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