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<br>Reference: number of all PIP applications | 24<br>47 | 28<br>39 | 21<br>31 | 23<br>43 |
| Time lag in months,<br>median (range) | 26<br>(7-161) | 35<br>(7-121) | 20<br>(9-241) | 30<br>(11-99) |
| Number of delayed applications for full waiver<br>Reference: number of all applications for full waiver | 10<br>26 | 11<br>19 | 12<br>22 | 8<br>9 |
| Time lag in months for delayed full waiver applications,<br>median (range) | 24<br>(12-71) | 19<br>(8-92) | 23<br>(9-137) | 46<br>(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.

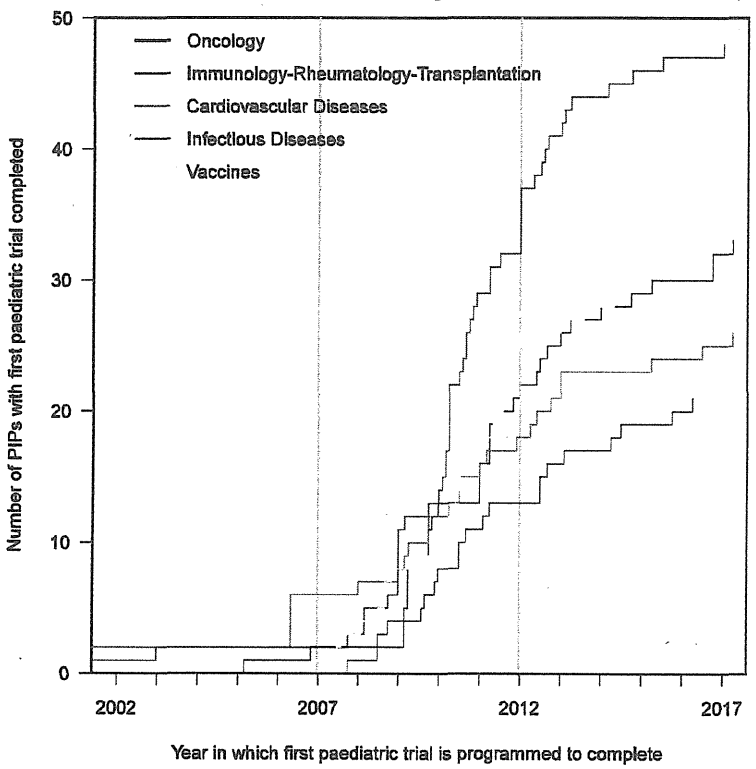
Overall, 58 of the 91 annual reports (64%) stated that the paediatric development was continuing as planned in that reporting year. The most frequent explanations as to why the paediatric development was not continuing as planned, were: difficulties with recruitment (21 annual reports), refusals/problems 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