult / paediatric use (mixed)?	Marketing authorisation holder	Member State(s)	Year of marketing authorisation
	Fluconazole Aurobindo kemény kapszula,Fluconazole- B.Braun 2mg/ml oldatos infúzió		Vitablans, Aurobindo Pharma (Malta) Limited, B. Braun Melsungen AG		
Fluoxetine hydrochloride	Fluoxetine vitabalans	Mixed	Vitabalans Oy	Hungary	2011
Folic acid	Folic acid	Not available	ESP Pharma Limited	Italy	2011
Glucose	Glucorange	Not reported	Polymed Srl	Italy	2010
Grass pollen allergen extract	ORALAIR 100 IR and 300 IR sublingual tablets, ORALAIR 300 IR sublingual tablets, GRAZAX 75.000 SQ-T peroralni liofilizat, Soluprick SQ Timothy grass (Phleum pratense) 10 HEP Solution for skin-prick test, Grazura 75, 000 SQ-T, Oral lyophilisate	Mixed	STALLERGENES S.A., 6 rue Alexis de Tocqueville, Antony, France, ALK-Abello A/S Boge Allé 6-8, Horsholm, Denmark,	Slovenia, Sweden	2006, 2009, 2010
Herbal substances	Sinupret forte filmtabletta	Mixed	Bionorica AG	Hungary	2011
Human antihepatitis B immunoglobulin	Keyven b, mencevax acwy	Not reported	Kedrion Spa, GlaxoSmithKline Biologicals SA	Italy	2009
Human coagulation factor VIII	Immunine 600 IU	Mixed	Baxter Poland Sp. z o.o.	Poland	2008
human coagulation factor	Immunine 1200	Mixed	Baxter Poland	Poland	2008

Active substance (INN)	Medicinal product	Paediatric-only or adult / paediatric use (mixed)?	Marketing authorisation holder	Member State(s)	Year of marke-ting authori-sation
VIII	IU		Sp. z o.o.		
Human coagulation factor VIII	Wilate 450 i.e./400 i.e. , 900 i.e./800 i.e. powder and solvent for solution for infusion	Mixed	Willfact 100 NE/ml por és oldószer oldatos injekcióhoz	Slovenia	2010
Human coagulation factor VIII	IMMUNINE 200 i.e., 600 i.e., 1200 i.e. powder and solvent for solution for injection or infusion	Mixed	BAXTER d.o.o Železna cesta 18, 1000 Ljubljana Slovenia	Slovenia	2008
Human coagulation factor VIII	Haemoctin 250 i.e., 500 i.e., 1000 i.e. powder and solvent for solution for injection	Mixed	Biotest Pharma GmbH, Landsteinerstrasse 5, Dreieich, Germany	Slovenia	2009
Human coagulation factor VIII	Willfact 100 NE/ml por és oldószer oldatos injekcióhoz	Mixed	LFB Biomedicaments	Hungary	2011
Human fibrinogen	Riastap 1 g powder for solution for injection / infusion	Mixed	CSL Behring GmbH Emil-von-Behring-Str. 76 35041 Marburg, Germany	Slovenia	2011
Human hemin	Normosang 25 mg/ml concentrate for solution for infusion	Mixed	Orphan Europe Immeuble "Le Guillaumet" 92046 Paris La Défense, France	Slovenia	2009
Human hepatitis B immunoglobulin	Hepatect CP 50 i.e./ml solution for infusion	Mixed	Biotest Pharma GmbH,Landsteinerstrasse 5, Dreieich,	Slovenia	2010

Active substance (INN)	Medicinal product	Paediatric-only or adult / paediatric use (mixed)?	Marketing authorisation holder	Member State(s)	Year of marketing authorisation
			Germany		
Human leukocyte interferon-alpha	Multiferon 3 mio i.e./0,5 ml solution for injection in prefilled syringe	Mixed	Swedish Orphan Biovitrum International AB, Drottninggatan 98, Stockholm, Sweden	Slovenia	2009
Human normal immunoglobulin (IVIg)	Octagam 100 mg/ml solution for infusion, GAMMANORM 165 mg/ml solution for injection, Intratect 50 g/l, solution for infusion, Venital	Mixed	Octapharma (IP) Ltd., The Zenith Building 26, Manchester, United Kingdom, Biotest Pharma GmbH, Landsteinerstrasse 5, Dreieich, Germany, Kedrion spa	Slovenia, Italy	2007, 2010, 2011
Human plasma derived coagulation factor IX	Haemonine 50 I.E./ml / 100 I.E./ml Pulver und Lösungsmittel zur Herstellung einer Injektionslösung	Mixed	Biotest Pharma GmbH	Austria	2009
Human protein	Subcuvia	Not reported	Baxter AG	Italy	2007
Ibuprofen	BRUFEN 200 mg, 400 mg, 600 mg film coated tablets, Nurofen for children with the flavor of orange and strawberry 40	Mixed, Paediatric	Abbott Laboratories d.o.o., Dolenjska cesta 242c, Ljubljana, Slovenia	Slovenia, Hungary, Italy	2010, 2011

Active substance (INN)	Medicinal product	Paediatric-only or adult / paediatric use (mixed)?	Marketing authorisation holder	Member State(s)	Year of marketing authorisation
	mg/ml oral suspension, Algoflex Baby 20mg/ml belsőleges szuszpenzió, Algoflex Norma 400 mg filmtabletta, Ibustar 20mg/ml belsőleges szuszpenzió gyermekek , IBUPAS				
Imipenem	Imipenem/Cilastatin Hospira 500 mg/500 mg por old. Inf.-hoz, Imipenem/Cilastatin Teva por old inf, Impecin 250 mg/250 mg por old. Inf.-hoz	Mixed	Hospira UK Limited, Teva Magyarország Zrt. Actavis Group PTC ehf	Hungary	2011
Influenza virus surface antigens (haemagglutinin and neuraminidase)* of strain A/California/7/2009 (H1N1)v like strain used (X-179A) 3.75 micrograms** per 0.25 ml dose	Celtura	Mixed	Novartis Vaccines and Diagnostics GmbH	Germany	2009
Iobenguane	Mibeg	Not reported	Mallinckrodt Medical B.V.	Italy	2011
Iobenguane (123I)	Adreview	Not reported	GE HEALTHCARE s.r.l.	Italy	2010
Isoconazole diflucortolone	Travocort 10 mg/g + 1 mg/g krém	Mixed	UniCorp Biotech Kft.	Hungary	2011
Lamotrigine	Lamotrigine Pfizer, Lamotrigine	Mixed	Pfizer	Hungary	2011

Active substance (INN)	Medicinal product	Paediatric-only or adult / paediatric use (mixed)?	Marketing authorisation holder	Member State(s)	Year of marketing authorisation
	Pfizer diszpergálódó tabletta				
Latanoprost	Xalatan eye drops solution 0,0005%, Laprosep 0,05 mg/ml old. Szemcsepp, Latanoprost Pfizer 0,05 mg/ml oldatos szemcsepp	Mixed	Pfizer Hellas AE, Extractum Pharma Zrt., Pfizer Kft.	Cyprus, Hungary	2010, 2011
Levetiracetam	Levil filmtabletta, Levetiracetam-Lupin, Levedia, Repident, Levetiracetam pharmaswiss, Levetiracetam Stada	Mixed	Meditop Gyógyszeripari Kft, Lupin Ltd, Magyar és Társa Bt., POLPHARMA SA, PharmaSwiss, STADA Arzneimittel AG	Hungary	2011
Levothyroxine sodium	Syntroxine	Mixed	Regiomedica GmbH, IBSA Farmaceutici Spa	Hungary, Italy	2009, 2011
Lidocaine and Tetracaine	Rapydan70 mg /70 mg, Medicated plaster (N)	Mixed	Eurocept International B.V., The NetherlandsWhen approved: EUSA Pharma (Europe) Ltd, United Kingdom	Sweden	2007
Losartan	COZAAR 2,5 mg/ml, Valezaar filmtabletta	Mixed	Merck Sharp & Dohme Romania S.R.L., Valeant Pharma Magyarország	Romania, Hungary	2009, 2011

Active substance (INN)	Medicinal product	Paediatric-only or adult / paediatric use (mixed)?	Marketing authorisation holder	Member State(s)	Year of marketing authorisation
			Kft		
Macrogol '3350'/Potassium chloride/Sodium bicarbonate/Sodium chloride	MOVICOL Lax 6,9 g powder for oral solution, Regolint, Movicol pediatric	Mixed	Norgine BV, Hogehilweg 7, Amsterdam ZO, The Netherlands, Laboratori Baldacci SpA, NORGINE ITALIA S.R.L.	Slovenia, Italy	2008, 2011
Meningococcus vaccine	Zetia	Not reported	MSD-SP Limited	Italy	2007
Meropenem	Meropenem Kabi 1000mg por old inj.v.inf.,Meropenem Kabi 500mg por old inj.v.inf., Meropenem Hospira por,	Mixed	Fresenius Kabi Hungary Kft., Hospira UK Limited	Hungary	2011
Mesalamine	Mezevant	Mixed	Shire Pharmaceutical Contracts Ltd	Hungary	2011
Metamizole	Amizolmet 500 mg/ml oldatos infúzió	Mixed	Sanitas A. B.	Hungary	2011
Metformin hydrochloride	Glucophage 1000mg Film-coated tablets, Glucophage 500 mg; Glucophage 850 mg; Film-coated tablets, GLUCOPHAGE 1000 mg film-coated tablets	Mixed	Merck Santé, s.a.s., Merck d.o.o. Dunajska cesta 119 1000 Ljubljana, Slovenia	Poland, Slovenia	2009, 2010
Methotrexate	Ebetrexat 2,5 mg, metothrexate Smg, 10 mg tabletta	Mixed	Ebewe Pharma Ges.m.b.H. Nfg.KG	Hungary	2011

Active substance (INN)	Medicinal product	Paediatric-only or adult / paediatric use (mixed)?	Marketing authorisation holder	Member State(s)	Year of marketing authorisation
Methylphenidate hydrochloride	Concerta, ritalin	Paediatric	Janssen-Cilag International N.V., Ritalin	Poland, Italy	2007, 2008
Montelukast	SINGULAIR, Montelukast MSD, Montelukast Sandoz 4 mg granulátum, Montelukast Orion 4 mg, rágótabletta, Montelukast Orion 5 mg rágótabletta, Montelukast Orion 10 mg filmtabletta, Montelukast Teva 4 mg granulátum, Monalux rágótabl., Mondeo 10 mg ftbl., Montelukast Accord 4mg-5 mg rágótabletta	Mixed	MSD Polska Sp. z o.o., SANDOZ Hungária Kereskedelmi Kft, Orion Corporation, Teva Magyarország Zrt., Krka, d.d, Actavis Group PTC ehf, Accord Healthcare Limited	Poland, Hungary	2009, 2010, 2011
Moxifloxacin	Vigamox, Vigamox 5 mg/ml eye drops, solution	Mixed	Alcon Polska Sp. z o.o., S.A. Alcon-Couvreur N.V., Rijksweg 14, Puurs, Belgium	Poland, Slovenia	2009
Mycophenolate mofetil	Mycophenolate mofetil Stada 250 mg kemény kapszula, Mycophenolate mofetil Stada 500 mg filmtabletta, Mycophenolate	Mixed	Stada Arzneimittel AG, Pharm V Solutions Ltd., Actavis Group PTC ehf., Ratiopharm GmbH	Hungary	2011

Active substance (INN)	Medicinal product	Paediatric-only or adult / paediatric use (mixed)?	Marketing authorisation holder	Member State(s)	Year of marketing authorisation
	mofetil Pharm V Solutions500 mg filmtabl, Mycophenolate mofetil Actavis 250 mg kemény kapsz, Mycophenolat Mofetil-ratiopharm 250 mg k. Kapsz, Mycophenolat Mofetil-Ratiopharm 500 mg ftbl.				
Neisseria meningitidis group A Neisseria meningitidis group C Neisseria meningitidis group Y Neisseria meningitidis group W135	Mencevax ACWY powder and solvent for solution for injection in prefilled syringe, Meningitec Meningococca	Mixed	GSK d.o.o., Knezov štradon 90, Ljubljana, Slovenia	Slovenia	2008
Neisseria meningitidis group A Neisseria meningitidis group C Neisseria meningitidis group Y Neisseria meningitidis group W135	Meningitec Meningococca	Not reported	John Wyeth and Brother Limited	Italy	2008
Nitrous oxide	Dinitrogén Oxid Siad cseppfolyósított gáz, Livopan túlnyomásos orvosi gáz, Dinitrogén-Oxid Rad-Med Pharma cseppfoly orvosi	Mixed	SIAD Hungary Gázokat Forgalmazó és Termelő Kft., AGA AB, RAD-MED-PHARMA Gyógyászati, Kereskedelmi és Szolgáltató Kft., AIR	Hungary, Italy	2011

Active substance (INN)	Medicinal product	Paediatric-only or adult / paediatric use (mixed)?	Marketing authorisation holder	Member State(s)	Year of marketing authorisation
	gáz, Kalinoxal 50%/50% túlnyomásos orvosi gáz, INALOSSIN		LIQUIDE SANTE INTERNATIONAL, Società Italiana Acetilene e Derivati		
Nutrition	Nutriflex Lipid peri emulziós infúzió, Smoflipid	Mixed, Not available	B. Braun Melsungen AG, FRESENIUS KABI ITALIA S.R.L.	Hungary, Italy	2007, 2011
Octocog alfa	Recombinate 250 iu, recombinate 500 iu, recombinate 1000 iu	Mixed	Baxter Polska Sp. z o.o.	Poland	2011
Omeprazole	Omeprazole pfizer	Mixed	Pfizer Kft.	Hungary	2011
Oxycodone	Codoxy retard tabletta	Mixed	G.L. Pharma GmbH	Hungary	2011
Oxygen	Oxigén Vifamed mélyhűtött orvosi gáz, Oxigén Vifamed túlnyomásos orvosi gáz, ARIA AIR LIQUIDE SANITA', ARIA CRIOSALENTO, ARIA MEDICAIR, ARIA OSSIGAS, ARIA RIVOIRA, ARIA SIAD, ARIA SICO, ARIA LINDE MEDICALE, OSSIGENO C.I.O., OSSIGENO	Mixed	Vifamed Bt., AIR LIQUIDE SANTE, CRIOSALENTO s.r.l., MEDICAIR ITALIA s.r.l., OSSIGAS s.r.l., RIVOIRA S.p.A., S.I.A.D. S.p.A, SICO S.p.A., LINDE MEDICALE s.r.l., CONSORZIO ITALIANO OSSIGENO, CRIOSALENTO S.R.L., EUROXAN srl,	Hungary, Italy	2009, 2010, 2011

Active substance (INN)	Medicinal product	Paediatric-only or adult / paediatric use (mixed)?	Marketing authorisation holder	Member State(s)	Year of marketing authorisation
	CRIOSALENTO, OSSIGENO EUROXAN, OSSIGENO IBO,OSSIGENO MEDICAIR, Ossigeno Ossigas, OSSIGENO SON-OX		INDUSTRIA BRESCIANA OSSIGENO S.R.L., MEDICAIR ITALIA S.R.L., OSSIGAS S.r.l., OSSIGENO SOCIETA' OSSIGENO NAPOLI		
Oxymetazoline-hydrochloride	Sinex Wick Eukaliptusz 0,5 mg/ml oldatos orrspray, Ossimetazolina Carlo Erba	Mixed	Wick Pharma Zweigniederlassung der Procter & Gamble GmbH, Carlo Erba OTC	Hungary, Italy	2008, 2011
Pantoprazole	Pantoprazol Krka gyomornedv-ellenálló tabletta, Adozol 20 mg gyomornedv-ellenálló tabletta, Adozol 20 mg gyomornedv-ellenálló tabletta, Pantoprazol Goodwill 40 mg por oldatos injekcióhoz, Acidostop ratiopharm 20 mg gyomornedv-ellenálló tabl	Mixed	Krka, d.d, Plus-Pharma Arzneimittel GmbH, Goodwill Pharma Kft., Ratiopharm GmbH	Hungary	2011
Paracetamol	Paracetamol Actavis 24 mg/ml	Mixed	Actavis Group PTC ehf, Sigillata Ltd.,	Hungary, Italy	2008, 2011

Active substance (INN)	Medicinal product	Paediatric-only or adult / paediatric use (mixed)?	Marketing authorisation holder	Member State(s)	Year of marketing authorisation
	belsőleges oldat, Doloramol 1000 mg, 250 mg, 500 mg filmtabletta, Paracetamol Actavis 10 mg/ml old. Inf., Paracetamol Panpharma 10 mg/ml old. Inf., Panadol Rapid 500 mg filmtabletta, Paracetamol Kabi 10 mg/ml oldatos infúzió, symptomed Wick Citrom ízű por belsőleges oldathoz, symptomed Wick Feketeribizli ízű por belsőleges oldathoz, GALAFIN		Panmedica, GSK Consumer Healthcare, Freseneus Kabi Hungary Kft.,Wick Pharma Zweigniederlassung der Procter & Gamble GmbH, Marvecspharma Services S.r.l.		
Paracetamol, ascorbic acid, fenilefrin	Coldrex Maxgrip mentol és erdei gyümölcs ízű por, Flumin Béres ftbl., LISOFLU	Mixed	GSK, Béres Házipatika Kft., Sanofi Aventis Spa	Hungary, Italy	2008, 2011
Parenteral nutrition	Periolimel N4E, Olimel N5E, Olimel N7, Olimel N7E, Olimel N9, Olimel N9E emulsion for infusion	Mixed	Baxter d.o.o., Železna cesta 18, Ljubljana, Slovenia	Slovenia	2011
Pelargonium sidoides	Kaloba, keyven,		Dr Willmar	Italy	2007,

Active substance (INN)	Medicinal product	Paediatric-only or adult / paediatric use (mixed)?	Marketing authorisation holder	Member State(s)	Year of marketing authorisation
extract	umkan		Schwabe Gmbh, Kedrion SpA, Dr Willmar Schwabe Gmbh & Co Kg		2010, 2011
Phenelzine	Margyl		Dimensione Ricerca SrL	Italy	2007
Piperacillin	Piperan por old. Inj.-hoz, Zytobact por old inj vagy inf	Mixed	Ranbaxy UK Limited, Teva Magyarország Zrt.	Hungary	2011
Potassium chloride, Magnesium chloride hexahydrate, Calcium chloride dihydrate, Sodium acetate trihydrate L-Malic acid	Sterofundin		B. BRAUN MELSUNGEN AG	Italy	2007
Propofol	Propofol Pfizer emulzós injkeció vagy infúzió, Curtega emulziós injekció vagy infúzió	Mixed	Pfizer	Hungary	2011
Racecadotril	Hidrasec 10 mg, Hidrasec 30 mg, granules for oral suspension, TIORFAN CHILDREN 30 and 10 mg	Paediatric	Bioprojet Europe Ltd., BIOPROJET FERRER	Poland, Italy	2011, 2007
Remifentanil	Remifentanil Hospira por oldatos injekcióhoz vagy infúzióhoz való koncentrátumhoz, Remifentanil Teva por	Mixed	Hospira UK Limited, Teva Gyógyszergyár Zrt.	Hungary	2011

Active substance (INN)	Medicinal product	Paediatric-only or adult / paediatric use (mixed)?	Marketing authorisation holder	Member State(s)	Year of marketing authorisation
	oldatos injekcióhoz vagy infúzióhoz való koncentrátumhoz				
Rifaximin	Flonorm, ximinorm		Alfa Biotech Srl, Alfa Wassermann SpA	Italy	2011
Rocuronium-bromide	Rocuronium-Teva oldatos injekció vagy infúzió	Mixed	Teva Magyarország Zrt.	Hungary	2011
Ropivacaine	Ropivacain B. Braun old. Inj.	Mixed	B. Braun Melsungen AG	Hungary	2011
Rosuvastatin calcium	Crestor	Mixed	Astra Zeneca AB	Poland	2009
Rupatadine	Rupafin 10 mg tablets	Lambda Therapeutics Limited	J. Uriach & Cía., S.A. Av. Camí Reial, 51-57 08184 Palau-solità i Plegamans, Spain	Slovenia	2008
Sodium alginate / Potassium hydrogen carbonate	Gaviscon advance	Mixed	Reckitt Benckiser (Poland) S.A.	Poland	2010
Sodium picosulphate	Pico-salax	Mixed	Ferring Magyarország Gyógyszerkereskedelmi	Hungary	2011
Somatropin	Saizen 5,83 mg/ml oldatos injekció, Saizen 8 mg/ml oldatos injekció	Mixed	Merck Kft	Hungary	2011
Spironolactone	Spitonep 25 mg tabletta, spitonep 50 mg tabletta	Mixed	Extractum Pharma Zrt.	Hungary	2011

Active substance (INN)	Medicinal product	Paediatric-only or adult / paediatric use (mixed)?	Marketing authorisation holder	Member State(s)	Year of marketing authorisation
Split influenza virus, inactivated containing antigen equivalent to A/California/7/2009 (H1N1)-like strain (A/California/7/2009 (NYMC X-179A))	Panenza suspension inyectable en vial multidosis, panenza suspension inyectable en jeringa precargada		Sanofi Pasteur S.A.	Spain	2009
Tacrolimus	Tacrolimus Astron kemény kapszula, Tacrolimus Lambda kemény kapszula, Tacrolimus Mylan kemény kapszula, Tacrolimus Sandoz kemény kapszula, Tacrolimus Intas,	Mixed	Astron Research Limited, Lambda Therapeutics Limited, Mylan S.A.S., Sandoz Hungária Kft, Intas Pharmaceuticals Limited	Hungary	2011
Tetrabenazine	Xenazina		Chiesi Farmaceutici SpA	Italy	2007
Trace minerals	Béres Csepp Extra belsőleges oldatos cseppek	Mixed	Béres Gyógyszergyár Zrt.	Hungary	2011
Tramadol	Noax 50 mg szájban diszp. Tbl.	Mixed	CSC Pharmaceuticals Handels GmbH	Hungary	2011
Tramadol / paracetamol	Zaldiar 37,5 mg/325 mg effervescent tablets, KOLIBRI, Tramadololo e Paracetamolo	Mixed	Grünenthal GmbH, Zieglerstrasse 6, Aachen, Germany, Alfa Wassermann SpA	Slovenia, Italy	2008
Triptorelin	Diphereline SR	Mixed	Ipsen Pharma	Hungary	2011

Active substance (INN)	Medicinal product	Paediatric-only or adult / paediatric use (mixed)?	Marketing authorisation holder	Member State(s)	Year of marketing authorisation
	22,5 mg por és oldószer szuszp. Injekc.				
Valsartan	Diovan 3mg/ml, Valmed filmtabletta, Valsartan propharma, Valsartan Arrow filmtabletta	Paediatric, Mixed	Novartis s.r.o., Helm AG, Propharma, Arrow	Czech Republic, Hungary	2010
Vancomycin	Vancomycin Actavis por old. Inf.-hoz, Vancomycin Kabi por oldatos injekcióhoz, Vancomycin Pharmaswiss por old. Inf.-hoz	Mixed	Actavis Group PTC ehf, Freseneus Kabi Hungary Kft., PharmaSwiss Česká republika s.r.o.	Hungary	2011
Ziprasidone hydrochloride	Zeldox	Not reported	Pfizer AB	Italy	2008
Not reported	Rifaximina	Not reported	ALFA WASSERMANN S.P.A	Italy	2011
Not reported	Rivonox	Not reported	Rivoira SPA	Italy	2011
Not reported	Torvast	Not reported	Parke-Davis	Italy	2007

7.2. Extension of therapeutic indication to include the paediatric population

Summary:

- The authorised paediatric indication would be reflected in the sections 4.1 (Table 17) and / or 4.2 (Table 18) of the SmPC.
- In total 11 Member States reported extensions of the authorised indications to the use in the paediatric population for medicinal products corresponding to 33 active substances.

Table 18: Paediatric indication added in SmPC section 4.1 (by year of first completed procedure).

Year	Procedure? (N / DC / MRP)	Marketing Authorisation Holder	Invented name	Active substance (INN)	Paediatric indication	Member States
2007	MRP	Glaxosmithkline	Malarone	Atovaquone / Proguanile hydrochloride*	Not reported	Italy
2007	MRP	Eli Lilly Italia Spa	Prozac and associated names	Fluoxetine hydrochloride*	Not reported	Italy
2007	MRP, N	Various	Various	Oxybutynin hydrochloride*	Not reported	Italy, United Kingdom
2007	MRP	Recordati Industria Chimica E Farmaceutica S.P.A.	Peptazol	Pantoprazole*	Not reported	Italy
2007 - 2008		Eli Lilly Oy	Humatrope and associated names	Somatropin*	Not reported	Italy, Finland
2008		Gebro Pharma Gmbh	Nocutil	Desmopressin *	Nocturnal enuresis (over 6 5 years of age) […]vasopressin - sensitive cranial diabetes insipidus.	Austria
2008		Teva Pharmaceuticals Ltd	Copaxone	Glatiramer acetate*	well-defined first clinical episode and are determined to be at high risk of developing clinically definite multiple sclerosis (CDMS) [...] limited published data suggest that the safety profile in adolescents from 12 to 18 years of age receiving Copaxone 20 mg subcutaneously every day is similar to that seen in adults	Finland, United Kingdom
2008		Sanofi	Imovax polio	Inactivated	aktiv immunisering	Sweden

Year	Procedure? (N / DC / MRP)	Marketing Authorisation Holder	Invented name	Active substance (INN)	Paediatric indication	Member States
		Pasteur Msd, Belgium	(n)	poliovirus 1-3	mot polio av spädbarn, barn och vuxna, både för primär immunisering och påföljande boosterdoser.	
2008	N	Astrazeneca AB, Sweden	Narop, 2 mg/ml Solution for injection/infusion (N)	Ropivacaine hydrochloride*	"Akut smärtlindring (per- och postoperativ) hos barn	Sweden
2009	MRP	Mylan AB	Ciprofloxacin Merck NM (now Mylan), 100 mg, 250 mg, 500 mg, 750 mg, Film-coated tablets (MRP)	Ciprofloxacin*	Broncho-pulmonary infections in cystic fibrosis caused by Pseudomonas aeruginosa, Complicated urinary tract infections and pyelonephritis, Inhalation anthrax (post-exposure prophylaxis and curative treatment)	Sweden, Italy
2009	MRP	Medias International	Smoflipid	dl-alfa-tocopherol, medium chain tiglycerides, purified fish oil, purified olive oil, soybean oil*	Not reported	Slovenia
2009		Bayer Schering Pharma Oy	Gadovist	Gadobutrol	Not reported	Finland
2009		Baxter AG	Subcuvia	Human normal immunoglobulin*	Not reported	Finland
2009	MRP	Glaxosmithkline S.P.A.	Priorix	Measles Mumps Rubella vaccine*	Vaccination agains measles, mumps, rubella	Italy
2009	MRP	Various	Various	Metformin hydrochloride*	Diabetes mellitus	Italy
2009	DC	Ibigen S.R.L.	Piperacillina e	Piperacillin	Not reported	Italy

Year	Procedure? (N / DC / MRP)	Marketing Authorisation Holder	Invented name	Active substance (INN)	Paediatric indication	Member States
			tazobactam ibigen (dcp)	sodium / tazobactam sodium*		
2009	MRP	Glaxosmithkline Spa	Relenza	Zanavimir*	Not reported	Italy
2009	MRP	Pfizer AB	Zeldox	Ziprasidone*	Treatment of manic or mixed episodes of moderate severity in bipolar disorder in adults and children and adolescents aged 10-17 years	Italy, Sweden
2009 - 2010	MRP	Merck Sharp & Dohme	Cozaar and associated names	Losartan	Hypertension	Romania, Italy, Finlan
2009 - 2011	MRP	Alk-Abelló A/S, Denmark	GRAZAX and associated names	Grass pollen allergen extract	Treatment of grass pollen induced rhinitis and conjunctivitis in adults and children (5 years or older), with clinically relevant symptoms and diagnosed with a positive skin prick test and/or specific IgE test to grass pollen.	Sweden, Italy
2010	N	Pfizer Hellas Ae	Lipitor and associated names	Atorvastatin	Hypercholesterolaemia children & adolescents over 10 years of age	Cyprus, Estonia, Romania, Finland
2010	MRP	Merck Sharp & Dohme Romania S.R.L.	Singulair	Montelukast	Asthma	Romania
2010		Astra Zeneca Oy	Crestor 5 mg, 10 mg, 20 mg, 40 mg tabletti, kalvo-päällysteinen	Rosuvastatin calcium	Not reported	Finland
2010		Fresenius	Smoflipid 200	Soiae oleum	Not reported	Finland

Year	Procedure? (N / DC / MRP)	Marketing Authorisation Holder	Invented name	Active substance (INN)	Paediatric indication	Member States
		Kabi Ab	mg/ml infuusioneste, emulsio	raffinatum triglyceride saturate media piscis oleum omega-3-acidis abundans*		
2010	MRP	Apotex Europe Bv	Sumatriptan tablets 50, 100mg	Sumatriptan succinate*	Not reported	United Kingdom
2010	MRP	Novartis Pharmaceuticals Uk Ltd	Diovan fctabs 40mg	Valsartan	Hypertension in children & adolescents 6 to 18 years of age	Cyprus, Estonia, Romania, Finland, Sweden
2010 - 2011	MRP	Pfizer Enterprises Sar	Xalatan and associated names	Latanoprost	Glaucoma	Estonia, Finland, Romania, Spain, Sweden
2011	N	Tillomed Laboratories Limited	Ciclofarm and associated names	Acyclovir*	Not reported	United Kingdom
2011	MRP	Astrazeneca UK Limited	Nexium	Esomeprazole	Children 1-11years old, Children over 4 years of age, In combination with antibiotics in treatment of duodenal ulcer caused by Helicobacter pylori	Slovenia, Sweden, Spain
2011	MRP	Merck Sharp & Dohme Bv, Netherlands	Ezetrol tabs	Ezetimibe	Primary non-familial hypercholesterolaemia/ heterozygous familial hypercholesterolaemia, adolescents 10 to 17 years of age	Cyprus
2011	N	Antigen International Limited	Antigen metoclopramide injection bp	Metoclopramide hydrochloride*	Not reported	United Kingdom

Year	Procedure? (N / DC / MRP)	Marketing Authorisation Holder	Invented name	Active substance (INN)	Paediatric indication	Member States
			10mg/2ml			
2011		Glaxosmithkline AB, Sweden	Zofran	Ondansetron*	Profylax och behandling av illamående och kräkningar inducerade av kemoterapi […] postoperativt illamående och kräkningar hos barn ? 1 månad.	Sweden
2011	DC	Merck Sharp & Dohme	Maxalt	Rizatriptan	Migraine	Czech Republic

* No agreed PIP for active substance available.

Table 19: Paediatric population added in SmPC section 4.2 (by year of first completed procedure).

Year	Procedure(N / DC / MRP)	Marketing Authorisation Holder	Invented name	Active substance (INN)	Paediatric indication	Member State
2007	MRP	Glaxosmithkline Spa	Malarone	Atovaquone / Proguanile hydrochloride	Not reported	Italy
2007	MRP	Eli Lilly Italia Spa	Prozac	Fluoxetine hydrochloride	Not reported	Italy
2007	MRP	Janssen Cilag Spa	Lyrinel	Oxybutynin hydrochloride	Not reported	Italy
2007	MRP	Nycomed S.P.A., Recordati Industria Chimica E Farmaceutica S.P.A.	Pantecta (mrp), peptazol (mrp)	Pantoprazole sodium sesquihydrate	Not reported	Italy
2007		Eli Lilly Oy	Humatrope 6 mg, 12 mg, 24 mg injektiokuiva-aine ja liuotin, liuosta varten	Somatropin	Not reported	Finland
2008		Gebro Pharma Gmbh	Nocutil 0,1 mg / 0,2 mg - Tabletten	Desmopressin	Nocturnal enuresis (over 6 5 years of age) […] treatment of vasopressin -	Austria

Year	Procedure(N / DC / MRP)	Marketing Authorisation Holder	Invented name	Active substance (INN)	Paediatric indication	Member State
					sensitive cranial diabetes insipidus	
2008	MRP	Eli Lilly Italia S.P.A.	Prozac (mrp)	Fluoxetine hydrochloride	Not reported	Italy
2008	MRP in UK	Teva Pharma-Ceuticals Limited	Copaxone 20 mg/ml injektioneste, liuos, esitäytetty ruisku, COPAXONE® 20MG/ML SOLUTION FOR INJECTION, PREFILLED SYRINGE	Glatiramer acetate	Not reported	Finland, United Kingdom
2008		Sanofi Pasteur Msd, Belgium	Imovax polio (n)	Inactivated poliovirus 1-3	aktiv immunisering mot polio av spädbarn, barn och vuxna, både för primär immunisering och påföljande boosterdoser. Imovax polio är också indicerat: - -för immunförsvagade patienter, deras närstående och individer för vilka oralt poliovaccin är kontraindicerat - -som booster till individer som tidigare erhållit oralt poliovaccin	Sweden
2008	N	Astrazeneca AB, Sweden	Narop, 2 mg/ml Solution for injection/infusion (N)	Ropivacaine hydrochloride	Akut smärtlindring (per- och postoperativ) hos barn	Sweden
2008	MRP in Italy	Pfizer Oy, Eli Lilly Italia Spa	Genotropin 5mg, 12mg, injektiokuiva-aine ja liuotin, liuosta varten,	Somatropin	Not reported	Finland, Italy

Year	Procedure(N / DC / MRP)	Marketing Authorisation Holder	Invented name	Active substance (INN)	Paediatric indication	Member State
			HUMATROPE			
2009	MRP	MYLAN S.P.A., Merck NM AB, Sweden (Transferred To Mylan AB, Sweden), Bayer Healthcare AG, Germany	CIPROFLOXACINA MYLAN GENERICS, Ciprofloxacin Merck NM (now Mylan), 100 mg, 250 mg, 500 mg, 750 mg, Film-coated tablets , Ciproxin 50 mg/ml, 100 mg/ml, granulat och vätska till oral suspension	Ciprofloxacin	Broncho-pulmonary infections in cystic fibrosis caused by Pseudomonas aeruginosa; Complicated urinary tract infections and pyelonephritis; Inhalation anthrax (post-exposure prophylaxis and curative treatment)	Italy, Sweden
2009	MRP	Medias International D.O.O., Leskoškova Cesta 9D, Ljubljana, Slovenia	Smoflipid 200 mg/ml Emulsion for infusion	Dl-alfa-tocopherol medium chain tiglycerides purified fish oil purified olive oil soybean oil	Not reported	Slovenia
2009	MRP	Ratiopharm Gmbh, Mylan S.P.A.	Fluoxetina ratiopharm, fluoxetina mylan generics	Fluoxetine hydrochloride	Not reported	Italy
2009		Bayer Schering Pharma Oy	Gadovist 1,0 mmol/ml injektioneste, liuos kerta-annosruisku Gadovist 1,0 mmol/ml injektioneste, liuos	Gadobutrol	Not reported	Finland
2009	MRP	Alk-Abelló A/S	Grazax(, grazura	Grass pollen allergen extract	Not reported	Italy
2009		Baxter AG	Subcuvia 160 g/l	Human normal	Not reported	Finland

Year	Procedure(N / DC / MRP)	Marketing Authorisation Holder	Invented name	Active substance (INN)	Paediatric indication	Member State
			injektioneste, liuos	immunoglobulin		
2009	MRP in Italy	Merck Sharp & Dohme B.V., Sigma-Tau Industrie Farmaceutiche Riunite Spa, Msd Italia S.R.L.	Cozaar 2.5 mg/ml jauhe ja liuotin oraalisuspensiota varten, Cozaar 12.5 mg, 50mg, 100mg, tabletti, kalvopäällys-teinen, LOSAPREX, NEO-LOTAN, LORTAAN	Losartan	Not reported	Finland, Italy
2009	MRP	Glaxosmithkline S.P.A.	Priorix	Measles mumps rubella	Not reported	Italy
2009	MRP	Hexal S.P.A., Laboratori Guidotti S.P.A.	Metformina hexal, metforalmille	Metformin hydrochloride	Not reported	Italy
2009	DC	Ibigen S.R.L.	Piperacillina e tazobactam ibigen (dcp)	Piperacillin sodium / tazobactam sodium	Not reported	Italy
2009	MRP	Glaxosmithkline Spa	Relenza	Zanavimir	Not reported	Italy
2009	MRP	Pfizer Italia S.R.L., Pfizer Ab, Sweden	ZELDOX, Zeldox 20 mg 40 mg 60 mg 80 mg capsules, hard ZELDOX 10 mg/ml Oral suspension	Ziprasidone	Treatment of manic or mixed episodes of moderate severity in bipolar disorder in adults and children and adolescents aged 10-17 years (prevention of episodes of bipolar disorder has not Heen established).	Italy, Sweden
2010	N	Pfizer Hellas Ae, Pfizer Europe Ma Eeig, Pfizer Oy, Pfizer Europe Ma	Lipitor fctabs 10mg, Lipitor fctabs 20mg, Lipitor fctabs 40mg, Sortis, Lipitor 10 mg,	Atorvastatin	hypercholesterolaemia children over 10 years of age	Cyprus, Estonia, Finland, Romania

Year	Procedure(N / DC / MRP)	Marketing Authorisation Holder	Invented name	Active substance (INN)	Paediatric indication	Member State
		Eeig	20mg, 40mg, 80mg, tabletti, kalvopäällys-teinen, Sortis 10 mg film coated tablets Sortis 20 mg film coated tablets Sortis 40 mg film coated tablets Sortis 80 mg film coated tablets			
2010		Fresenius Kabi Ab	Smoflipid 200 mg/ml infuusioneste, emulsio	Dl-alfa-tocopherol medium chain tiglycerides purified fish oil purified olive oil soybean oil	Not reported	Finland
2010	MRP for Estonia, N for Sweden	Pfizer Enterprises Sar, Pfizer Ab, Sweden	Xalatan, Xalatan, 50 microgram/ml	Latanoprost	Sänkning av det intraokulära trycket hos barn med förhöjt intraokulärt tryck och barnglaukom.	Estonia, Sweden
2010	MRP	Merck Sharp & Dohme Romania S.R.L.	COZAAR 12,5 mg film coated tablets	Losartan	Not reported	Romania
2010	MRP	Merck Sharp & Dohme Romania S.R.L.	Singulair 4 mg/sachet granules	Montelukast	Not reported	Romania
2010		Astra Zeneca Oy	Crestor 5 mg, 10 mg, 20 mg, 40 mg tabletti, kalvo-päällysteinen	Rosuvastatin calcium	Not reported	Finland
2010	MUTUAL RECOGNITI	Apotex Europe Bv	Sumatriptan tablets 50,	Sumatriptan succinate	Not reported	United Kingdo

Year	Procedure(N / DC / MRP)	Marketing Authorisation Holder	Invented name	Active substance (INN)	Paediatric indication	Member State
	ON		100mg			m
2010	MRP	Novartis Pharmaceuticals UK Ltd, Novartis Finland OY, NOVARTIS PHARMA Gmbh, Novartis Sverige AB	Diovan fctabs 40mg, 80mg, 160mg, 320mg, Diovan, Diovan 40 mg, 80 mg, 160mg, 320 mg, tabletti, kalvo-päällysteinen, Diovan, 40 mg, 80 mg, 160 mg, 320 mg, Film-coated tablet	Valsartan	Hypertension in children from 6 years to less than 18 years of age	Cyprus, Estonia, Finland, Romania, Sweden
2010		Pfizer Oy	Orbeus 10 mg, 20 mg, 40 mg, 80 mg, tabletti, kalvopäällys-teinen		Not reported	Finland
2011	N	Tillomed Laboratories Limited	Aciclovir tablets bp 200, 400, 800mg; aciclovir dispersible tablets 200,400mg, cyclofarm limited aciclovir dispersible tablets/virovir dispersible	Acyclovir	Not reported	United Kingdom
2011	MRP	Astrazeneca UK Limited, 15 Stanhope Gate, London, United Kingdom, Astrazeneca Farmacéutica Spain, S.A., Astrazeneca AB, Sweden	Nexium 10 mg gastro-resistant granules, NEXIUM MUPS 20 mg comprimidos gastrorresistentes, AXIAGO 20 mg comprimidos gastrorresistentes, AXIAGO 10 mg granulado gastrorresistent	Esomeprazole	Adolescents from the age of 12 years Gastroesophageal Reflux Disease (GERD) - treatment of erosive reflux esophagitis - long-term management of patients with healed esophagitis to prevent relapse - symptomatic treatment of	Slovenia, Spain, Sweden

Year	Procedure(N / DC / MRP)	Marketing Authorisation Holder	Invented name	Active substance (INN)	Paediatric indication	Member State
			e para suspensión oral, sobres, NEXIUM 10 mg granulado gastrorresistente para suspensión oral, sobres, NEXIUM 20 mg Gastro-resistant tablets, NEXIUM 10 mg Gastro-resistant granules for oral suspension, sachet, NEXIUM 40 mg Powder for solution for injection/infusion		gastroesophageal reflux disease (GERD) In combination with antibiotics in treatment of duodenal ulcer caused by Helicobacter pylori / oral suspension primarily indicated for: Children 1-11years old Children over 4 years of age In combination with antibiotics in treatment of duodenal ulcer caused by Helicobacter pylori	
2011	MRP	Merck Sharp & Dohme Bv, Netherlands	Ezetrol tabs 10mg	Ezetimibe	Primary non-familial hypercholesterolaemia/ heterozygous familial hypercholesterolaemia, adolescents 10 to 17 years of age	Cyprus
2011	MRP	Alk-Abelló A/S, Denmark	GRAZAX 75,000 SQ-T Oral lyophilisate	Grass pollen allergen extract	Treatment of grass pollen induced rhinitis and conjunctivitis in adults and children (5 years or older), with clinically relevant symptoms and diagnosed with a positive skin prick test and/or specific IgE test to grass pollen.	Sweden
2011		Pfizer Oy, Pfizer Europe Ma Eeig, Pfizer, S.A.	Xalatan 50 mikrog/ml silmätipat,liuos l, XALATAN	Latanoprost	Children from 1 year old to 11 years old Gastro-oesophageal	Finland, Romania, Spain

Year	Procedure(N / DC / MRP)	Marketing Authorisation Holder	Invented name	Active substance (INN)	Paediatric indication	Member State
			0,005%, XALATAN		reflux disease Treatment of endoscopically-proven erosive reflux oesophagitis Long-term management of patients with healed oesophagitis to prevent relapse Children > 4 years old In combination with antibiotics in the treatment of duodenal ulcer caused by Helicobacter pylori Reduction of elevated intraocular pressure in paediatric patients with elevated intraocular pressure and paediatric glaucoma	
2011	NATIONAL	Antigen International Limited	Antigen metoclopramide injection bp 10mg/2ml	Metoclopramide hydrochloride	Not reported	United Kingdom
2011		Glaxosmithkline AB, Sweden	Zofran, 4 mg, 8 mg Film-coated tablet tablet,	Ondansetron	Barn Profylax och behandling av illamående och kräkningar inducerade av kemoterapi hos barn ≥ 6 månader. Profylax och behandling av postoperativt illamående och kräkningar hos barn ≥ 1 månad.	Sweden

Year	Procedure(N / DC / MRP)	Marketing Authorisation Holder	Invented name	Active substance (INN)	Paediatric indication	Member State
2011	N & MRP	Tillomed Laboratories Limited, Synthon Bv	Oxybutynin hydrochloride tablets 2.5, 5mg, urimin tablets 5mg	Oxybutynin hydrochloride	Not reported	United Kingdom

7.3. New route of administration or new pharmaceutical form for paediatric use

Summary:

- Overall the medicines for which Member States (12 in total) have reported the variation to authorise a new route of administration, or a new pharmaceutical form, correspond to medicines with an agreed PIP (7 out of the 11 active substances), that underwent an Article 29 referral procedure (section 5.) or that have been captured in Article 45 (section 8.1.2.).
- For in total 11 active substances, new pharmaceutical forms and / or new routes of administration were becoming available since coming into force of the Paediatric Regulation. In the majority, this was linked to requirements under the Paediatric Regulation.

Table 20: List of paediatric relevant line extensions (addition of new route of administration or a new pharmaceutical form) authorised in Member States.

Year	Procedure? (N / DC / MRP)	Marketing authorisation holder	Invented name	Active substance (INN)	Paediatric formulation / route of administration	Member States
2010		Pfizer Corporation Austria GmbH	Sortis and associated names	Atorvastatin	Chewable tablets	Austria, Cyprus, Czech Republic, Estonia, Lithuania, Slovenia, Spain, United Kingdom
2011	DCP	Sanofi Pasteur SA	Pediacel	DTP/Hib/Polio vaccine	New route of administration, Prefilled syringe	Poland, United Kingdom
2007	N	AstraZeneca AB	Nexium and associated names	Esomeprazole	Paediatric formulation: Granules for oral suspension in sachet	Sweden
2011		Abbott Laboratories	Brufen	Ibuprofen*	New paediatric formulation: oral suspension	Slovenia
2009	MRP	Merck Sharp & Dohme	Cozaar and associated	Losartan	Paediatric formulation:	Cyprus, Estonia, Italy,

Year	Procedure? (N / DC / MRP)	Marketing authorisation holder	Invented name	Active substance (INN)	Paediatric formulation / route of administration	Member States
			names		Powder for oral solution, oral suspension	Spain, United Kingdom,
2009	DCP	Merck Santé, s.a.s.	Glucophage	Metformin hydrochloride*	New paediatric formulation: Powder for oral solution in sachets	Poland, Sweden
2008		GlaxoSmithKline GmbH & Co. KG	Priorix-Tetra	MMRV vaccine*		Italy
2009		Merck Sharp & Dohme GmbH	Singulair	Montelukast	Granules, Chewable tablet	Austria, Czech Republic, Lithuania
2011	MRP/RUP	Merck Sharp & Dohme	Maxalt	Rizatriptan	Tablet, oral lyophilisate, oral use	Lithuania
2009		Ferring	Zomacton	Somatropin*		Italy
2010	MRP	Novartis Pharma GmbH	Diovan and associated names	Valsartan	Paediatric formulation: oral solution, divisibility of the tablet	Austria, Cyprus, Czech Republic, Estonia, Finland, Italy, Romania, Slovenia, Spain, Sweden, United Kingdom

* No agreed PIP available

7.4. Variation to include statement on waiver or deferral

- The statement on a waiver or deferral would be added to the section 5.1 of the SmPC.
- Data were provided by only 6 Member States and in each case, for no more than 1 year in between 2009 and 2011. Information from the UK on 2 active substances for which statements on a waiver were included had been included in the 2010 Report to the European Commission (Table 7, p 13).
- The EMA Report to the European Commission (2010) had identified 2 nationally authorised medicinal products, for which the statement on deferral and / or waiver had been inadvertently omitted. Since, the statement could be added in a variation for 1 medicine (Sativex [Tetranabinex / Nabidiolex]).

7.5. Variation to include paediatric dosing information or recommendations

Summary:

- The statement on a waiver or deferral would be added to the section 4.2 of the SmPC.
- In total 9 Member States provided information (219 data entries) covering the years 2007 to 2011, corresponding to in total 80 active substances. Scrutinising the data, some data entries were for medicines that had no relevant use in the paediatric population and therefore no dosing information. No all data entries reported the year of the variation.
- The number of active substances were summarised per year of the variation and whether there was an agreed PIP and therefore a link to the Paediatric Regulation, see Table 8 in core report (section 5.1).

7.6. Variation with paediatric data linked to off label use included into SmPC

No Member State presented data specifically on this question.

7.7. Variations under Article 36.1.2 - data of completed PIP, which study results failed to lead to a paediatric indication

Table 21: Variations assessing paediatric data that were in compliance with a completed, agreed PIP, but which study results did not lead to any paediatric indication

No.	Procedure? (N / DC / MRP)	INN (Invented Name)	Marketing authorisation holder	Condition that was targeted in the PIP but no paediatric use but was authorised	Year of variation	Member State(s) reporting variation
1	MRP, N	Anastrozole (Arimidex)	AstraZeneca AB	Treatment of short stature in pubertal boys with growth hormone deficiency, in combination with exogenous growth hormone, Treatment of testotoxicosis	2009	Spain, Sweden, united Kingdom
2	MRP	Montelukast (Singulair and associated names)	Merck Sharp and Dohme	Treatment of episodic (intermittent) asthma (6 months to less than 6 years)	2010	Slovenia, Spain, Sweden, United Kingdom
3	MRP	Rizatriptan (benzoate) (Maxalt and assoiated names)	Merck Sharp and Dohme	Treatment of migraine	2011	Slovenia, Spain

* Not all Member States may have reported variations.

8. Article 45 and 46 outcomes

New paediatric indications granted subsequent to variations triggered by assessments of studies submitted under Article 45 or 46 of the Paediatric Regulation. The new paediatric indications for the centrally authorised medicines are listed in section 4.2. of this report. The new paediatric indications of medicinal products authorised through national / decentral / mutual recognition procedure were:

1. Amlodipine: SmPC section 4.2: "Children with hypertension from 6 years to 17 years of age: The recommended antihypertensive oral dose in pediatric patients ages 6-17 years is 2.5 mg once daily as a starting dose, up-titrated to 5 mg once daily if blood pressure goal is not achieved after 4 weeks. Doses in excess of 5 mg daily have not been studied in pediatric patients (see section 5.1 Pharmacodynamic Properties and section 5.2 Pharmacokinetic Properties)."
2. Baclofen: SmPC Section 4.1: "Paediatric population: Baclofen Intrathecal is indicated in patients aged 4 to <18 years with severe chronic spasticity of cerebral origin or of spinal origin (associated with injury, multiple sclerosis, or other spinal cord diseases) who are unresponsive to orally administered antispastics (including oral baclofen) and/or who experience unacceptable side effects at effective oral doses."
3. Bisacodyl: SmPC Section 4.2: "Children aged 10 years or younger with chronic constipation should only be treated under the guidance of a physician. Bisacodyl should not be used in children aged 2 years or younger."
4. Flumazenil: SmPC Section 4.1: "For the reversal of conscious sedation induced with benzodiazepines in children > 1 year of age"
5. Lisinopril: SmPC Section 4.2: "Use in Hypertensive Paediatric Patients aged 6-16 years: The recommended initial dose is 2.5 mg once daily in patients 20 to <50 kg, and 5 mg once daily in patients .50 kg. The dosage should be individually adjusted to a maximum of 20 mg daily in patients weighing 20 to <50 kg, and 40 mg in patients .50 kg."
6. Milrinone: SmPC Section 4.1: "In paediatric population <National approved name> is indicated for the short-term treatment (up to 35 hours) of severe congestive heart failure unresponsive to conventional maintenance therapy (glycosides, diuretics, vasodilators and/or angiotensin converting enzyme (ACE) inhibitors), and for the short-term treatment (up to 35 hours) of paediatric patients with acute heart failure, including low output states following cardiac surgery."
7. Propranolol: SmPC Section 4.2: "Arrhythmias: Dosage should be individually determined and the following is only a guide: Children and adolescents: 0.25 - 0.5mg/kg 3-4 times daily, adjusted according to response. Max 1 mg/kg 4 times daily, total daily dose not to exceed 160 mg daily. Intravenous Dosage: […] The intravenous injection is intended for the emergency treatment of cardiac arrhythmias only. Children and adolescents: 0.025-0.05mg/kg injected slowly, preferably under ECG control and repeated if necessary every 6-8 hours"

Before the entry into force of the Paediatric Regulation (2005-2008) and in a process similar to the assessments under Article 45 of the Paediatric Regulation, the CMD(h) has conducted in its "worksharing project" the assessment of paediatric studies submitted by Marketing Authorisation Holders for 21 active substances used in the paediatric population. The reports have been made public here: http://www.hma.eu/270.html.

8.1. Article 45

In accordance with Article 45 of the Paediatric Regulation, marketing authorisation holders were required to submit to the competent authorities all paediatric studies completed by the date of entry into force of the Regulation. These studies were to be submitted by 26 January 2008. Upon assessment of the data, the competent authority may update the SmPC and package leaflet and may vary the marketing authorisation.

For products authorised through national/decentralised/mutual recognition procedure, the extent of information received has been enormous. Information has been received for almost one thousand active substances, with several documents for each of them (some may relate to the same study). To cope with the workload, there is an ongoing worksharing exercise between Member States and the assessment is being performed in waves, co-ordinated by the CMD(h).

8.1.1. Centrally authorised medicines

Summary:

- For centrally authorised medicinal products, data (study results) were submitted for 55 active substances, corresponding to 61 medicinal products. In 2011, the CHMP completed the assessment of the last submitted data. In total, the SmPCs of 12 medicinal products were changed subsequent to the assessment. The publication of all assessment reports / outcomes of the assessment of studies submitted through Article 45 is made in the respective EPAR web pages of the EMA website (see http://www.ema.europa.eu/).

Table 22: List of Article 45 CAP outcomes resulting in changes of the SmPC.

No.	Year	Active substance	Trade name	Marketing authorisation holder	Outcome of assessment, recommended SmPC change(s)
1	2009	Pegfilgrastim	Neulasta	Amgen Europe B.V.	Section 4.2, 4.8, 5.1 and 5.2
2	2009	Ritonavir	Norvir	Abbott Laboratories Limited	Section 5.1
3	2009	Mangafodipir	Teslascan	GE Healthcare AS	Section 4.2
4	2009	Interferon beta-1a	Avonex	Biogen Idec Limited	Sections 4.2, 4.8 and 5.1
5	2009	Oseltamivir	Tamiflu		Sections 4.1, 4.2, 4.8 and 5.2
6	2010	Interferon beta-1a	Avonex	Biogen Idec Ltd.	Sections 4.2, 4.8 and 5.1
7	2010	Perflutren	Optison	GE Healthcare AS	Sections 4.2 and 5.1
8	2010	Zonisamide	Zonegran	Eisai Ltd.	Section 5.2

8.1.2. Medicinal products authorised through national/mutual recognition/decentralised procedure

Summary:

- The following table is based on the CMD(h) reporting the completion of the assessment of studies submitted under Article 45 of the Paediatric Regulation ("List of active substances for which data has been submitted in accordance with Article 45 of the Paediatric Regulation (January 2012)", available here: http://www.hma.eu/99.html). The reports on the assessments under Article 45 are made public by the CMD(h) on this webpage: http://www.hma.eu/269.html.

- Information provided by the Member States was added to the table to indicate the years and the Member States' implementation of recommendations to change the SmPC according to the CMD(h) assessment outcome and recommendations. Data on variations in relation to Article 45 or 46 were provided by only 13 Member States (Austria, Belgium, Cyprus, Finland, France, Hungary, Italy, Portugal, Romania, Slovenia, Spain, Sweden and United Kingdom).
- Of 89 active substances for which the CMD(h) completed the assessment by 31 December 2011 of studies submitted under Article 45, 73 assessment reports were made public, some of which are for more than 1 active substance. The main outcome of the assessment and the most important recommended changes to the SmPCs were, across the 73 active substances: safety information to be added (3 active substances); new paediatric study results to be added (9); a new paediatric indication to be added (7) and clarifications on paediatric use (34).
- For 18 active substances, no change to the SmPC was necessary subsequent to the assessment of paediatric studies submitted under Article 45. These active substances appear to correspond to medicines that are already authorised for a paediatric use.
- In total, the various sections of SmPCs were recommended to be changed: for 8 active substances in section 4.1 (indication), for 22 active substances in 4.2 (posology and administration), for 10 active substances in 4.4 (warnings), for 7 active substances in section 4.8 (undesirable effects), for 11 active substances in section 5.1 (pharmacodynamics) and for 11 active substances in section 5.2 (pharmacokinetics).

Table 23: Outcomes resulting in changes to the SmPC and implementation of assessment of paediatric studies submitted under Article 45 for medicinal products authorised through national/mutual recognition/decentralised procedure

Active substance (INN)	**Recommended changes to product information**	**Outcome of assessment and recommended changes**	**Years**	**Member States reporting variation implementing recommendations**
Alendronic acid	Sections 4.2 & 5.1	Paediatric information clarified	2009-2011	Italy, Hungary, Slovenia, Sweden, United Kingdom
Amikacin	Sections 4.1, 4.2, 4.4, 4.5, 4.6 & 5.2	Paediatric information clarified	2010-2011	Belgium, Finland, Italy, United Kingdom
Amiodarone	Sections 4.2, 4.3, 4.4, 5.1 & 5.2	Paediatric information clarified	2011	Belgium, Finland, Slovenia, Spain, United Kingdom
Amlodipine	Sections 4.2, 5.1 & 5.2	New indication	2010-2011	Belgium, Finland, Italy, Romania, Slovenia, Sweden, United Kingdom
Amoxicillin	Sections 4.2, 4.4 and 5.2	Paediatric information clarified	2010-2012	Austria, Belgium, Italy, Slovenia, Sweden, United Kingdom
Apis mellifera - Lyophilised bee venom[1]	Sections 4.1, 4.2, 4.3 & 4.4	Paediatric information clarified	2010	United Kingdom
Baclofen	Sections 4.1, 4.2	New indication	2011	Belgium, Finland, Romania, United

[1] Covers also vespula spp. / lyophilised wasp venom

Active substance (INN)	Recommended changes to product information	Outcome of assessment and recommended changes	Years	Member States reporting variation implementing recommendations
	& 4.4			Kingdom
Betula verrucosa (pendula), allergen extracts from birch/alder/ hazel (betula), allergen extract from birch (betula)	Section 4.2	Paediatric information clarified	2010	United Kingdom
Bisacodyl	Section 4.2	New indication	2010-2011	Belgium, Italy, Slovenia, Sweden, United Kingdom
Calcitonin (salmon synthetic)	Section 4.2	No change	2009-2011	Finland, Slovenia, United Kingdom
Canis familiaris (553)	Section 4.2	Paediatric information clarified	2010	United Kingdom
Chondroitin sulfate	Section 4.2	Paediatric information clarified	2011	Italy
Clarithromycin	Sections 4.1 & 4.2	Paediatric information clarified	2011	Belgium, Finland, Hungary, Italy, Romania, United Kingdom
Clobazam	Section 4.2	Paediatric information clarified	2011	United Kingdom
Clonidine	Sections 4.2 & 5.1		2011	Belgium, Sweden, United Kingdom
Dermatophagoides pteronyssinus	Section 4.2	Paediatric information clarified	2010	United Kingdom
Dermatophagoides farinae / Dermatophagoides pteronyssin	Section 4.2	Paediatric information clarified	2010	United Kingdom

Active substance (INN)	Recommended changes to product information	Outcome of assessment and recommended changes	Years	Member States reporting variation implementing recommendations
us				
Diclofenac	Sections 4.2, 4.3 & 4.8	Paediatric information clarified	2011	Belgium, Finland, Italy, Romania, Slovenia, Spain, Sweden, United Kingdom
Ethosuximide	Syrup formulation Sections 4.2 & 5.1 Capsule formulation Sections 4.2 & 5.1	Paediatric information clarified	2011	Belgium, United Kingdom
Famciclovir	See outcome of Art.30 Procedure in April 2010	Paediatric information clarified	2011	Cyprus, Finland, Italy, United Kingdom
Felis domesticus	Section 4.2	Paediatric information clarified	2010	United Kingdom
Felodipine	Sections 5.1 & 5.2	New study data	2010-2011	Belgium, Cyprus, Finland, Spain, Sweden, United Kingdom
Fentanyl	Fentanyl patches Sections 4.1 & 4.2 Fentanyl Injection Sections 4.2, 4.3 & 4.4 Fentanyl Lozenge Sections 4.1, 4.2, 5.1, 5.2 & 5.3	Paediatric information clarified	2009-2011	Austria, Finland, Italy, Spain, Sweden, United Kingdom
Flumazenil	Sections 4.1, 4.2 & 5.2	New indication	2011	Finland, Spain, United Kingdom

Active substance (INN)	Recommended changes to product information	Outcome of assessment and recommended changes	Years	Member States reporting variation implementing recommendations
Gentamicin	Intravenous and intramuscular use Sections 4.1, 4.2, 4.4, 5.2 Topical otic Section 4.4 Topical use other than otic None Intrathecal use None	New safety information	2010-2011	Belgium, Finland, Sweden, United Kingdom
Glucosamine	Sections 4.2 and 4.4	Paediatric information clarified	2010	Belgium, Finland, Italy, United Kingdom
Isradipine	Section 4.2	Paediatric information clarified		None
Itraconazole	Sections 4.2, 4.8, 5.1 & 5.2	Paediatric information clarified	2011	Belgium, Finland, United Kingdom
Levothyroxine	Section 4.2	Paediatric information clarified	2009-2011	Belgium, Cyprus, Finland, Romania, Sweden, United Kingdom
Lisinopril	Sections 4.2, 4.8, 5.1 & 5.2	New indication	2009-2011	Cyprus,Finland, Sweden, United Kingdom
Mepivacaine	Section 4.2 & 4.3	Paediatric information clarified	2010-2011	Belgium, Finland, Romania, Sweden, United Kingdom
Mesalazine	Section 4.2	Paediatric information clarified	2010-2011	Belgium, Cyprus, Finland, Slovenia, Sweden, United Kingdom
Metoclopramide	i.v. Form Sections 4.1, 4.2, 4.3, 4.4, 4.8 & 4.9 Oral & Rectal Forms Sections 4.1, 4.2, 4.3, 4.4, 4.8 & 4.9	New safety information	2008, 2011, 2012	Belgium, France, Spain, Sweden, United Kingdom
Metronidazole,	Sections 4.1, 4.2 & 4.8	Paediatric information	2010-2011	Belgium, Cyprus, Finland, Italy, Sweden, United Kingdom

Active substance (INN)	Recommended changes to product information	Outcome of assessment and recommended changes	Years	Member States reporting variation implementing recommendations
Metronidazole / Spiramycin		clarified		
Milrinone	Sections 4.1, 4.2 4.4, 4.8, 5.1, 5.2 & 5.3	New indication	2011	Belgium, Sweden, United Kingdom
Mirtazapine	Sections 4.2, 4.8 & 5.1	New study data	2010-2011	Austria, Finland, Romania, Sweden, United Kingdom
Neridronic acid	Sections 4.1 & 4.2	Paediatric information clarified		Italy
Oxazepam	Section 4.4	New safety information	2010	Sweden, United Kingdom
Oxybutynin	Section 4.1 & 4.4	Paediatric information clarified	2010-2011	Belgium, Spain, Sweden, United Kingdom
Paclitaxel	Section 4.2	Paediatric information clarified	2010-2011	Finland, Italy, Slovenia, Spain, Sweden, United Kingdom
Phleum pratense / Modified, adsorbed grass pollen	Section 4.2	Paediatric information clarified	2010	Portugal, Spain, United Kingdom
Propofol	Sections 4.4 & 5.2	Paediatric information clarified	2010-2011	Belgium, Finland, Sweden, United Kingdom
Propranolol	Sections 4.2 & 4.8	New indication	2011	Belgium, Spain, Sweden, United Kingdom
Quinapril	Sections 5.1 & 5.2	New study data	2011-2012	Belgium, Romania, United Kingdom
Remifentanil	Sections 4.1, 4.2, 4.4 & 5.1	Paediatric information clarified	2010-2011	Finland, Romania, Slovenia, Spain, Sweden, United Kingdom
Rifaximin	Sections 4.1, 4.2 & 5.1	New study data	2010	Spain
Risedronic acid[2]	Sections 4.2 & 5.1	New study data	2010-2011	Austria, Finland, Italy, Romania, Spain, Sweden, United Kingdom
Simvastatin	Sections 4.2, 4.4, 4.8, 5.1 & 5.2	New study data	2009-2010	Belgium, Finland, Italy, Slovenia, Sweden, United Kingdom
Timolol	Sections 4.2,	Paediatric	2011	Belgium

[2] Covers also the sequential treatment with risedronic acid, calcium and colecalciferol

Active substance (INN)	Recommended changes to product information	Outcome of assessment and recommended changes	Years	Member States reporting variation implementing recommendations
	4.4, 5.1 & 5.2	information clarified		
Topiramate	Sections 4.4, 4.8 & 5.1	New study data	2010-2011	Finland, Slovenia, Sweden, United Kingdom
Tranexamic acid	Section 4.2, 4.3, 4.4, 4.8, 5.1 & 5.2	New study data	2010-2011	Belgium, United Kingdom
Triptorelin	Sections 4.2, 4.4 and 4.8	Paediatric information clarified	2010-2011	Slovenia, Spain, United Kingdom
Vespula spp. / Lyophilised wasp venom	Sections 4.1, 4.2, 4,3 & 4.4	Paediatric information clarified	2010	United Kingdom

8.2. Article 46

8.2.1. Centrally authorised medicines

Summary:

- For centrally authorised products, 108 procedures ("FUM", follow-up measures) of evaluation of studies submitted through this Article have been finalised by 2011. This figure may cover the same study(ies) submitted for more than one product and for more than one procedure. In 2 of them, the data have submitted directly through a variation procedure.
- In total, 55 active substances were addressed by 105 submitted studies. Subsequent to these 108 procedures, the CHMP recommended 15 changes to the product information for 13 active substances.
- In total, the various sections of SmPCs were recommended to be changed: for 1 active substance in section 4.1 (indication), for 8 active substances in 4.2 (posology and administration), for 2 active substances in 4.4 (warnings), for 3 active substances in section 4.8 (undesirable effects), for 10 active substances in section 5.1 (pharmacodynamics) and for 6 active substances in section 5.2 (pharmacokinetics).

Table 24: List of Article 46 CAP outcomes resulting in SmPC changes

Year	Number of procedures	Active substance(s)	Trade name	Marketing authorisation holder	Outcome of assessment, recommended SmPC change(s)
2009	1	Cinacalcet	Mimpara	Amgen Europe B.V	Section 5.2
2009	1	Telithromycin	Ketek	Aventis Pharma S.A.	Section 4.2 and 5.2
2010	1	Aripiprazole	Abilify	Otsuka	Sections 4.2 and

Year	Number of procedures	Active substance(s)	Trade name	Marketing authorisation holder	Outcome of assessment, recommended SmPC change(s)
				Pharmaceutical Europe Ltd.	5.1
2010	1	Palonosetron hydrochloride	Aloxi	Helsinn Birex Pharmaceuticals Ltd.	Sections 4.2, 5.1 and 5.2
2010	1	Pramipexole dihydrochloride monohydrate	Mirapexin/ Sifrol	Boehringer Ingelheim International GmbH	Section 5.3
2010	1	Pramipexole dihydrochloride monohydrate	Mirapexin/ Sifrol	Boehringer Ingelheim International GmbH	Sections 4.2 and 5.1
2010	1	Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)	Prevenar	Wyeth Lederle Vaccines S.A.	Section 5.1
2010	1	Fondaparinux sodium	Arixtra	Glaxo Group Ltd.	Sections 5.1, 5.2
2010	1	Nitric oxide	INOmax	INO Therapeutics AB	Sections 4.2 and 5.1
2011	1	Virus, live attenuated, measles, virus, live attenuated, mumps, virus, live attenuated, rubella, virus, live attenuated, varicella*	Proquad	Sanofi Pasteur MSD, SNC	Section 4.8
2011	1	Adalimumab	Humira	Abbott Laboratories Ltd.	Sections 1, 4.1, 4.2, 5.1, 5.2, 6.3, 6.5
2011	1	Tenofovir disoproxil fumarate	Viread	Gilead Sciences International Ltd.	Sections 4.2, 4.4, 4.6, 4.8 5.1, 5.2 and 5.3
2011	2	Rufinamide	Inovelon	Eisai Ltd.	Section 4.8
2011	1	Adefovir dipivoxil	Hepsera	Gilead Sciences International Ltd.	Sections 4.2 and 5.1
2011	1	Tenofovir disoproxil fumarate	Viread	Gilead Sciences International Ltd.	Sections 4.4, 5.1

* One or more procedures still ongoing

8.2.2. Medicinal products authorised through national/mutual recognition/decentralised procedure

Summary:

- In 2009, studies have been received for 70 nationally authorised medicinal products and those authorised through mutual recognition, or decentralised procedures, for assessment under Article 46 of the Paediatric Regulation.
- In 2010, a total of 56 studies were submitted in respect of nationally authorised medicinal products and those authorised through mutual recognition, or decentralised procedures, for assessment under Article 46 of the Paediatric Regulation. The assessment was finalised for 19 products and the assessment report was published for 13 of these studies, recommending to change the SmPCs of the medicinal products corresponding to 6 active substances.
- In 2011, a total of 45 studies were submitted in respect of nationally authorised medicinal products and those authorised through mutual recognition, or decentralised procedures, for assessment under Article 46 of the Paediatric Regulation. The assessment was finalised for 20 procedures and the assessment was published for 17 of these studies, recommending for 4 of them to amend the SPCs.
- The data provided by the Member States included entries for active substances, for which assessments under Article 45 and / or 46 are scheduled but have not yet been started or completed; these entries are not listed below.
- The assessment reports are being made public by the CMD(h) here: http://www.hma.eu/291.html.
- The following table lists the completed assessments of studies submitted under Article 46 of the Paediatric Regulation and, where necessary, the implementation by the Member States reporting variations. In total, for 20 active substances, 25 assessments were completed, out of which 6 recommended changes to the SmPC of the concerned medicinal products, mostly in the sections 4.2 (posology) and 5.2 (pharmacokinetics).

Table 25: Article 46 non-CAP

Year	**Active substance (INN)**	**Medicinal product**	**Pharmaceutical form(s)**	**Recommended changes to Product information**	**Outcome of assessment and recommended changes**	**Member States reporting variation implementing recommendations**
2011	Alfuzosin	Xatral	Film-coated tablet, prolonged-release tablet	Section 4.2, 5.1	New study data	Belgium, Cyprus, Sweden
2009, 2011	Atomoxetine	Strattera (2 procedures)	Capsules	None	No change necessary	None
2010	Donepezil	Aricept	Film-coated tablets, oral solution	None	No change necessary	None
2010 - 2011	Esomeprazole	Nexium	gastro-resistant granules for oral suspension/	Sections 4.2 and 5.1	New study data	Spain, Sweden

Year	Active substance (INN)	Medicinal product	Pharmaceutical form(s)	Recommended changes to Product information	Outcome of assessment and recommended changes	Member States reporting variation implementing recommendations
			sachet			
2010 - 2011	Famciclovir	Famvir and associated names (2 procedures)	Film-coated tablets	Sections 4.2, 5.1 and 5.2	Paediatric information clarified (in conjunction with Article 45)	Cyprus, Finland, Italy
2011	Gabapentin	Neurontin	Oral solution, film-coated tablet	None	No change necessary	None
2010	Granisetron	Kytril	Ampoules, Tablets	Sections 4.4, 4.5 and 4.8	Safety information added	Portugal
2011	Glimepiride	Amaryl	Tablets	None	No change necessary	None
2011	Human coagulation factor XIII	Fibrogammin P	Powder and solvent for intravenous injection	None	No change necessary	None
2011	Influenza vaccine	Afluria/Enzira	Suspension for injection in a pre-filled syringe	None	No change necessary	None
2010 - 2011	Lansoprazole	Agopton	Capsule, oro-dispersible tablet	Section 4.2	Paediatric information clarified	Austria, Finland, Italy, Romania
2010 - 2011	Montelukast	Singulair (2 procedures)	Chewable tablets	None	No change necessary	None
2010	Pimecrolimus	Elidel (3 procedures)	Cream	None	No change necessary	None
2011	Inactivated poliomyelitis vaccine	Poliorix	Solution for injection	None	No change necessary	None
2010 - 2011	Ropinirole	Adartrel	Film-coated tablets	Section 5.2	New study data	Finland, Spain, Romania
2010	Salmeterol xinafoate / Fluticasone propionate	Seretide Diskus/ Seretide Eudraler	Powder for inhalation, Pressurised suspension	Sections 4.2 and 5.2	New study data	Finland, Slovenia, Spain, Sweden, Romania

Year	Active substance (INN)	Medicinal product	Pharmaceutical form(s)	Recommended changes to Product information	Outcome of assessment and recommended changes	Member States reporting variation implementing recommendations
		and associated names	for inhalation			
2010	Somatropin	Genotropin and associated names	Powder and solvent for solution for injection	None	No change necessary	None
2010	Tacrolimus	Prograf	Hard capsules	None	No change necessary	None
2011	DTP-Polio vaccine	Tetravac and associated names	Suspension for injection	None	No change necessary	None
2010	Valproate sodium	Depakin and associated names	Modified release granules	None	No change necessary	None

9. Questionnaires and annual surveys

9.1. Overview of received data

Table 26: Member States having provided any data from National Competent Authorities (NCA) and from National Competent Authorities (NPO). The data provided did not cover all questions for some Member States.

Member State	2007-2009 NCA	2007-2009 NPO	2010 NCA	2010 NPO	2011 NCA	2011 NPO
Austria	X		X	X	X	X
Belgium	X	X	X	X	X	
Bulgaria	X	X		X		X
Cyprus	X	X	X	X	X	
Czech Republic	X	X	X	X	X	X
Denmark	X	X	X	X	X	X
Estonia	X		X	X	X	X
Finland	X		X	X	X	X
France	X	X		X	X	
Germany	X	X	X	X	X	X
Greece			X	X		
Hungary	X		X	X	X	X
Ireland	X	X	X	X	X	X
Italy	X	X	X	X	X	X

Member State	2007-2009 NCA	2007-2009 NPO	2010 NCA	2010 NPO	2011 NCA	2011 NPO
Latvia	X		X		X	
Lithuania	X	X		X	X	X
Luxembourg	X	X		X		X
Malta	X	X	X	X	X	X
The Netherlands	x		X	X	X	X
Poland			X	X	X	X
Portugal	X		X	X	X	X
Romania	X			X	X	X
Slovakia	X			X		X
Slovenia	X	X		X	X	X
Spain				X	X	
Sweden	X		X	X	X	X
United Kingdom	X	X	X	X	X	X

9.2. Questionnaire to Member States (annual survey)

L:\NCAannual.doc

9.3. Questionnaire to National Patent Offices (annual survey)

L:\NPO.doc

9.4. Questionnaire to Member States (survey 2007-2011)

L:\NCA5year.doc