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REPORT FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT AND THE COUNCIL

Better Medicines for Children — From Concept to Reality

General Report on experience acquired as a result of the application of Regulation (EC) No 1901/2006 on medicinal products for paediatric use

(Text with EEA relevance)

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1. INTRODUCTION

'Better Medicines for Children' was the ambitious title of a consultation paper of February 2002, in which the European Commission presented its vision for regulatory actions on paediatric medicinal products[1]. At that time, many of the products used in children were not specifically studied or authorised in children. Instead, doctors often used products authorised for adults, sometimes in different dosages, with the associated risks of inefficacy and/or adverse reactions.

The consultation paper built on a 5-year discussion process that started in 1997 with a round table meeting at the premises of the European Medicines Agency (EMA) and was the blueprint for the subsequent legislative act. It outlined many of the measures that are to be found in the Paediatric Regulation (Regulation (EC) No 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use[2], hereinafter 'the Regulation').

The Regulation was adopted some five years after the consultation paper, on 12 December 2006. It entered into force on 26 January 2007 and its main provisions were applicable from 26 July 2008 (Article 7) and 26 January 2009 (Article 8), respectively.

Five years on, it is time to take stock of developments and report to the European Parliament and the Council on the experience acquired as a result of the Regulation, in accordance with its Article 50(2). Are we already seeing the emergence of 'better medicines for children'?

This report does not yet provide comprehensive answer, as it is subject to certain limitations; it should therefore be regarded as an interim report that presents a first impression of the experience gained. In view of the development cycles of medicinal products, it will take at least 10 years to gain a full understanding of the impact of the legislation. This factor has already been accounted for in the legislation which requires the Commission to provide a second, more comprehensive report in 2017 which, in accordance with Article 50(3) of the Regulation, must include an analysis of the economic impact of the rewards and incentives, together with an analysis of the Regulation's implications for public health, with a view to proposing any necessary amendments. However at this stage, some analyses and interim conclusions can be made.

This document has been prepared in consultation with Member States, the EMA and interested parties. The Commission particularly values the '5-year Report to the European

[1] http://ec.europa.eu/health/files/pharmacos/docs/doc2002/feb/cd_pediatrics_en.pdf.

[2] OJ L 378, 27.12.2006, p. 1; amended by Regulation (EC) No 1902/2006 of the European Parliament and of the Council of 20 December 2006, OJ L 378, 27.12.2006, p. 20.

Commission' presenting the views of the EMA and its Paediatric Committee[3], and the responses to the public consultation the Commission undertook at the end of 2012[4].

2. THE PAEDIATRIC REGULATION

In 2010 around 21 % of Europeans were children, representing more than 100 million people. Children represent a vulnerable population group with developmental, physiological and psychological differences from adults. They are not merely 'small adults'. Age- and development-related research, and the availability of suitable medicinal products, is consequently particularly important.

Studies carried out before the Regulation was adopted showed that over 50 % of the medicines used for children had not been tested for use in this specific age group. What is more, only a limited number of medicinal products had been developed specifically with children in mind. Companies had already developed a range of products against a number of diseases prior to the Paediatric Regulation, particularly in sectors such as childhood immunisation by means of vaccines. However, the availability of child-appropriate medicines was generally unsatisfactory. Accordingly, the Regulation was seen as a response to the absence of sufficient numbers of suitable, authorised medicinal products, with appropriate dosages and pharmaceutical forms, to treat conditions in children in the European Union (EU).

There are several reasons for the lack of paediatric medicines. It would, however, be too simplistic to pin the blame on pharmaceutical companies for not carrying out enough research and development (R&D) to adapt medicinal products to the needs of the paediatric population. This reluctance has long mirrored a general social and ethical paradigm that children should be protected from clinical research. Only in the last two decades has there been a shift to the current consensus of better protecting children through clinical research.

Economic factors certainly rendered paediatric R&D less attractive in terms of achieving an adequate return on investment. Children are not a homogenous sub-group — subpopulations range from neonates to teenagers, with different biological and pharmacological characteristics. Age-appropriate research makes the process more expensive and complex for organisations that are active in this sector.

However, the absence of specifically tested products often left healthcare professionals with no alternative but to use products 'off-label', with the associated non-negligible risks of inefficacy or adverse reactions. Such a situation was contrary to the general goal to provide high-quality medicinal products to the entire EU population.

To address this problem, the Regulation establishes a system of obligations, rewards and incentives, together with horizontal measures to ensure that medicines are regularly researched, developed and authorised to meet the therapeutic needs of children. Other than the Orphan Regulation[5], which is limited to providing various incentives, the Paediatric Regulation has a direct impact on companies' R&D expenditure. While not questioning that medicinal development is company driven, it compels companies to consider the potential paediatric use of medicinal products they develop.

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3 5-year report to the European Commission — General report on experience acquired as a result of the application of the Paediatric Regulation, prepared by the European Medicines Agency with its Paediatric Committee, http://ec.europa.eu/health/files/paediatrics/2012-09_pediatric_report-annex1-2_en.pdf.

4 http://ec.europa.eu/health/human-use/paediatric-medicines/developments/2013_paediatric_pc_en.htm.

5 Regulation (EC) No 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan medicinal products, OJ L 18, 22.1.2000, p. 1.

The key objectives of the Regulation are:

- to ensure high-quality research into the development of medicines for children;
- to ensure, over time, that the majority of medicines used by children are specifically authorised for such use with appropriate forms and formulations;
- to ensure the availability of high-quality information about medicines used by children.

The key measures included in the Regulation are:

- setting up an expert committee within the EMA: the Paediatric Committee;
- requiring companies to submit data on the use of a medicine in children in accordance with an agreed paediatric investigation plan when applying for marketing authorisation for medicines and line-extensions for existing patent-protected medicines;
- a system of waivers from the requirement for medicines unlikely to benefit children and a system of deferrals in relation to the timing of the requirement, to ensure that medicines are tested in children only when it is safe to do so and to prevent the requirements delaying the authorisation of medicines for adults;
- a reward for complying with the requirement in the form of a six-month extension to the Supplementary Protection Certificate;
- a reward, in respect of orphan medicines, for compliance in the form of an extra two years of market exclusivity added to the existing ten years awarded under the EU's Orphan Regulation;
- a new type of marketing authorisation, the Paediatric Use Marketing Authorisation (PUMA), to attract new paediatric indications for off-patent products;
- measures to maximise the impact of existing studies on medicines for children;
- an EU inventory of the therapeutic needs of children to focus the research, development and authorisation of medicines;
- an EU network of investigators and trial centres to carry out the required R&D;
- a system of free scientific advice for the industry, provided by the EMA;
- a public database of paediatric studies;
- a provision on EU funding for research to stimulate the development and authorisation of off-patent medicines for children.

The Regulation gives the EMA and its Paediatric Committee primary responsibility for handling paediatric investigation plans, deferrals and waivers. This provides the Agency with concrete decision-making powers.

The operational costs of the Paediatric Regulation are partly covered by a contribution from the EU budget (see Table 8), as its main activities do not attract any fees. For the period 2007-12, the EU budget contribution amounted to more than EUR 39 million. In addition, Member States' national competent authorities contribute resources in kind, especially staff time for the assessment of paediatric investigation plans (see Table 12).

3. MAJOR MILESTONES IN IMPLEMENTING THE REGULATION

To implement the Paediatric Regulation successfully, complementary measures needed to be adopted and supplementary action taken as stipulated in the legislation.

The Agency implemented the Regulation in a timely manner. The Paediatric Committee was duly established and held its first meeting on 1-2 July 2007, and has met monthly since. The Commission guideline on the format and content of applications for a paediatric investigation

plan (Article 10) was published in September 2008[6]. The Agency put in place the necessary procedures and database for the scientific evaluation of paediatric investigation plans and for the adoption of decisions under the Regulation.

The European Network for Paediatric Research at the EMA (Enpr-EMA) was set up after the EMA Management Board adopted the implementing strategy in 2008, launched in 2009 and has met regularly since 2010 (Article 44).

The results of the survey of all existing uses of medicinal products in the EU paediatric population were published in December 2010[7] (Article 42) and were used as a basis for the inventory of therapeutic needs (Article 43).

In March 2011, the European Union Database on Clinical Trials (EudraCT) was modified and made publicly accessible via the public website 'clinicaltrialregister.eu', for protocol-related information on paediatric trials included in paediatric investigation plans or submitted under Article 46. Information relating to results should be available by the end of 2013. To that end, the Commission published in 2009 guidance on the information concerning paediatric clinical trials to be entered into EudraCT and on the information to be made public by the EMA[8]. In 2012 and 2013, further specifications on the posting and publication of result-related information[9] and the format of data fields followed[10] (Article 41). Subject to a confirmatory announcement from the Agency, clinical trial sponsors have to submit all results of paediatric trials to the EMA without delay, regardless of whether they were conducted inside or outside the EU, with a view to their publication in 'clinicaltrialregister.eu'[11].

Commission Regulation (EC) No 658/2007[12] was amended in 2012[13] (Article 49) to allow the Commission to impose financial penalties for infringements of the Paediatric Regulation.

With regard to labelling medicinal products with a paediatric indication with a symbol (Article 32), the Paediatric Committee advised the Commission against using one as the precise meaning of a symbol may be misunderstood by parents or carers. That is why the Commission informed stakeholders in 2008 that it is not in a position to select a symbol.

Where existing medicinal products are authorised for a new paediatric indication in accordance with the requirements of the Regulation, the marketing authorisation holder has to place the product with this new paediatric indication on the market within two years. For this purpose, in 2013 the Agency set up a register[14] of the applicable deadlines (Article 33).

The Paediatric Regulation has unfortunately not yet been incorporated in the Agreement on the European Economic Area because the EU and the three EEA-EFTA states — Iceland,

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6 Communication from the Commission — Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals, OJ C 243, 24.9.2008, p. 1.

7 http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/01/WC500101006.pdf.

8 OJ C 28, 4.2.2009, p. 1.

9 Commission Guideline — Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006, OJ C 302, 6.10.2012, p. 7.

10 http://ec.europa.eu/health/files/eudralex/vol-10/2013_01_22_tg_en.pdf.

11 https://www.clinicaltrialsregister.eu.

12 Commission Regulation (EC) No 658/2007 of 14 June 2007 concerning financial penalties for infringement of certain obligations in connection with marketing authorisations granted under Regulation (EC) No 726/2004 of the European Parliament and of the Council, OJ L 155, 15.6.2007, p. 10.

13 Commission Regulation (EU) No 488/2012 of 8 June 2012, OJ L 150, 9.6.2012, p. 68.

14 Register of deadlines to place a product on the market (EMA/137292/2013).

Liechtenstein and Norway — have been unable to agree on the appropriate terms of adaptation, especially in relation to Article 49(3) of the Regulation.

4. MAIN ACHIEVEMENTS

4.1. Better and safer research

Before the Paediatric Regulation entered into force, many pharmaceutical companies considered the adult population their key market. Research into the potential use of an adult product in the paediatric population was often side-lined or not considered at all. With the obligations introduced by the Regulation, forcing companies to screen every new (adult) product for its potential paediatric use, the situation has been turned around. Feedback from companies confirms a fundamental change of culture: undertakings now consider paediatric development to be an integral part of the overall development of a product.

The requirement to develop and discuss with the Paediatric Committee a paediatric investigation plan, which normally should be submitted not later than upon completion of the human pharmaco-kinetic studies in adults, obliges companies to think about paediatric use early on so as to avoid any delays in general product development. The plan brings with it a research and development programme which aims to ensure that the necessary data are generated for the authorisation of paediatric indications.

By the end of 2012 the Agency had agreed 600 paediatric investigation plans (see Table 1). Of these, 453 were for medicines that were not yet authorised in the EU (Article 7), while the remainder related to new indications for patent-protected products (Article 8) or paediatric-use marketing authorisations (Article 30).

These plans cover a broad range of therapeutic areas. At the forefront are Endocrinology-Gynaecology-Fertility-Metabolism (11%), Infectious diseases (11%) and Oncology (11%), but no particular area dominates (see Table 3).

In order to take account of new information during medicine development, agreed paediatric investigation plans need to be modified. Statistics show that several requests for modification are submitted for each agreed plan (see Table 2). To date, the Committee has already adopted more opinions on modifications than on the initial agreement of the investigation plan.

By end of 2012, 33 of all approved paediatric investigation plans had been completed (see Table 4), which has led to the approval of new medicines with specific paediatric indications.

4.1.1. European Union funding to support research

The EU supports research into paediatric medicinal products through its multi-annual Framework Programme for Research and Technological Development. Under Article 40 of the Regulation, the Union has a specific obligation to fund research into off-patent medicinal products. Support is granted to projects which have successfully undergone a peer review by independent experts in response to calls for proposals, announced regularly by the Commission. In order to ensure that funds are directed into researching medicinal products with the highest needs, the Paediatric Committee has adopted a priority list of off-patent active substances[15] for which studies are required.

To date, 16 projects covering at least 20 off-patent active substances have received EU funding, amounting to total support of EUR 80 million (see Annex III).

[15] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004017.pdf.

4.1.2. Scientific advice

Applicants may request scientific advice from the EMA and/or national competent authorities on pharmaceutical, non-clinical or clinical issues relating to the development of medicines. Scientific advice is a well-known and successful procedure for answering specific questions at any stage of the research and development process. Since the Paediatric Regulation entered into force, paediatric-related advice and protocol assistance from the Scientific Advice Working Party, which is provided free of charge, increased significantly (see Table 5) despite the fact that issues of pharmaceutical, non-clinical and clinical development are also part of the discussions of a paediatric investigation plan. To facilitate collaboration with the Paediatric Committee, joint procedures have been created within the EMA.

4.1.3. Clinical trials with children

Medicines for use in children need to be tested with appropriate formulations in the paediatric population to ensure their safe and effective use. Hence it is generally accepted that the Paediatric Regulation will lead to more clinical trials in children. The figures in the EudraCT database have not yet shown an increase in paediatric trials. The number remained stable between 2006 and 2012, averaging 350 trials per year with some fluctuations (see Table 6). It should be pointed out, however, that while the number of paediatric trials remained stable, the number of clinical trials in all populations decreased between 2007 and 2011.

Moreover, until recently EudraCT was limited to paediatric trials commencing in the EU. Data on paediatric trials that are part of a paediatric investigation plan and conducted outside the EU have only become publicly available since spring 2011.

It should also be noted that the initiation of a considerable percentage of clinical trials included in a paediatric investigation plan has been deferred in order to avoid delays in the authorisation of the corresponding product for adults. Hence, the impact of the Paediatric Regulation on paediatric trials will become more apparent in EudraCT in the years to come. There has, however, been an evident increase in the number of paediatric study participants, in particular for the age group from 0 to 23 months, who were normally not included in trials prior to 2008 (see Table 7). Allowing neonates and infants to benefit from research is a positive sign as these have been the most neglected groups so far.

4.1.4. Optimised framework and coordination

The Paediatric Regulation fosters a comprehensive network of expertise in paediatric matters within the EU. In this context the role of the Paediatric Committee is pivotal, as it brings together a high level of expertise and competence.

The Committee has contributed to the scientific guidelines published by the EMA and has so far convened 22 expert workshops on the development of medicines for children.

In addition, the European Network for Paediatric Research at the EMA (Enpr-EMA) was established in 2009. While a closely-knit network of experts existed prior to the introduction of the Regulation in disease areas such as paediatric oncology, Enpr-EMA provides the added value of a holistic approach by bringing together national and European networks, investigators and centres with specific expertise in designing and conducting high-quality studies in children.

However, question still remain as to whether this expertise translates into sufficient capacity within the EU to conduct trials in specialised investigation settings. Well-developed research networks capable of facilitating the necessary research to fulfil the commitments included in paediatric investigation plans do exist in some but not all Member States.

4.1.5. International cooperation

On an international level, the EMA has developed international links with medicines agencies in the United States, Canada and Japan. Of particular interest is the cooperation with the US Food and Drug Administration given that, already in the late 1990s, the United States introduced legislation that stimulated the development of medicinal products for paediatric use by means of a combination of incentives and obligations. This cooperation is also of great interest to stakeholders as it may give companies the possibility of satisfying the legislation in both regions with the same studies.

In addition, the EMA participates actively in the Paediatric medicines regulatory network[16], which was created in 2010 as part of the WHO's Better Medicines for Children initiative.

4.2. More medicines available for children

Over 12 years (from 1995 to 2006), 108 of all 317 indications of 262 centrally authorised medicines included the paediatric population. Since the Paediatric Regulation entered into force, 31 out of 152 new medicines have been authorised for paediatric use; 10 of which met the conditions of Article 7. This is not more than a 'snapshot' of the effects of the Regulation as this figure is likely to increase in the future, as a considerable number of the new, already authorised, medicines are subject to an investigation plan where completion was deferred to avoid delays in the authorisation of the adult product. It follows that in the years to come many more of those 152 new medicines are expected to be authorised for paediatric use.

Annual reports on deferred paediatric studies of authorised medicines indicate that the majority of paediatric investigation plans are running to schedule. Paediatric research is on-going at the same rate across therapeutic areas such as oncology, vaccines and immunology-rheumatology-transplantation.

Furthermore, by the end of 2011, 72 new paediatric indications had been approved for medicines already authorised, including 30 indications (18 centralised) arising from the obligation in Article 8. Moreover, 26 new pharmaceutical forms were authorised for paediatric use, including 18 adapted forms for centrally authorised medicines.

As far as Paediatric Use Marketing Authorisation is concerned, to date only one authorisation has been granted. This falls short of initial expectations.

A detailed inventory of centrally authorised products is provided in Annex II.

– Rewards and incentives

Companies that have complied with the obligations of the Regulation may benefit from a reward once the product concerned is authorised or the product information is amended. The reward takes the form of a 6-month extension of the supplementary protection certificate (SPC) provided for by Regulation (EC) No 469/2009[17] or, in the case of an orphan medicinal product, by an extension of the ten-year period of orphan market exclusivity to twelve years.

No orphan rewards have been awarded yet. In this regard it is observed that some companies withdrew the orphan designation of a product in order to qualify for the SPC reward rather than the orphan reward, which seems to be more attractive from an economic perspective. As far as SPC extensions are concerned, national patent offices in 16 Member States had, by the

[16] http://www.who.int/childmedicines/paediatric_regulators/en/.

[17] Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products, OJ L 152, 16.6.2009, p. 1. This Regulation is a codification of Council Regulation (EEC) No 1768/92.

end of 2011, granted 6-month extensions to 11 medicinal products, which resulted in a total of more than 100 national SPCs.

It should be pointed out that a ruling of the European Court of Justice further increased the value of the paediatric reward, as it made clear that the initial certificate could have a negative or zero duration, which could then become positive, once the paediatric extension was granted[18].

4.3. Increased information on medicines used in children

To provide better information on the use of medicinal products in children, Article 45 of the Paediatric Regulation requires companies holding data on the safety or efficacy of authorised products in the paediatric population to submit these studies to the competent authorities. In this way the data can be assessed and, where appropriate, the authorised product information amended. Article 46 of the Regulation also requires companies to submit newly generated paediatric data.

Since 2008, more than 18 000 study reports on roughly 2 200 medicinal products have been submitted, revealing the large amount of existing paediatric information available at company level.

These study reports have been, and continue to be, assessed by the competent authorities thanks to an impressive work-sharing project (see Tables 10 and 11). For nationally authorised products, this has led to the publication of assessment reports covering more than 140 active substances and, in a considerable number of cases, to recommendations for changes to the summaries of product characteristics of authorised products, resulting in 65 actual changes. For centrally authorised products, by 2011 the Agency had completed the assessment of all the data submitted under Article 45, covering 55 active substances in 61 centrally approved medicinal products. The summaries of product characteristics of 12 medicinal products were changed following the assessment.

5. LESSONS LEARNT

5.1. Better access to treatment

One of the explicit goals of the Paediatric Regulation is to increase the number of products that are researched, developed and authorised for use in children, and to reduce the off-label use of medicinal products in the paediatric population.

The main tool to achieve this result is to oblige companies to establish a paediatric investigation plan for each newly developed product or for the line extension of an already authorised product that is still under patent protection. The plan is meant to ensure — under the supervision of the Paediatric Committee — that the necessary data are generated so as to determine the conditions under which a medicinal product may be authorised to treat children. Since 2008, more than 600 paediatric investigation plans have been approved. However, only a minority of them has been completed to date; the vast majority are still on-going. This is due to the long development cycles of medicinal products, often lasting more than a decade and

[18] Case C-125/10 *Merck Sharp & Dohme v Deutsches Patent- und Markenamt*, not yet published in the ECR, paragraph 37: 'if the SPC application had to be refused because the calculation provided for in Article 13(1) of Regulation No 1768/92 results in a negative or zero duration, the holder of the basic patent could not obtain an extension of protection conferred by such a patent, even if it conducted all the studies according to the approved paediatric investigation plan, under Article 36 of Regulation No 1901/2006. Such a refusal would be liable to adversely impact on the useful effect of Regulation No 1901/2006 and might jeopardise the objectives of that regulation, namely the compensation of effort made to evaluate the paediatric effects of the medicinal product at issue.'.

the near-systematic deferral of paediatric studies. The high number of deferrals may not have been initially expected, but are currently a reality, as for most of the medicinal products that have been authorised so far, the R&D programme started before the entering into force of the Regulation. Consequently, the paediatric requirements could not be taken into account from the beginning of the product development.

While the Paediatric Regulation has led to some new authorisations that include paediatric indications, the regulatory instrument is recent, and it will probably take at least a decade before it can be judged in terms of its output. In terms of pharmaceutical forms, there is however already a visible positive impact.

In this context, criticism has been voiced that the Regulation will fail to ensure a breakthrough in areas of particular paediatric need, such as paediatric oncology. This argument is related to the fact that the starting point for the majority of paediatric investigation plans is an ongoing R&D programme for a medicinal product for adults. An intrinsic consequence of this approach is that these products primarily target adult conditions. They are developed in areas where there is a need (or a market) in the adult population. This need in the older population does not necessarily correspond to the paediatric population's need.

Moreover, the Regulation grants waivers from its obligations where the disease or condition for which the specific medicinal product is intended occurs only in adult populations. This legislative approach creates friction in the case of diseases that are specific and exclusive to children. It also limits the powers and possibilities of the Paediatric Committee when reviewing and agreeing to a paediatric investigation plan as regards the scope of studies that the Committee may request from applicants following the objective and scientific-based assessment of the compound concerned[19].

These constraints and boundaries have to be taken into account when judging the impact the Regulation is likely to make. In addition, the effect of instruments such as the Orphan Regulation have to be considered given that, for example, all paediatric cancers are rare diseases and fall under the EU policy framework on rare diseases.

All in all, the achievements highlighted in chapter 4 of this report and the number of products with new paediatric indications show that there are some encouraging signs after this first five-year period; it is however, too early for comprehensive answers.

5.2. The PUMA concept: a disappointment

The Paediatric Regulation introduced a new type of marketing authorisation — the Paediatric Use Marketing Authorisation (PUMA). As an incentive to carry out research into the potential paediatric use of off-patent medicinal products that have been authorised for adults, this marketing authorisation offers 8 years of data and 10 years of market exclusivity to any new off-patent product developed exclusively for use in the paediatric population. Thus, the main goal of the PUMA concept is to stimulate research in existing products. This scheme has been supported by EU funding through the EU Framework Programmes for Research and Technological Development.

However, to date only one PUMA has been granted, with a few more projects currently in the pipeline.

Neither industry nor academic networks have embraced this opportunity as fully as the Regulation intended. It would seem that the incentive of data and market exclusivity does not work for these products, or at least that the market opportunities in this sector are currently considered insufficient to outweigh the inherent economic risks of pharmaceutical

[19] Case T-52/09 *Nycomed v EMA*, not yet published.

development. Researchers are not engaging in trials with medicines that have been on the market for years. Companies seem to fear that market exclusivity will not prevent physicians from continuing to use competitor products with the same active ingredient off-label, at lower costs, or that substitution for cheaper adult forms takes place at the level of pharmacies. Moreover, national pricing and reimbursement rules in Member States often do not allow for the additional research needed to obtain the PUMA to be rewarded in price negotiations[20].

Against this background the PUMA concept has failed so far to fulfil the initial expectations.

The EMA will in future accept paediatric investigation plans for a PUMA that cover only certain age groups and not the entire paediatric population. This may offset some of the reservations that currently hamper better endorsement of the PUMA concept.

5.3. No impact on adult development

Studies prior to the adoption of the Regulation have suggested a theoretical risk that the requirements for research in children could lengthen the overall drug development process[21]. The Regulation has met this risk head-on. In order to avoid any delays in authorising medicines for other populations, it allows for the granting of deferrals relating to the initiation or completion of some or all of the measures contained in a paediatric investigation plan.

Experience shows that the deferral is a widely used instrument, which suggests that the risk of delays in the processing of adult applications is minimal. There have been some transitional problems in cases where the adult programme was already established when the Regulation entered into force, but these issues seem to have been resolved.

A concern that was raised initially was that some companies would become reluctant to develop new indications, pharmaceutical forms and new routes of administration in small markets and for products with low sales, to avoid being bound by the paediatric obligation under Article 8 of the Regulation. However, there is no evidence of such effect. Moreover, it may also be argued that the incentive of a potential six-month extension of the SPC served to counterbalance such an effect as it may have led companies to examine more thoroughly the benefits of a line extension, taking into account the economic value of the paediatric reward.

Still, industry stakeholders claim that in rare cases the development for new medicinal products has been delayed or abandoned in the expectation or as a consequence, of additional costs and requirements associated with paediatric development. Overall, there is, however, no evidence that the Regulation has a considerable negative impact on products for other populations.

Rather, there are some concerns that the requirements under the Regulation may cause delays in the authorisation of products with paediatric-only indications, as they bring added complexity to the R&D and regulatory process for products that already directly target children. The added value of the submission of a paediatric investigation plan in these cases will be assessed further in the 2017 report.

5.4. Reaping the benefits of existing information

There was widespread speculation prior to the adoption of the Paediatric Regulation as to how many studies would be submitted by pharmaceutical companies in accordance with Articles

[20] See the results of the public consultation conducted by the Commission in preparation of this Report.

[21] Cf. Commission Staff Working Document. Proposal for a Regulation of the European Parliament and of the Council on medicinal products for paediatric use and amending Council Regulation (EEC) No 1786/92, Directive 2001/83/EC and Regulation (EC) No 726/2004. Extended impact assessment (COM/2004/599/F).

45 and 46. The fact that competent authorities received more than 18 000 studies reveals the considerable amount of paediatric information that existed at company level.

Certainly, it is true that not all the information submitted met modern requirements for scientific data and clinical research, and that the work-sharing process of evaluating the information is rather long and resource intensive.

Nevertheless, compared to the PUMA concept, this scheme proved more successful in terms of output, and in recommending and implementing changes to the summary of product characteristics of authorised products. In its public consultation, the Commission called Articles 45 and 46 the 'hidden gems' of the Regulation.

One drawback that remains, however, is reluctance by marketing authorisation holders to update the summary of product characteristics on a voluntary basis. This said, the Regulation contains mechanisms to overcome such reluctance as it empowers competent authorities to directly update the summary and vary the marketing authorisation accordingly. Moreover, in accordance with Article 23 of Directive 2001/83/EC[22] and Article 16 of Regulation (EC) No 726/2004[23], marketing authorisation holders are obliged to ensure that the product information is kept up to date with the current scientific knowledge. While preference should be given to cooperative approaches, the enforcement tools may need to be used if companies do not overcome their reservations.

On the whole, the requirements of Articles 45 and 46 have provided an efficient and appropriate instrument for collecting and evaluating existing paediatric studies.

5.5. Clinical trials with children

It is generally accepted that the Paediatric Regulation will lead to more clinical trials with children, but that its aims should be achieved without subjecting children to unnecessary clinical trials.

The youngest paediatric-age subsets, including neonates, are particularly sensitive. It will be a constant challenge to balance the therapeutic needs of these age groups with their specific vulnerability when considering and deciding on the appropriateness of specific clinical trials or the specific settings of studies in this age subset. Efforts are therefore continuously being made to explore alternative means, e.g. the use of extrapolation, modelling and simulation techniques to reduce the number of study subjects as much as possible. The Paediatric Committee is actively contributing to facilitate the development and use of such means, including non-conventional trial design.

Another challenge is how to avoid duplicating trials for different paediatric investigation plans from different applicants. Companies embarking on product development in similar areas may be required by the agreed paediatric investigation plan to conduct studies within similar settings. While collaborative approaches between companies would be highly desirable, and have occurred on rare occasions, they often conflict with companies' understandable reluctance to share data with competitors in the early stages of product development and participate in direct comparisons. This situation could lead to competition among companies to find investigators and study participants as well as the duplication of trials which are unnecessary from a scientific and ethical point of view.

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[22] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, OJ L 311, 28.11.2001, p. 67.

[23] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, OJ L 136, 30.4.2004, p. 1.

The Paediatric Committee is able to waive paediatric trial requirements where the specific medicinal product does not represent a significant therapeutic benefit over an existing treatment for paediatric patients, including once the product is authorised (Article 11). However, this option does not provide a way out in the early stages of product development, where the Committee has to ensure equal treatment and non-discriminatory approaches.

The key to avoiding such unnecessary trials is transparency with regard to ongoing and completed trials. The situation continues to be monitored.

Finally, it is in the interest of the EU that paediatric trials stemming from paediatric investigation plans are conducted within the EU. This has less to do with the standards under which a trial is conducted, given that clinical trials carried out outside the EU have to meet the ethical and scientific requirements of the EU provisions on clinical trials[24], than with the fact that studies within the EU may provide patients there with early access to innovative medicines. To date, there is insufficient data on the ratio between paediatric trials conducted within and outside the EU. However, in view of the upgraded functionalities of the EudraCT database, it is expected that more data will be available in 2017 for the second report.

5.6. Spreading the news — getting new information to patients and healthcare professionals

If the Regulation is to be a success, it is not only necessary that data on the use of a specific product in the paediatric population are collected, but that these data are then also appropriately communicated to, and used by, paediatricians in their day-to-day work for the benefit of their patients.

In this regard some studies published in the medical literature suggest a failure on the part of practitioners to recognise the actual amount of off-label prescribing to children. Moreover, it is claimed that the prescribing habits of practitioners are often strongly influenced by personal experience rather than by evidence-based information for paediatric medicine[25].

These studies, in making generalisations, may not have taken into account the heterogeneity of healthcare professionals, whose receptiveness varies greatly according to their work setting and specific area of specialisation. At the same time, such observations may point to a substantial hurdle in achieving the goal of the Paediatric Regulation.

National competent authorities as well as organisations for healthcare professionals seem particularly qualified to consider appropriate ways of ensuring an adequate flow of information. Some Member States have already established a number of tools to communicate effectively and efficiently with healthcare professionals, e.g. by means of regular meetings, web-based information distribution systems or national formularies.

5.7. Is the burden greater than rewards?

There can be no doubt that the Paediatric Regulation places a considerable additional burden on pharmaceutical companies with its obligations regarding research on products for use in children. However, this approach was adopted because market forces alone proved insufficient to stimulate adequate research.

The Regulation requires companies to submit paediatric investigation plans at an early stage of product development. However, research on some active substances may be discontinued

[24] Directive 2001/20EC of the European Parliament and of the Council on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, OJ L 121, 1.5.2001, p. 34.

[25] 5-year report to the European Commission (see footnote 3), page 41.

at later stages should further studies fail to show potential with respect to the safety and efficacy of the product. For every successful authorised medicinal product there are many that fail to make the finishing line.

Hence, not all approved paediatric investigation plans will be completed, as companies may decide to stop the corresponding adult development. It is too early still to obtain reliable statistics that show the ratio between completed and non-completed paediatric investigation plans, but in the current context not all approved plans will eventually result in an approved medicine with a paediatric indication.

In terms of output, this entails some unnecessary effort in compiling and screening paediatric investigation plans. To what extent this is offset by the benefit of early submission, which ensures that the paediatric development fits smoothly into the overall product development, need further monitoring.

A further point of concern is the high number of modifications to paediatric investigation plans. Figures seem to suggest that nearly all plans have to be modified at least once. Conceptually though this does not come as a surprise, in view of the early submission of paediatric investigation plans, the length of adult and paediatric developments and the substantial deferrals granted. An R&D plan frequently has to be adapted or amended to take account of initial results. Recruitment problems or necessary design changes in the trials may also lead to modifications. While it is acknowledged that substantial amendments or modifications to the plan have to be subject to discussions with the Paediatric Committee, this is less obvious for minor changes. In this context, the level of detail required by the EMA has been repeatedly criticised. In the past five years, the EMA and its Paediatric Committee have made efforts to provide for some flexibility in the plan so to allow a margin of manoeuvre that takes account of uncertainties in relation to certain parameters of a trial.

In any case, the Commission intends to review its Communication on the format and content of applications for agreement or modification of a paediatric investigation plan to take into account the experience gained, including the considerable number of modification requests.

On a positive note, it can be noted that companies are applying for the rewards provided by the Regulation, primarily the 6-month extension of the Supplementary Protection Certificate, which have been introduced to offset the additional burden. The economic value of the reward depends on the turnover of the product concerned. In the case of blockbuster products the amount may be considerable, while for niche products the effect is small.

An in-depth evaluation of the economic impact will be included in the 2017 report in order to draw conclusions on the balance between burden and rewards, and public health benefits.

6. OUTLOOK — A FAIRY-TALE ENDING AHEAD?

‘Better Medicines for Children — From Concept to Reality’ is the title of this report. Readers may suggest that, based on the evaluation referred to above, it would be more appropriate to add a question mark. It is evident that it is too early still to make a firm statement. Despite more than five years of experience, the true impact of the Regulation on the health of children will only become apparent over time as experience is accumulated in the longer term.

There are encouraging signs though. Paediatric development has become a more integral part of the overall development of medicinal products in the EU. A number of new products with paediatric indications and age-appropriate pharmaceutical forms have been authorised and made available to patients. A high number of agreed paediatric investigation plans indicates that further products are in the pipeline.

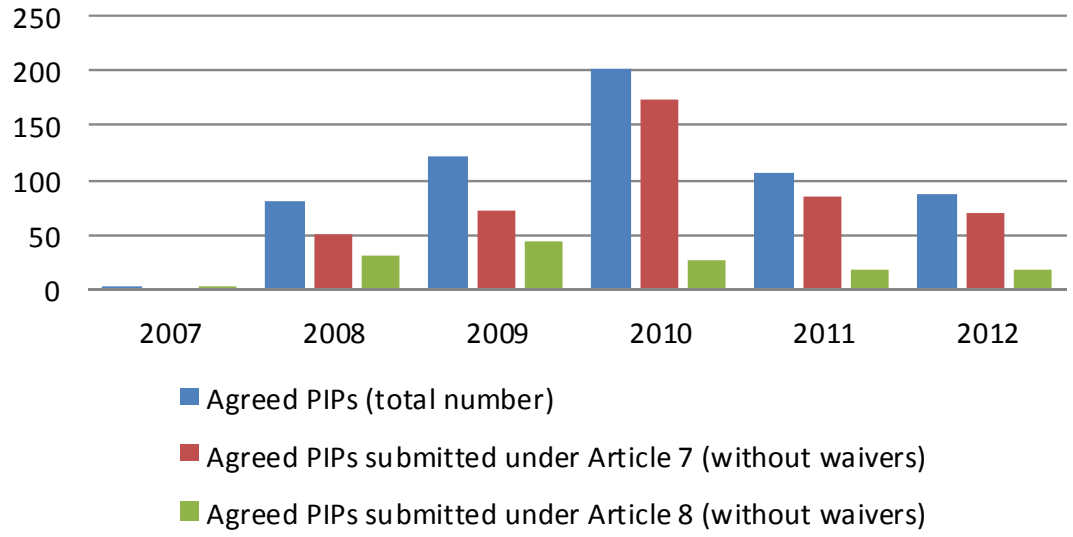
However, it needs to be pointed out that it would be wrong to expect the Regulation to be able to solve all problems. Instead, it is a major catalyst to improve the situation of young patients.

Finally, some weaknesses and deficits have also become apparent in the last five years. Their impact on the overall performance of the Regulation has to be closely monitored. On the basis of the actions outlined above, the Commission intends to fine-tune the current implementation together with the EMA.

Even if better medicines for children are not yet a reality, it should be the ambition of all stakeholders involved that this piece of legislation will be for the greater good of children, so that in the 2017 report, the discussion will focus not on whether a question mark should be added to the title of the report, but on whether it should be an exclamation mark instead!

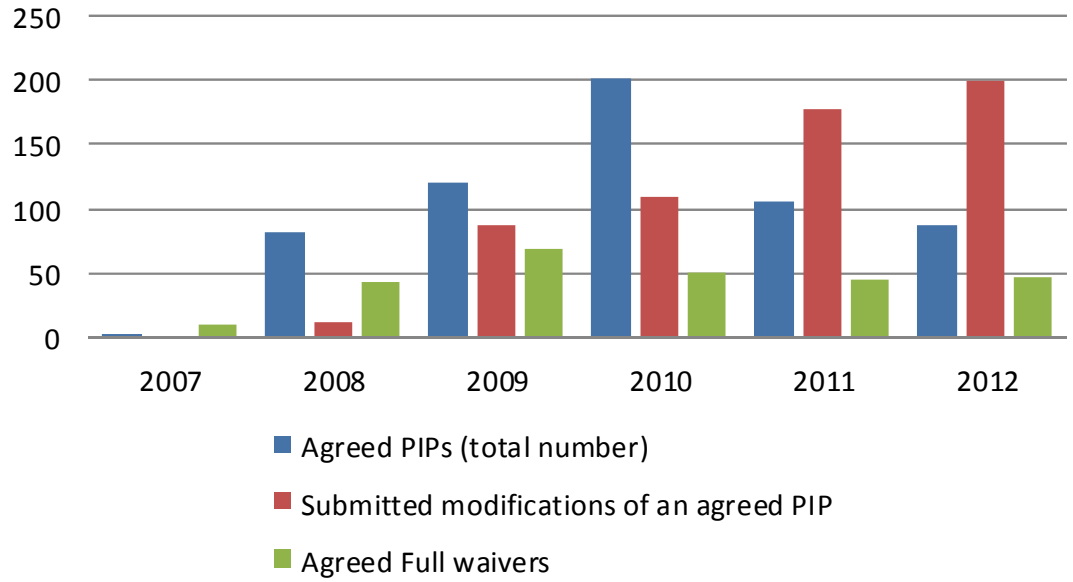
ANNEX I — Figures and Tables

Table 1: Agreed paediatric investigations plans (PIPs) 2007-2012



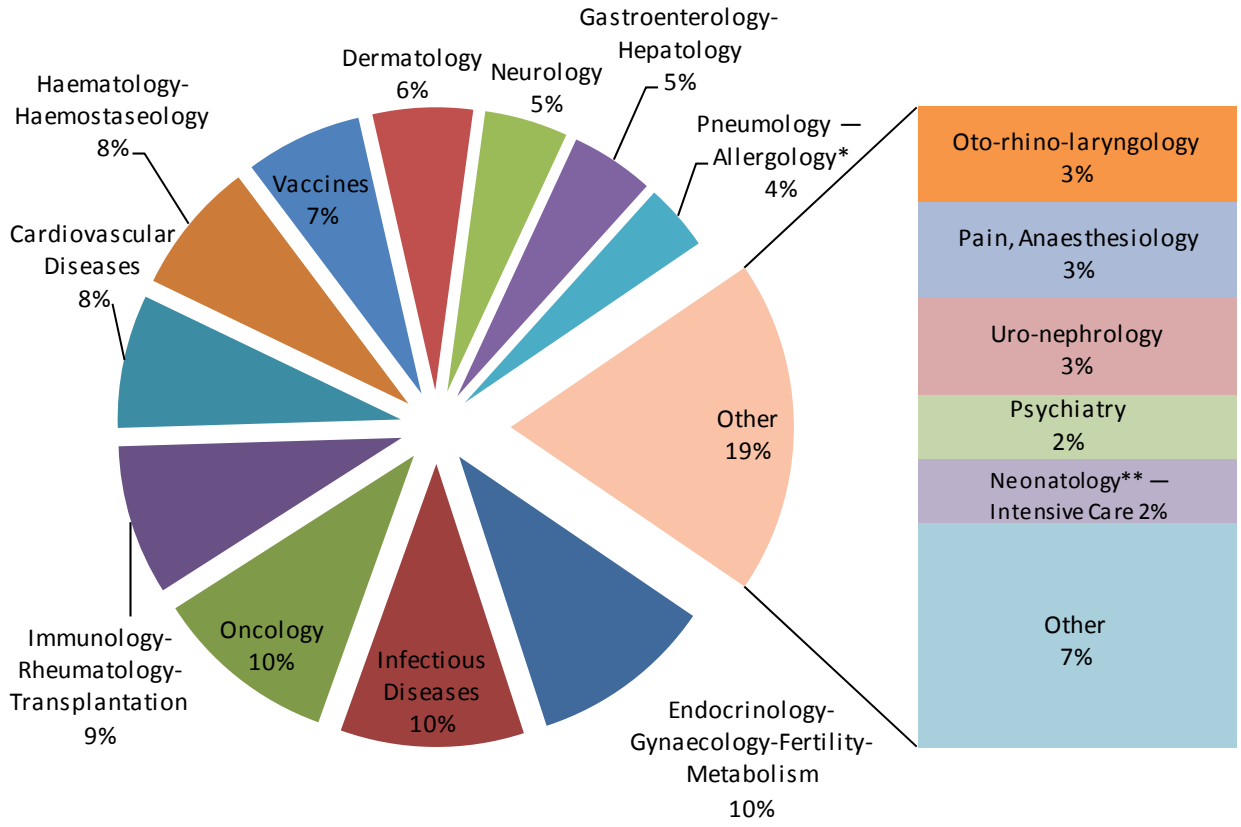
Source: EMA Paediatric database. The numbers on agreed PIPs correspond to EMA decisions.

Table 2: Agreed paediatric investigations plans (PIPs) compared to full waivers and modifications 2007-2012



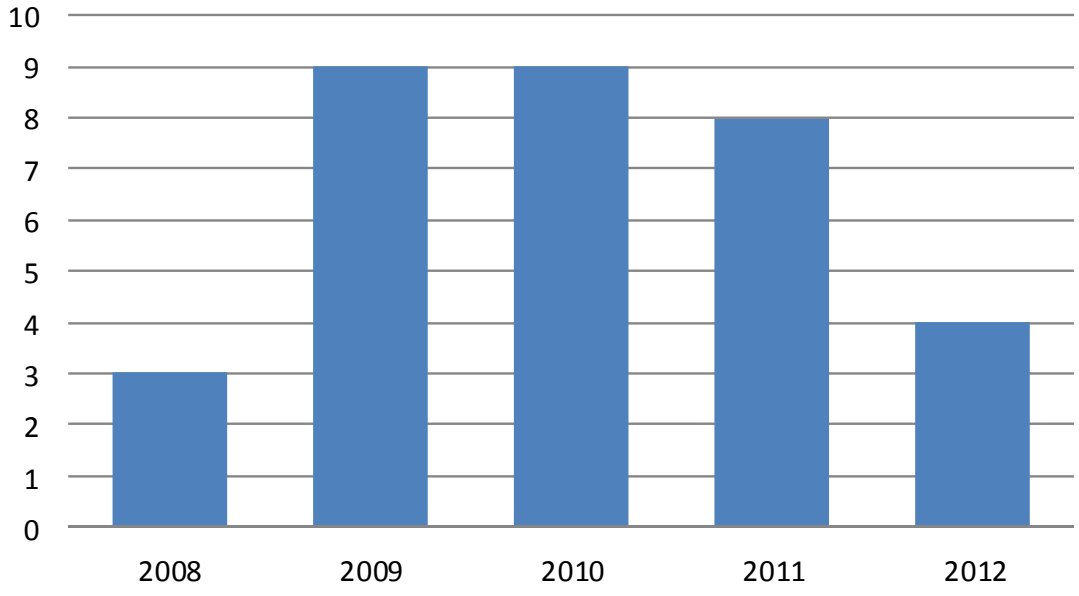
Source: EMA Paediatric database. The numbers on agreed PIPs and waivers correspond to EMA decisions.

Table 3: Therapeutic areas addressed by the paediatric investigation plans (2007-2011)



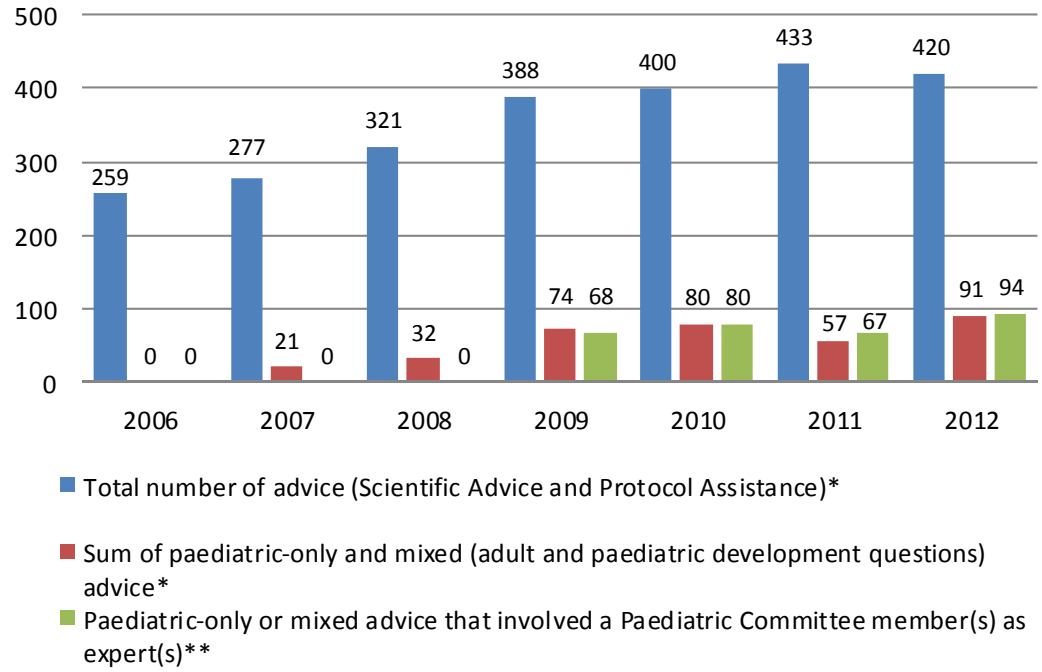
Source: EMA Paediatric database. * Excluding allergen products. ** Applications that exclusively address a use in neonates.

Table 4: Number of compliance opinions adopted by the Paediatric Committee per year



Source: EMA Paediatric database.

Table 5: Scientific advice and protocol assistance, including follow-ups (provided by the EMA Scientific Advice Working Party and the Committee for Human Medicinal Products, per year)



Source: EMA databases. * Year of advice letter. ** Year of start of procedure.

Table 6: Paediatric clinical trials by year of authorisation

	2005	2006	2007	2008	2009	2010	2011	2012
Paediatric trials (number)	254	316	355	342	404	379	334	332
Paediatric trials that are part of an agreed PIP*	2	1	2	6	16	30	76	76
Proportion of paediatric trials that are part of an agreed PIP among paediatric trials*	1 %	0 %	1 %	2 %	4 %	8 %	23 %	23 %
Total number of trials (adults and / or children)	3 350	3 979	4 749	4 512	4 445	4 026	3 809	3 698
Proportion of paediatric trials of all trials	8 %	8 %	7 %	8 %	9 %	10 %	9 %	9 %

Source: EudraCT Data Warehouse using a predefined query on 6 March 2013 and counting the first authorised trial only, in the case of more than one Member State.

* This partial information requires sponsors to use a Clinical Trial Application form that was only available from November 2009, for use with version 8 of EudraCT (available from 2011).

Table 7: Number of children to be enrolled in clinical trials

Number of subjects	2006	2007	2008	2009	2010	2011	2012
Preterm newborns	0	0	0	207	82	2 281	1 712
Newborns	0	0	5	64	169	1 105	1 172
Infants and toddlers	330	21	20	59	351	2 788	3 141
Children	2 142	181	200	2 230	2 055	10 325	20 677
Adolescents	368	111	205	1 577	2 861	9 054	13 193
Sum of above	**2 840**	**313**	**430**	**4 137**	**5 517**	**25 553**	**39 895**
Reference: number of paediatric trials	316	355	342	404	379	334	332

Source: EudraCT Data Warehouse using a pre-defined query on 6 March 2013, modified by excluding studies for 'immunological medicinal products'

Table 8: EU budget contribution to the Paediatric Regulation and the EMA expenditure

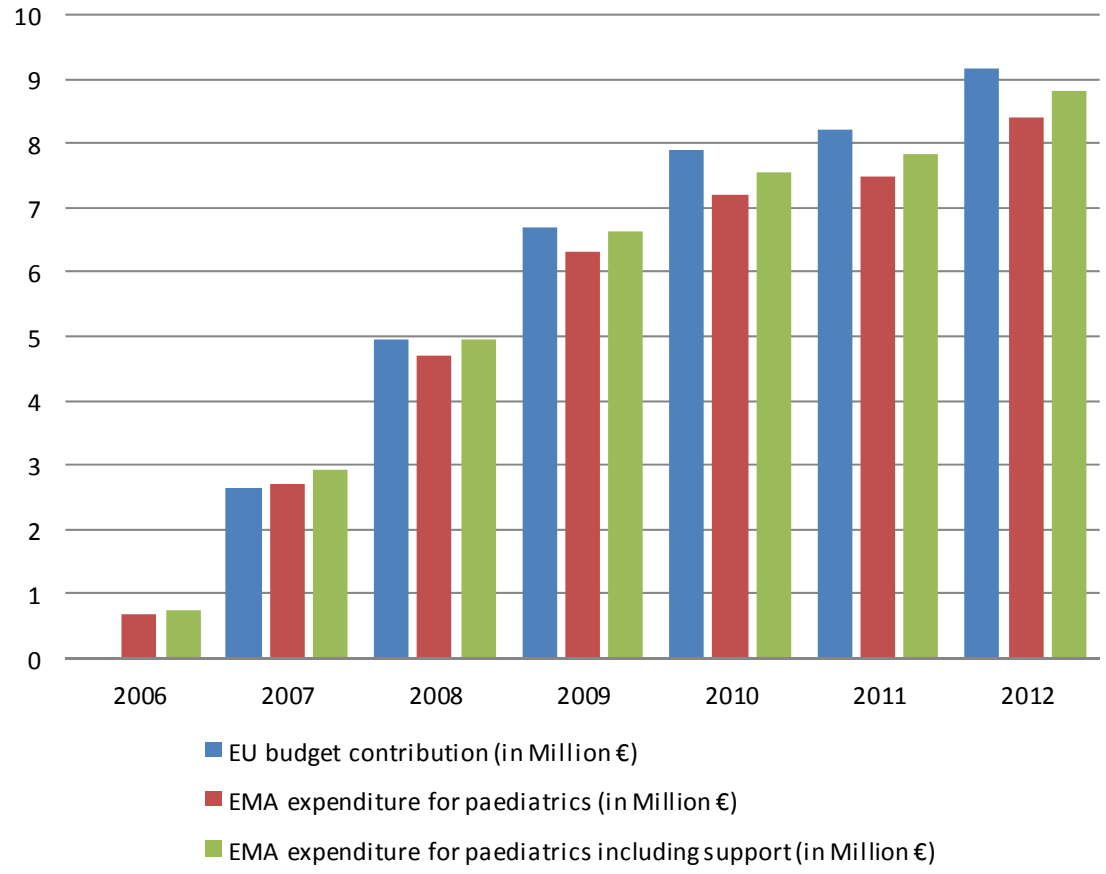


Table 9: Percentage of European Medicines Agency's human resources working in the paediatric area from 2006 (inner circle) to 2012 (outer circle)

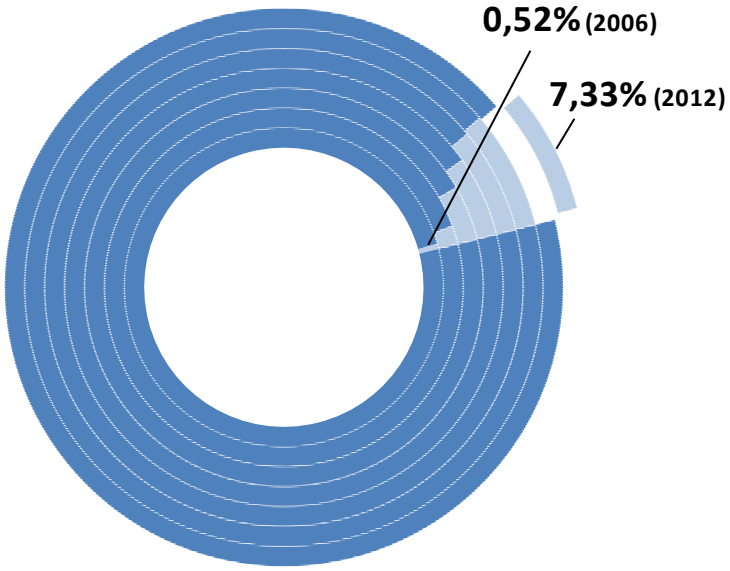


Table 10: Member States acting as rapporteurs for the assessment of studies submitted in accordance with Article 46 (paediatric work-sharing procedures)

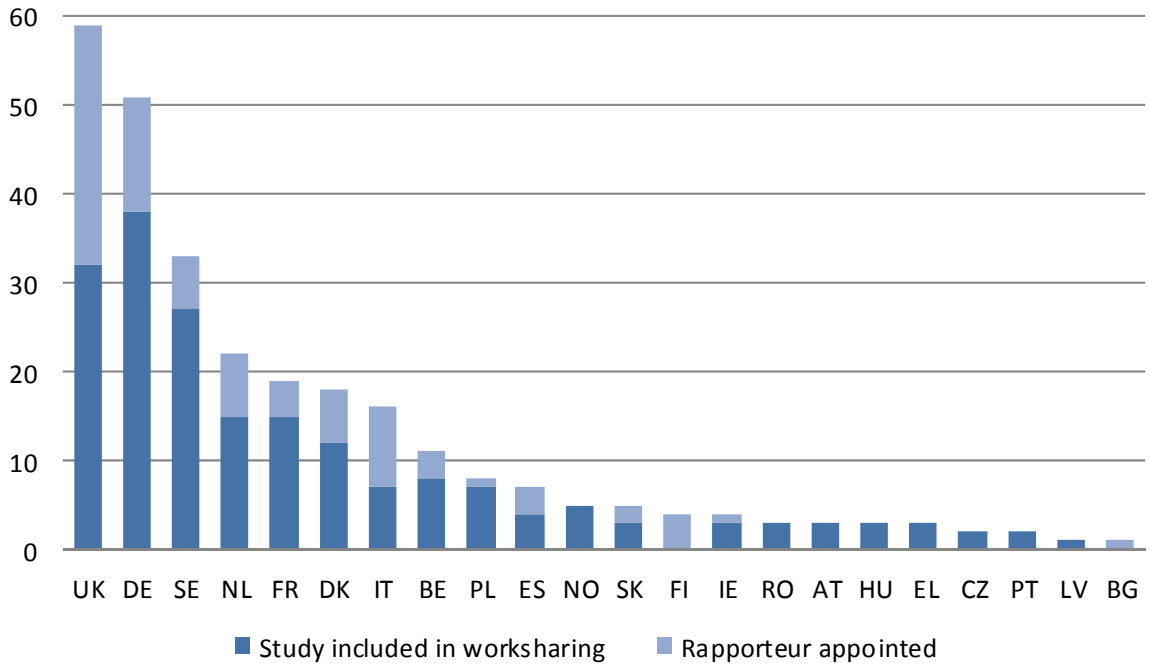


Table 11: Member States acting as rapporteur for the assessment of studies submitted in accordance with Article 45 (paediatric work-sharing procedures)

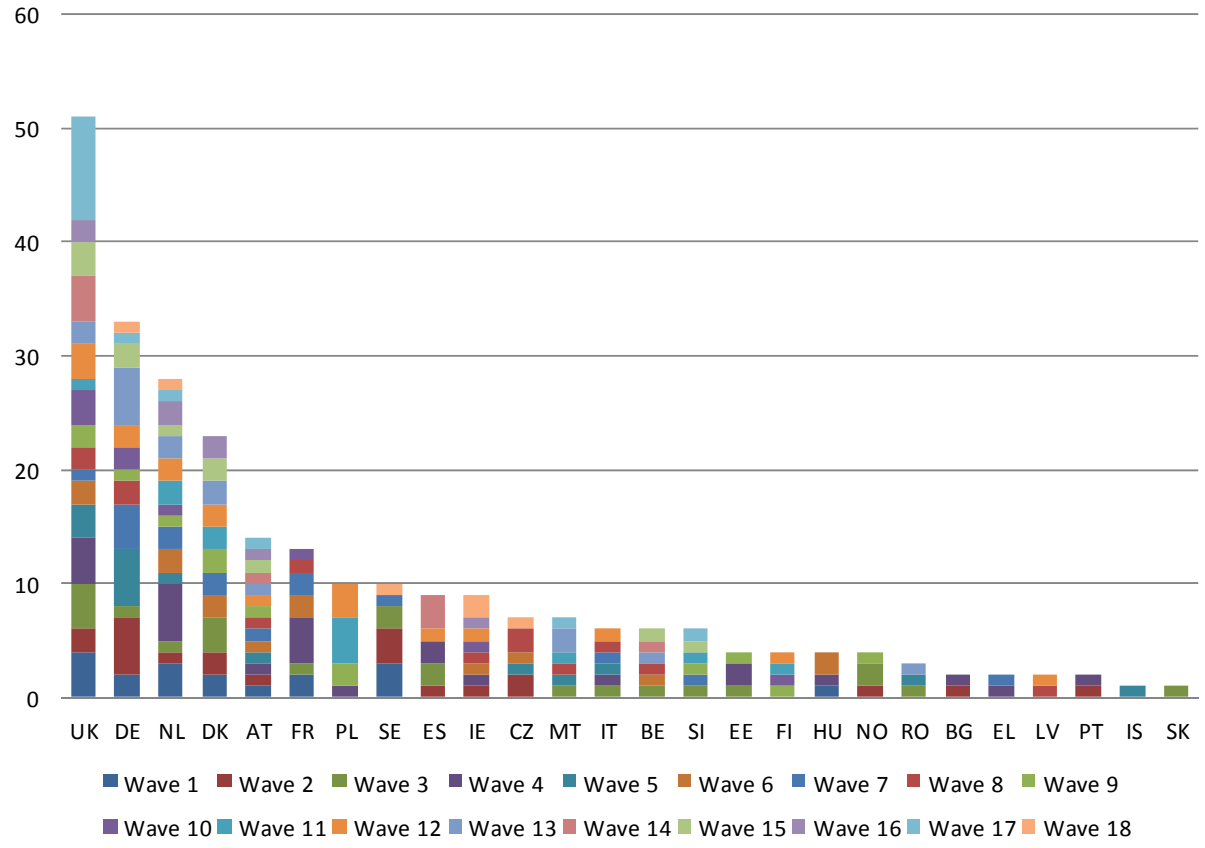
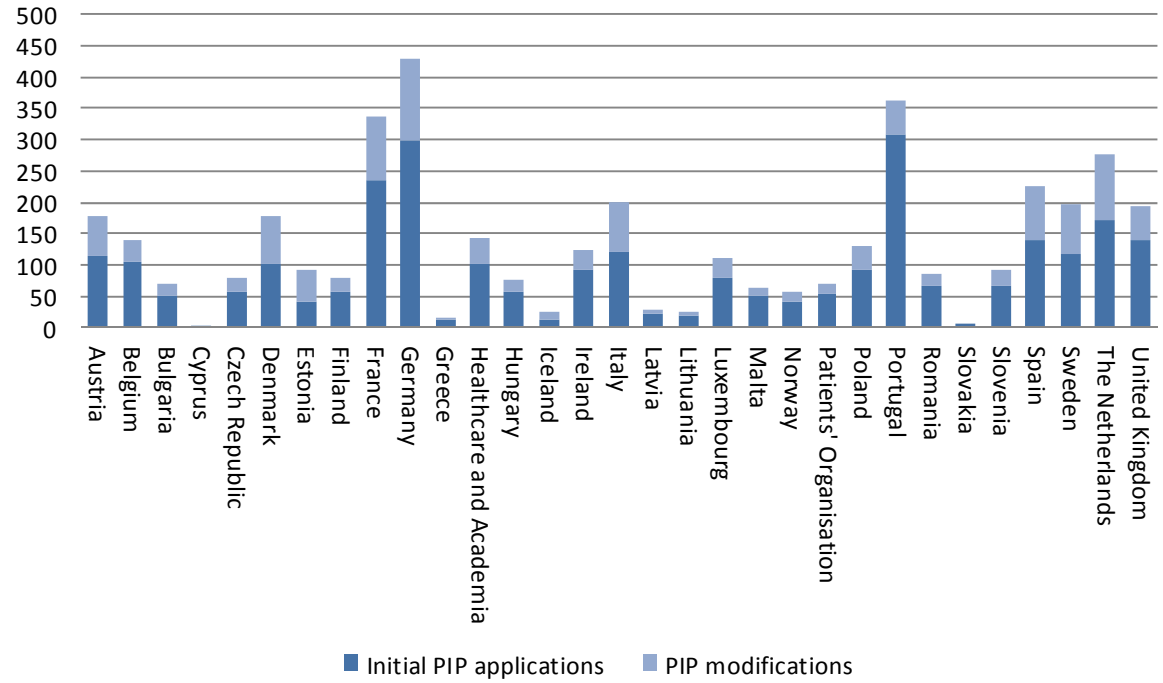


Table 12: Member States acting as rapporteurs/peer reviewers in EMA's Paediatric Committee procedures (initial PIP/waiver or modification of an agreed PIP)



ANNEX II — Detailed inventory of centrally authorised medicinal products for paediatric use since the entry into force of the Paediatric Regulation

Table 13: Medicinal products authorised centrally since 2007, which include a paediatric indication

Active substance(s)	Trade name	Year of authorisation	Requirement to fulfil Paediatric Regulation at first authorisation?	Indication is paediatric-only or 'mixed' (adult and paediatric)?
Retapamulin	Altargo	2007	No	Mixed
Nelarabine	Atriance	2007	No	Mixed
Human papillomavirus vaccine [types 16, 18]	Cervarix	2007	No	Mixed
Hydroxocobalamin	Cyanokit	2007	No	Mixed
Idursulfase	Elaprase	2007	No	Mixed
Gadoversetamide	Optimark	2007	No	Mixed
Betaine anhydrous	Cystadane	2007	No	Mixed
Stiripentol	Diacomit	2007	No	Paediatric only
Mecasermin	Increlex	2007	No	Paediatric only
Rufinamide	Inovelon	2007	No	Mixed
Hydroxycarbamide	Siklos	2007	No	Mixed
Human normal immunoglobulin (ivig)	Flebogamma DIF	2007	No	Mixed
Fluticasone furoate	Avamys	2008	No	Mixed
Human normal immunoglobulin	Privigen	2008	No	Mixed
Lacosamide	Vimpat	2008	No	Mixed
Micafungin	Mycamine	2008	No	Mixed
Sapropterin	Kuvan	2008	No	Mixed
Sugammadex	Bridion	2008	No	Mixed
Tocofersonal d-alpha tocopheryl polyethylene glycol succinate	Vedrop	2009	No	Paediatric only
Mifamurtide	Mepact	2009	No	Mixed
Rilonacept	Rilonacept Regeneron	2009	No	Mixed
Tacrolimus	Modigraf	2009	No	Mixed
Pneumoccocal polysaccharide conjugate vaccine (adsorbed)	Synflorix	2009	No	Paediatric only
Canakinumab	Ilaris (PIP not yet completed)	2009	Yes	Mixed
Pneumoccocal polysaccharide conjugate vaccine (13-valent, adsorbed)	Prevenar 13 (PIP not yet completed)	2009	Yes	Paediatric only
Meningococcal group a, c, w135 and y conjugate vaccine	Menveo	2010	Yes	Mixed
Velaglucerase alfa	Vpriv (PIP not yet completed)	2010	Yes	Mixed
Influenza vaccine (live attenuated, nasal)	Fluenz (Waiver)	2011	Yes	Paediatric only
C1 inhibitor, human	Cinryze (PIP not yet completed)	2011	Yes	Mixed
Dihydroartemisinin / piperaquine phosphate	Eurartesim (PIP not yet completed)	2011	Yes	Mixed

Active substance(s)	Trade name	Year of authorisation	Requirement to fulfil Paediatric Regulation at first authorisation?	Indication is paediatric-only or 'mixed' (adult and paediatric)?
Midazolam	Buccolam	2011	Yes (PUMA)	Paediatric only
Everolimus	Votubia (PIP not yet completed)	2011	Yes	Mixed
Tobramycin	Tobi Podhaler (PIP not yet completed)	2011	Yes	Mixed
Nomegestrol / estradiol	Ioa, Zoely	2011	Yes	Mixed
Colistimethate sodium	Colobreathe	2012	Yes	Mixed
Mercaptopurine	Xaluprine	2012	No	Mixed
Catridecacog	NovoThirteen	2012	Yes	Mixed
Efavirenz	Efavirenz Teva	2012	No	Mixed
Ivacaftor	Kalydeco	2012	Yes	Mixed
Desloratadine	Desloratadine ratiopharm	2012	No	Mixed
Desloratadine	Desloratadine Actavis	2012	No	Mixed
Perampanel	Fycompa	2012	Yes	Mixed

Table 14: List of centrally authorised medicinal products for which the therapeutic indication was extended to or amended for the paediatric population

Active substance(s)	Trade name	Date	Subject of the extension
Levetiracetam	Keppra	2007/ 2009	Extension of the indication to include adjunctive therapy in the treatment of primary generalised tonic-clonic (PGTC) seizures in adults and adolescents from 12 years of age with idiopathic generalised epilepsy; Extension of indication to include the adjunctive treatment of partial seizures with or without secondary generalisation in children from 1 month to <4 years old
Pneumococcal saccharide conjugated vaccine, adsorbed	Prevenar	2007	Extension of the indication to include new information on efficacy against disease caused by Streptococcus pneumoniae serotypes 4, 6B, 9V, 14, 18C, 19F and 23F in otitis media; Extension of indication from active immunisation against bacteraemic pneumonia to active immunisation against pneumonia
Infliximab	Remicade	2007	Extension of indication to include treatment of severe active Crohn's disease in children aged 6 to 17 years
Darbepoetin alfa	Aranesp	2007	Extension of indication for CRF patients, which restricted the use of Nespo to paediatric subjects ≥ 11 years of age
Fosamprenavir	Telzir	2007	Extension of indication of Telzir in combination with ritonavir for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults in combination with other antiretroviral medicinal products to include paediatric populations
Lamivudine / zidovudine	Combivir	2007	Extension of indication to include paediatric patients and replacement of film-coated tablets by scored film-coated tablets
Desloratadine	Aerius	2007	Extension of indication from 'chronic idiopathic urticaria' to 'urticaria'

Active substance(s)	Trade name	Date	Subject of the extension
Insulin glulisine	Apidra	2007	Extension of indication to include 6 year olds and older children based on the results of 2 paediatric studies
Human papilloma virus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)	Gardasil	2008	Extension of indication to include the prevention of high-grade vaginal dysplastic lesions (VaIN 2/3)
Adalimumab	Humira	2008/ 2011	Extension of indication to include treatment of active polyarticular juvenile idiopathic arthritis in adolescents from 13 to 17 years of age; Extension of indication to include treatment of active polyarticular juvenile idiopathic arthritis in the paediatric population aged from 4 to 12 years.
Caspofungin	Cancidas	2008	Extension of the indication to include the paediatric population
Etanercept	Enbrel	2008/ 2011	Extension of indication to include the treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies; Extension of indication to include lower age range for polyarticular juvenile idiopathic arthritis 'from the age of 4 years' to 'from the age of 2 years'
Miglustat	Zavesca	2009	Extension of indication to include the treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type-C disease
Tacrolimus	Protopic	2009	Extension of indication to 'maintenance treatment' further to completion of one study in adult patients and one in paediatric patients
Tipranavir	Aptivus	2009	Extension of indication to include the treatment of HIV-1 infection in highly pre-treated adolescents 12 years of age or older with virus resistant to multiple protease inhibitors
Omalizumab	Xolair	2009	Extension of indication to children from 6 to <12 years of age as add-on therapy to improve allergic asthma control
Aripiprazole	Abilify	2009	Extension of indication to include treatment of schizophrenia in adolescents 15 years and older
Peginterferon alfa-2b	PegIntron	2009	Extension of indication of the combination therapy peginterferon alfa-2b and ribavirin to include treatment of the paediatric population
Ribavirin	Rebetol	2009	Extension of indication of the combination therapy peginterferon alfa-2b and ribavirin to include treatment of the paediatric population
Abatacept	Orencia	2010	Extension of indication to include the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis in paediatric patients 6 years of age and older who have had an insufficient response to other DMARDs including at least one TNF inhibitor
Atazanavir sulphate	Reyataz	2010	Extension of indication for Reyataz capsules to include the treatment of HIV-infected children and adolescents above the age of 6 in combination with other antiretroviral medicinal products
Measles, mumps and rubella vaccine (live)	M-M-RVAXPRO	2010	Extension of indication to include administration to healthy children from 9 months of age
Nitric oxide	Inomax	2011	Extension of indication to include the treatment of pulmonary hypertension peri- and post heart surgery in children

Active substance(s)	Trade name	Date	Subject of the extension
Tenofovir disoproxil fumarate	Viread	2011	Amendment of indication based on the results of a safety and efficacy study in treatment-experienced adolescents aged 12 to 18 years old
Paliperidone	Invega	2011	Extension of indication to include treatment of psychotic or manic symptoms of schizoaffective disorder
Sildenafil	Revatio	2011	Extension of indication in paediatric patients aged 1 year to 17 years old with pulmonary arterial hypertension
Human normal immunoglobulin (ivig)	Kiovig	2011	Extension of indication to include treatment of multifocal motor neuropathy and hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation in adults and children
Tocilizumab	Roactemra	2011	Extension of indication to include treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids
Pneumococcal polysaccharide conjugate vaccine (adsorbed)	Synflorix	2011	Extension of indication to increase the upper age limit of infants and children from 2 years to 5 years
Insulin detemir	Levemir	2011	Extension of indication as add-on therapy to liraglutide treatment; Extension of indication to children aged 2-5 years
Eculizumab	Soliris	2011	Extension of indication to include atypical haemolytic uremic syndrome (aHUS). Additional vaccination and antibiotic prophylaxis recommendation have also been added in section 4.2 for treatment of aHUS in adults and children
Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed)	Cervarix	2011	Extension of indication to children from 9 years
Etanercept	Enbrel	2012	Extension of the Juvenile idiopathic arthritis (JIA) indication to include children and adolescents with extended oligoarticular JIA from the age of 2 years, children and adolescents with enthesitis-related arthritis from the age of 12 years, and children and adolescents with psoriatic arthritis from the age of 12 years
Measles, mumps, rubella and varicella vaccine (live)	Proquad	2012	Extension of the age range in the indication to children from 9 months of age onwards under special circumstances, i.e. outbreak control

For a more detailed inventory, including information on nationally authorised products and new routes of administration or new pharmaceutical forms, please refer to Annex II of the '5-year Report to the European Commission' of the EMA.

ANNEX III — List of funded projects

List of projects on off-patent medicines funded by the European Commission through the EU Framework Programme Health: area 4.2 results, off-patent medicines calls 2, 3, 4 and 5.

- HEALTH.2007-4.2-1 Adapting off-patent medicines to the specific needs of paediatric populations.
- HEALTH.2009-4.2-1 Adapting off-patent medicines to the specific needs of paediatric populations.
- HEALTH.2010.4.2-1 Off-Patent Medicines for Children. FP7-HEALTH-2010-single-stage.
- HEALTH.2010.4.2-2 International paediatric initiative. Network of Excellence.
- HEALTH.2011.4.2-1 Investigator-driven clinical trials on off-patent medicines for children.

Table 15: Funded off-patent medicines projects (beginning up to 1 January 2012) and agreed PIPs, if available.

No.	Acronym	Year start	Objectives	Agreed PIP
1	KIEKIDS	2011	To develop an innovative, age-adapted, flexible and safe paediatric formulation of **ethosuximide** for the treatment of absence and of myoclonic epilepsies in children	NA
2	NEO-CIRC	2011	To provide safety and efficacy data for **dobutamine**, to perform pre-clinical studies, to develop biomarker(s) of hypotension and to adapt a formulation for newborns	EMEA-001262-PIP01-12
3	TAIN	2011	To develop a neonatal formulation of **hydrocortisone** for the treatment of congenital and acquired adrenal insufficiency and for use in oncology (brain tumours and leukaemia)	EMEA-001283-PIP01-12
4	GRIP	2011	To implement an infrastructure matrix to stimulate and facilitate the development and safe use of medicine in children	NA
5	DEEP	2011	To evaluate Pharmacokinetics (PK) & Pharmacodynamics (PD) of **deferiprone** in in 2-10 years old children in order to produce an approved paediatric investigation plan to be used for regulatory purposes	EMEA-001126-PIP01-10
6	TINN2	2011	To evaluate PK & PD of **azithromycin** against urea plasma and in BPD in neonates	EMEA-001298-PIP01-12
7	HIP Trial	2010	To evaluate the efficacy safety, PK, PD of **adrenaline** and **dopamine** in the management of neonatal hypotension in premature babies and to develop and adapt a formulation of both suitable for newborns in order to apply for a Paediatric Use Marketing Authorisation	NA / EMEA-001105-PIP01-10
8	PERS	2010	Focuses on two indications, the use of **risperidone** in children and adolescents with conduct disorder who are not mentally retarded, and the use of risperidone in adolescents with schizophrenia	EMEA-001034-PIP01-10

No.	Acronym	Year start	Objectives	Agreed PIP
9	NeoMero	2010	European multicentre network to evaluate pharmacokinetics, safety and efficacy of **meropenem** in neonatal sepsis and meningitis	EMEA-000898-PIP01-10
10	NEMO	2009	To evaluate the efficacy safety, PK, PD, mechanisms of action of **bumetanide** in neonatal seizures, including the effect on neurodevelopment and to develop and adapt a bumetanide formulation suitable for newborns in order to apply for a Paediatric Use Marketing Authorisation	NA
11	NEUROSIS	2009	Efficacy of **budesonide** in reducing bronchopulmonary dysplasia	EMEA-001120-PIP01-10
12	EPOC	2009	To evaluate pharmacokinetics and pharmacodynamics of **doxorubicin**	NA
13	LOULLA & PHILLA	2008	Development of oral liquid formulations of **methotrexate** and 6-**mercaptopurine** for paediatric acute lymphoblastic leukaemia	NA / NA
14	NeoOpioid	2008	To compare **morphine** and **fentanyl** in pain relief in pre-term infants	EMEA-000712-PIP01-09
15	O3K	2008	Oral liquid formulations of **cyclophosphamide** and **temozolomide**	EMEA-000530-PIP02-11 / NA
16	TINN	2008	Aims to evaluate PK & PD of **ciprofloxacin** and **fluconazole** in neonates	NA

NA = not available or not applicable

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

Table 16: Investigator-driven clinical trials of off-patent antibiotics

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

NA = not available