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10-year Report to the European Commission

General report on the experience acquired as a result of the application of the Paediatric Regulation¹

Prepared by the European Medicines Agency and its Paediatric Committee

Note: The report covers in principle the period from January 2007 to December 2015. This version of the report is an update to the one provided to the European Commission in 2016. The scope of the update was to include data from 2016 into key analyses such as the number of paediatric medicine authorisations and paediatric clinical trials; the reporting periods are indicated in the respective analyses.

¹ [Paediatric Regulation](#) (EC) No 1901/2006 of the European Parliament and of the Council on Medicinal Products for Paediatric Use



Table of Contents

Table of Contents	2
Summary	4
More medicines for children	4
Better information on the use of medicines in children	5
More ethical and high quality paediatric research	6
Observations and challenges	8
Conclusion	9
Sources and coverage	9
Data sources	9
Reporting period	9
1. New medicines for children	10
1.1. New medicines, new indications and new pharmaceutical forms	10
1.2. Effect of the Paediatric Regulation on the authorisation of medicines for children	12
1.3. Examples of achievements through the Paediatric Regulation	14
1.4. Article 29 procedures	14
1.5. Paediatric Use Marketing Authorisation (PUMA)	15
1.6. Statements of compliance in marketing authorisations	16
1.7. Comparison of EU with other regions	17
2. Information on medicines for children	18
2.1. Articles 45 and 46	18
2.2. Changes to product information	19
3. Paediatric research and development	21
3.1. Paediatric investigation plans	21
3.2. Modifications of agreed PIPs	23
3.3. Age-appropriate forms and formulations	32
3.4. Addressing needs of neonates	34
3.5. Scientific advice on paediatric development	37
3.6. Paediatric research incentives	38
3.7. Paediatric clinical trials	39
3.8. Inclusion of paediatric age groups in agreed PIP studies	44
3.9. Interactions with ethics committees	48
3.10. Extrapolation, modelling and simulation in PIPs	50
3.11. Innovation in PIPs	52
3.12. Animal studies for safer paediatric research	53
3.13. Medicines for children with cancer	57
3.14. Class waiver revisions	62
3.15. European Network for Paediatric Research at the EMA (Enpr-EMA)	63
3.16. External experts, workshops and scientific guidelines	65
3.17. PIPs for orphan medicines	67
3.18. Timely planning and conduct of paediatric development	68
4. Other initiatives	71
4.1. Participation of children and young people in PDCO activities	71

4.2. International activities	72
4.3. Paediatric Pharmacovigilance	73
4.4. Meetings with stakeholders/applicants	76
4.5. Streamlining the handling of applications	77
4.6. Publications relating to the Paediatric Regulation	78
4.7. Training courses on the Paediatric Regulation	79
5. Involvement of Member States and EMA	81
5.1. NCA resources	81
5.2. EMA resources	82
6. Lessons learned.....	83
6.1. Balance of obligations and rewards.....	84
6.2. Availability of paediatric medicines	86
6.3. Research in neglected areas and populations	86
6.4. Role of EnprEMA.....	87
6.5. Research into off-patent products for children	88
6.6. Scope of PIPs and waivers	88
6.7. PIPs and their life-cycle.....	89
6.8. Paediatric expertise and committees.....	89
6.9. Funding of paediatric regulatory activities.....	90
6.10. Appropriate use of authorised medicinal products	90
7. References	91
8. Glossary/Abbreviations	95

Summary

Article 50 (3) of Regulation (EC) No 1901/2006 on medicinal products for paediatric use ([Paediatric Regulation](#)) stipulates that *by 26 January 2017, the Commission shall present a report to the European Parliament and the Council on the experience acquired as a result of the application of Articles 36, 37 and 38. The report shall include an analysis of the economic impact of the rewards and incentives, together with an analysis of the estimated consequences for public health of this Regulation, with a view to proposing any necessary amendments.*

This report aims to measure the impact of the [Paediatric Regulation](#) on achieving its objectives to facilitate the development and accessibility of medicines for use in children, to ensure that medicines used to treat them are subject to ethical research of high quality and are appropriately authorised, and to improve the information available. It will complement the economic impact report by the Commission.

The Paediatric Regulation has had a very positive impact on paediatric drug development, as shown by the data collected over the first ten years since its inception. It has led to:

- more medicines for children as well as better and more information for prescribers and patients;
- better paediatric research and development;
- more regulatory support for paediatric matters and
- paediatrics now being an integral part of medicine development.

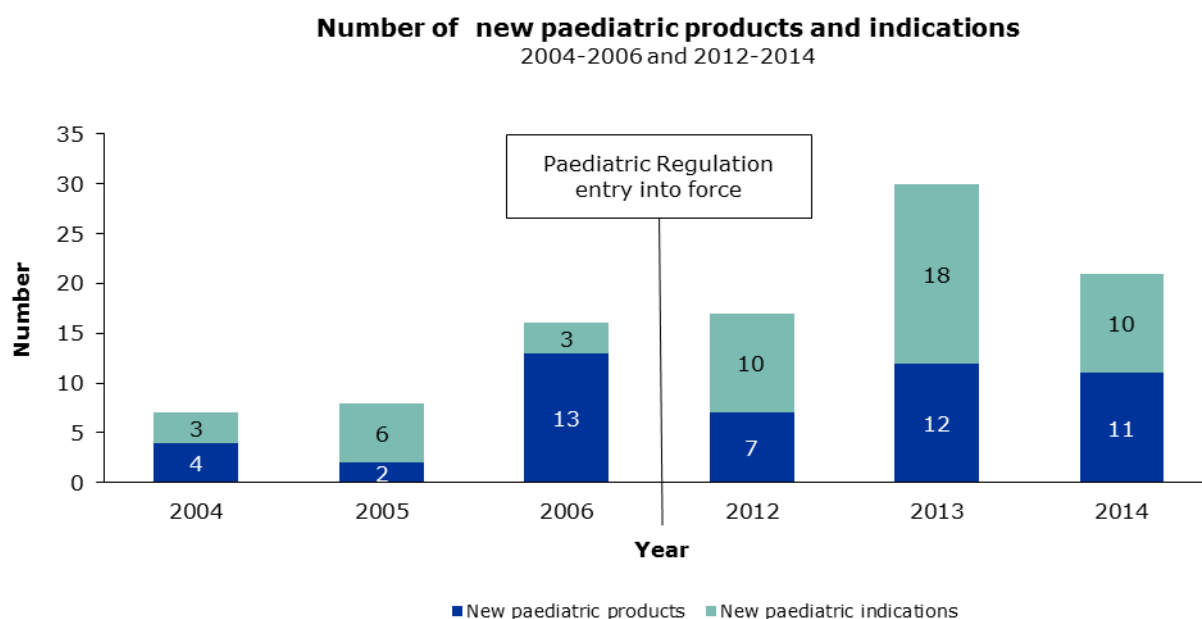
More medicines for children

Lack of authorised medicines and consequent off-label use is a significant problem in the paediatric population due to the difficulty in conducting clinical trials, the relatively low patient numbers and the generally smaller size of the market. In neonates, the situation is particularly challenging due to the vulnerability of newborns and even lower patient numbers.

However, since the implementation of the Regulation, from 2007 until 2016, 267 new medicines for use in children and 43 new pharmaceutical forms appropriate for children were authorised in the EU.

The increasing numbers of medicines becoming available to children are illustrated by an analysis of the medicines authorised via the centralised procedure (CAPs) for the three years immediately before the Paediatric Regulation entered into force compared with the three most recent years at the time of the analysis. The latter reference period was selected in order to demonstrate a potential impact of the Regulation, which was not expected to be seen immediately after entry into force of the Regulation as medicine development is a lengthy process. The number of new medicines/indications receiving authorisation for use in children more than doubled over the second reference period: 68 compared with 31 (Figure 1.)

Figure 1. Number of centrally authorised medicines for children in 2004-2006 and 2012-2014 (new initial marketing authorisations, new paediatric indications)



Source: EMA databases (SIAMED, DREAM).

Better information on the use of medicines in children

In addition to supporting new indications and products, data on the use of medicines in children (e.g. safety information, warnings, contraindications) is also valuable as it improves the product information. Evidence from the reference periods above indicates significant improvement of availability of such information, such as the addition of new study results and new recommendations into the product information. The number of changes relating to paediatric use increased from 68 to 180 in the second reference period.

A large number of paediatric studies for already authorised medicinal products had been completed before 2007, but never submitted to a regulatory agency (around 19,000 reports on completed paediatric studies, in about 1,000 active substances). These were provided by pharmaceutical companies to the EMA (for centrally authorised medicines) and to the national competent authorities (with assessment co-ordinated by CMDh²) for nationally authorised products, as mandated by Article 45 of the Paediatric Regulation. By the end of 2015, 62 Article 45 assessments of centrally authorised medicines and 2219 for nationally authorised medicines were completed, which resulted in approximately 140 updates of the product information and 16 new paediatric indications including in areas where no paediatric medicines were approved. This represents a significant outcome based on data that would have not otherwise been utilised.

Moreover, information on ongoing and completed paediatric medicine developments has become public knowledge through publication of EMA decisions on paediatric investigation plans (PIP³) and information on paediatric clinical trials. This provides guidance for new drug developments and assists in prevention of duplications.

² The Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) is a medicines regulatory body representing the EU Member States, Iceland, Liechtenstein and Norway

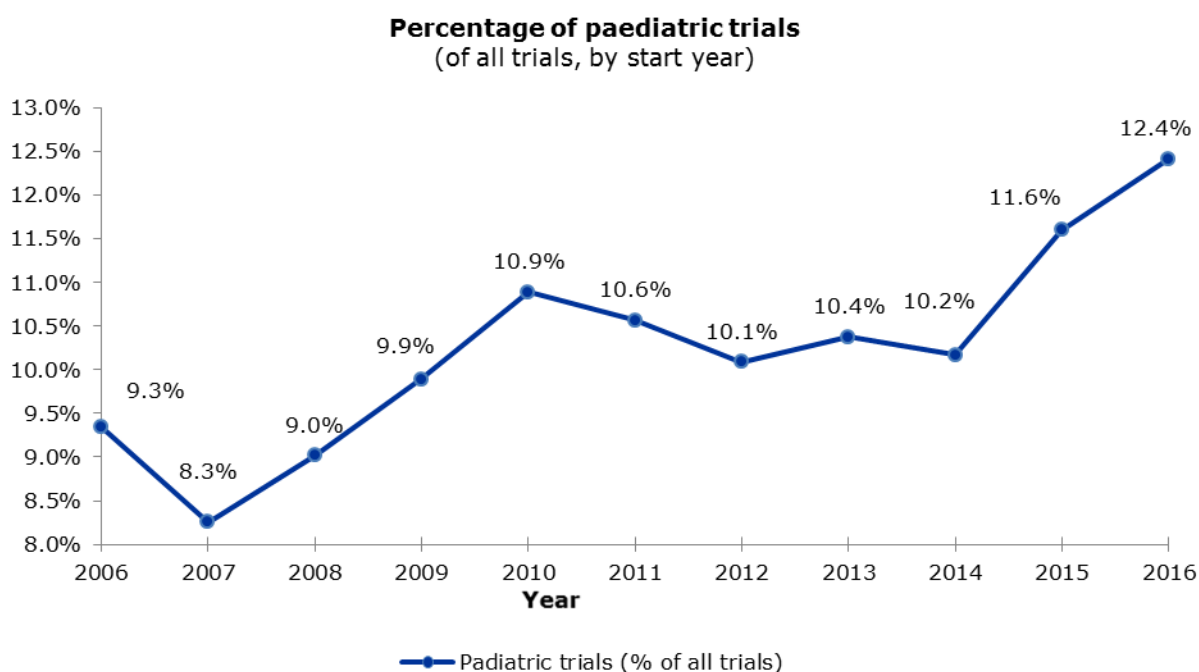
³ Paediatric Investigation Plan (PIP): a research and development programme aimed at ensuring that the necessary data are generated for determining the conditions in which a medicinal product may be authorised for the paediatric population.

More ethical and high quality paediatric research

Even though approaches such as extrapolation and modelling and simulation are increasingly part of paediatric medicine development to optimise available data from other populations and reduce the number of children needed in clinical studies, clinical research with children is essential for paediatric drug development in the majority of cases.

The first decade of the new paediatric legislation saw an increase of paediatric trials that were proposed by applicants, discussed by the Paediatric Committee and then included in agreed paediatric investigation plans (PIP) among all newly initiated paediatric trials. Paediatric trials in PIPs increased to about 80 per year and to a proportion of about 25-30% of all paediatric trials as recorded in the EU Clinical Trials database (EudraCT) (Figure 8.). As many paediatric trials in agreed PIPs are deferred until sufficient data on safety and efficacy are available in adults or older age-groups, it is expected that they will only be recorded in EudraCT in the future. It is also noted that a number of clinical trials including children are conducted to answer experimental questions of clinical interest, but are not necessarily aimed at new marketing authorisations. Therefore, these trials are not part of PIPs. Overall, the percentage of clinical trials involving children per year compared to all clinical trials per year increased from 9.3% in 2006 to 12.4% in 2016 (Figure 2.).

Figure 2. Proportion of clinical trials that include children



Note: A paediatric trial is a trial that includes at least one participant below 18 years of age.

Source: EudraCT database

Importantly, clinical trials open for recruiting neonates (a particularly neglected paediatric subpopulation) were included in over a quarter of all agreed PIPs, often at the request of the PDCO as the pharmaceutical companies rarely proposed studies in this age group. The number of neonates planned to be included in the trials loaded into the EudraCT database has increased by more than 40-fold between the two periods compared: from 470 in 2007-2009 to more than 19,900 in 2014-2016.

When focusing on paediatric trials which are expected to contribute data for regulatory submissions in the scope of the Paediatric Regulation (i.e. by excluding non-commercial, extension and phase 4 trials among others) the number of studies conducted in Europe almost doubled from 96 in 2007-2009 to 164 in 2014-2016.

By the end of 2016, the PDCO had adopted 950 opinions on the agreement of a PIP and in 475 (33%) cases had granted an exemption (waiver⁴) from conducting paediatric studies in one or more conditions. In addition, EMA provided scientific advice on paediatric development in 799 procedures. More than 350 product developments were reported to have benefited from scientific advice by Member States.

PIPs are the Regulation's main tool to ensure that previously unmet therapeutic needs in children are researched and appropriate medicines are developed. Since the survey of paediatric uses in 2006, PIPs have been agreed for a substantial proportion of medicines previously used off-label in the paediatric population. A total of 169 PIPs have also been agreed for medicines that have additionally received orphan designation, and there has been a progressive increase in the number of PIPs for conditions that are also rare diseases.

Challenges in carrying out paediatric research, including the rarity of many childhood diseases, heterogeneity of the population and issues regarding consent, mean that efforts are needed to obtain good evidence with as few subjects as possible and prevent unnecessary clinical trials. New approaches that have been agreed include in particular extrapolation approaches in more than 50 PIPs to date. In addition, innovative trial designs, as well as explicit integration of modelling and simulation into the development, allowed paediatric developments even in areas with historically very limited or no paediatric research.

To facilitate the conduct of clinical studies, the European Network for Paediatric Research at the EMA (Enpr-EMA) was set up, as mandated by the Paediatric Regulation. Enpr-EMA is an umbrella network of 39 national and international networks recognised amongst other things for their paediatric research experience and acts as a platform for sharing good practices as well as a pan-European voice for promoting research into medicines for children.

The PDCO closely collaborates with other committees and working parties of the EMA. PDCO members are systematically involved as experts in scientific advice, marketing authorisation and pharmacovigilance procedures in which paediatric questions are concerned.

EMA also collaborates with the FDA and Japanese, Canadian and Australian regulators in a discussion forum (cluster) to facilitate regulatory discussions on global development of paediatric medicines. By the end of 2016, the cluster had held 129 virtual meetings, with exchange of information on paediatric developments of common interest. A collaboration with other international partners such as the World Health Organization (WHO) with their initiative "Better Medicines for Children" and their Paediatric Medicines Regulators' Network (PmRN), as well as various academic groups was also actively promoted. The EMA is a partner of the Global Research in Paediatrics (GRiP) consortium, and helped to launch a Master programme on paediatric drug development and evaluation.

Children and their families are core stakeholders in these activities, and in addition to the three patient representatives who sit as PDCO members, EMA and PDCO have facilitated direct participation of children and young people in their activities, including agreement to set up a young people's working group as part of EMA's Patients and Consumers Working Party, and collection of children's opinions on their medicines in a survey in 2015.

⁴A waiver is granted when the use of the medicine in the targeted condition is not of paediatric relevance or interest, or the medicine is likely to be ineffective or unsafe.

The EMA also engages in regular interactions with trade associations and individual pharmaceutical companies (e.g. early paediatric interaction meetings, pre-submission meetings), in particular with Small and Medium Sized Enterprises (SME), to support them in carrying out their applications correctly and to minimise administrative burdens.

Observations and challenges

The Paediatric Regulation contains a system of obligations and rewards which has proven to be effective in stimulating paediatric development of medicines as demonstrated by the high number of agreed PIPs, paediatric clinical trials, and new medicines for children. However, after nine years of experience it is obvious that incentives alone are not as effective. For example, the PUMA (Paediatric Use Marketing Authorisation) was introduced to stimulate voluntary paediatric research into off-patent medicines which are of interest to children but only two PUMAs have been authorised. Also, for only 14 of all anti-cancer medicines, PIPs were proposed for the investigation of cancers that are specific to childhood or are not studied in adult patients.

By the end of 2016 more than 130 PIPs have been completed and more than 800 are ongoing. Several variables impact on the duration and the timing of completion of a PIP. Most completed PIPs are those submitted in the early years due to the long duration of clinical development programmes. Other factors impacting on the timing of PIP completion include rarity of the disease, and availability of other medicines for the same disease, albeit off-label, which hinders recruitment into clinical trials.

Applicants are required to submit PIPs not later than upon completion of human pharmacokinetic studies in adults. Although this creates an opportunity for discussion of paediatric matters early on during the development, it is challenging to consider all aspects of medicine development for children at a time when important characteristics even of the adult development are not yet known. PIP opinions which are too detailed at such an early stage can be difficult to agree and counterproductive because emerging data will inevitably lead to changes. Given the fact that currently only applicants are allowed to request a modification of the agreed PIP, a submission at an early stage of the product development prompts the PDCO to include all the necessary details in the original PIP opinion; otherwise the developed plan would be less than comprehensive. Considering a life cycle approach of the PIP in line with the development progress with additional time points for interaction on PIP refinement could be given consideration as an area for improvement.

PIPs which are submitted late in relation to the overall development may lead to an unnecessary delay of the paediatric marketing authorisation. Moreover, this may result in the potential loss of opportunities, such as the opportunity to conduct studies jointly in adult and paediatric populations.

Research into previously neglected populations, which are particularly vulnerable and difficult to study, has been promoted by the Regulation. Neonates, in particular, represent a population with high unmet needs. Since the implementation of the Regulation twenty-six percent of all agreed PIPs include studies in neonates. However, with the intention of protecting neonates, trials have often been deferred so that knowledge on safety and efficacy of the medicine in older age groups is obtained beforehand. These deferrals may lead to continuing off-label use. The issue is currently being discussed and general understanding seems to support significantly earlier conduct of neonatal studies, as the relevance of evidence obtained in older age groups appears to be limited.

Conclusion

The Paediatric Regulation has had a very positive impact on paediatric drug development, as shown by the data collected over the first nine years since its inception. Paediatric considerations have become an integral part of pharmaceutical development across the European Union and are taken into account from the outset of the life-cycle of each medicine. Not least through initiatives like Enpr-EMA, a new spirit of collaboration and open exchange of ideas has been fostered. This has facilitated systematic paediatric medicine development as set out in PIPs, and contribution to paediatric research and development by all stakeholders, which are leading to more medicines for children and more information on paediatric use of medicines.

A culture shift that promotes awareness and the generation of quality data in paediatric clinical research has led to a substantial increase in the proportion of clinical trials including children in the last few years. This is expected to eventually translate into new authorised medicines and improved paediatric information. Since the publication of the [5-year Report to the European Commission](#), several process improvements have been implemented by EMA. Opinions of agreed PIPs are now less detailed to allow flexibility and to accommodate changes based on emerging data during the medicine development. Furthermore, to encourage discussions on the paediatric needs that could be addressed with a specific medicine so called early paediatric interaction meetings have been introduced. Such changes are expected to reduce the administrative burden, to further improve the positive impact of the Paediatric Regulation and make even more medicines available to children with appropriate information.

Sources and coverage

Data sources

The report, prepared at the request of the European Commission, contains data collected by the European Medicines Agency (EMA) in collaboration with the Paediatric Committee of the EMA (PDCO) and EU Member States. Various data sources were used, including EMA databases. In certain cases information was provided by organisations outside of the EMA (e.g. FDA, PMDA, and Health Canada). The precision or level of detail of the data used for each analysis and the differing recording systems on which they were based may vary, e.g. electronic databases versus spreadsheets, data collections from projects necessary to the operation of the Paediatric Regulation, etc.

Reporting period

The report covers the period from January 2007 to December 2015 and builds upon experience and data presented in the [5-year Report to the European Commission](#). Key analyses such as the number of paediatric medicine authorisations and paediatric clinical trials were updated to include also data from 2016. Data from before the operation of the Paediatric Regulation have been included where available and relevant. References to other reporting periods are duly noted in the report.

1. New medicines for children

1.1. New medicines, new indications and new pharmaceutical forms

Centrally authorised medicines

Since the entry into force of the Paediatric Regulation and up to 31 December 2016, 101 new medicines were centrally authorised for paediatric use out of 399 (26%). (Line listings are included in the Annex.) Of these 60 met the conditions of Article 7 of the Paediatric Regulation, i.e. had an agreed PIP in place. As expected due to medicine development time, this number has been increasing every year, and in 2015 and 2016 nearly all paediatric indications approved in new medicines were a result of the applicability of the Paediatric Regulation.

With respect to variations of already centrally authorised medicines, 99 new paediatric indications were authorised, including 78 indications related to Article 8 of the Paediatric Regulation. Of all paediatric indications approved via the variation procedure, 73% are now linked to the Paediatric Regulation.

For centrally authorised medicines, 27 new pharmaceutical forms/routes of administration/strengths were authorised for paediatric use, and 15 of these were linked to the requirements of the Paediatric Regulation.

Nationally authorised medicines including decentralised procedure (DCP) and mutual recognition procedure (MRP)

For nationally authorised medicines ten new medicines with a paediatric indication have been authorised from 2007-2016 and a total of 57 new paediatric indications of already authorised medicines were approved during the same period.

Table 1. Overview of paediatric medicine changes (by year of authorisation, or variation).

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
<i>New medicines with a paediatric indication:</i>											
Centralised procedure, linked to requirements of the Paediatric Regulation	NA	0	2	2	7	7	12	7	8	15	60
Centralised procedure, not linked to requirements of the Paediatric Regulation*	12	6	5	0	0	3	9	4	1	1	41
<i>Total of all centralised authorisations (for reference)</i>	<i>39</i>	<i>25</i>	<i>41</i>	<i>17</i>	<i>30</i>	<i>35</i>	<i>53</i>	<i>53</i>	<i>59</i>	<i>47</i>	399
National procedure (including DCP, MRP)	0	0	2	0	1	1	1	1	2	2	10

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
Total of new paediatric medicines	12	6	9	2	8	11	22	12	11	18	111
<i>New paediatric indications:</i>											
Centralised procedure, linked to requirements of the Paediatric Regulation	NA	NA	2	1	14	10	16	10	9	16	78
Centralised procedure, not linked to requirements of the Paediatric Regulation*	7	6	6	2	0	0	0	0	0	0	21
National procedure (including DCP, MRP)	5	4	11	7	6	7	9	6	1	1	57
Total of new paediatric indications	12	10	19	10	20	17	25	16	10	16	156
Total of new paediatric medicines and indications	24	16	28	12	28	28	47	28	21	34	267
<i>New paediatric pharmaceutical forms:</i>											
Centralised procedure, linked to requirements of the Paediatric Regulation	NA	NA	0	0	3	2	4	2	2	2	15
Centralised procedure, not linked to requirements of the Paediatric Regulation*	3	1	2	2	4	0	0	0	0	0	12
National (DCP, MRP) procedure	1	1	4	2	3	1	0	1	1	2	16
Total of new paediatric pharmaceutical forms	4	2	6	4	10	3	4	3	3	4	43

Note: NA = not applicable as requirements of Article 7 and 8 of the Paediatric Regulation were not in force. * Not linked to the requirements of the Paediatric Regulation (e.g. generics, hybrid medicines, biosimilars etc.; and applications made before the Paediatric Regulation came into force).

Sources: Questionnaires to Member States for national procedures (see Annex); EMA databases (SIAMED, PedRA); SmPCs of centrally authorised products.

1.2. Effect of the Paediatric Regulation on the authorisation of medicines for children

The aim of this analysis, conducted in 2015, was to investigate whether the Paediatric Regulation has led to more medicines being authorised for children in the European Union, by comparing data collected from three years immediately before the Paediatric Regulation came into force (2004-2006) with the last three full years at the time of the analysis (2012-2014). Additionally, it was investigated whether more information on paediatric use is now available in the SmPCs of centralised authorised products.

From 2004 to 2006, 30 new medicines and new indications were centrally authorised for paediatric use. From 2012 to 2014, this number more than doubled to 63 new medicines and new indications. The number of authorised products with a new paediatric posology increased from 21 in 2004-2006 to 35 in 2012-2014.

Additionally, in February 2017 data from 2014-2016 were analysed. During this latest period, 74 new medicines were centrally authorised for paediatric use.

Table 2. Centralised medicines with paediatric indication (new MA and type II variation extension of indication)

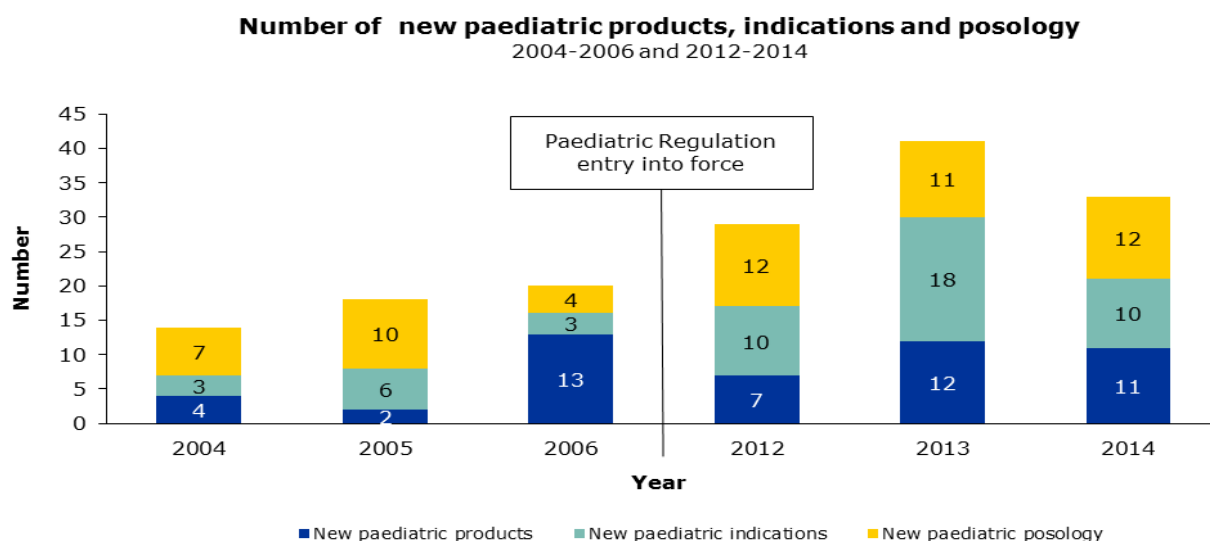
Reference period	Paediatric MAs and variations	Total of all MAs and variations for new indications	Proportion of paediatric MAs and variations of total
2004-2006	30	217	14%
2012-2014	63	249	25%
2014-2016	74	295	25%

Note: This analysis excludes medicines that are not subjected to the obligations of the Paediatric Regulation (e.g. generics, hybrid medicines, biosimilars, etc.).

Source: EMA database (SIAMED).

Detailed information regarding paediatric SmPC changes can be found in the Annex.

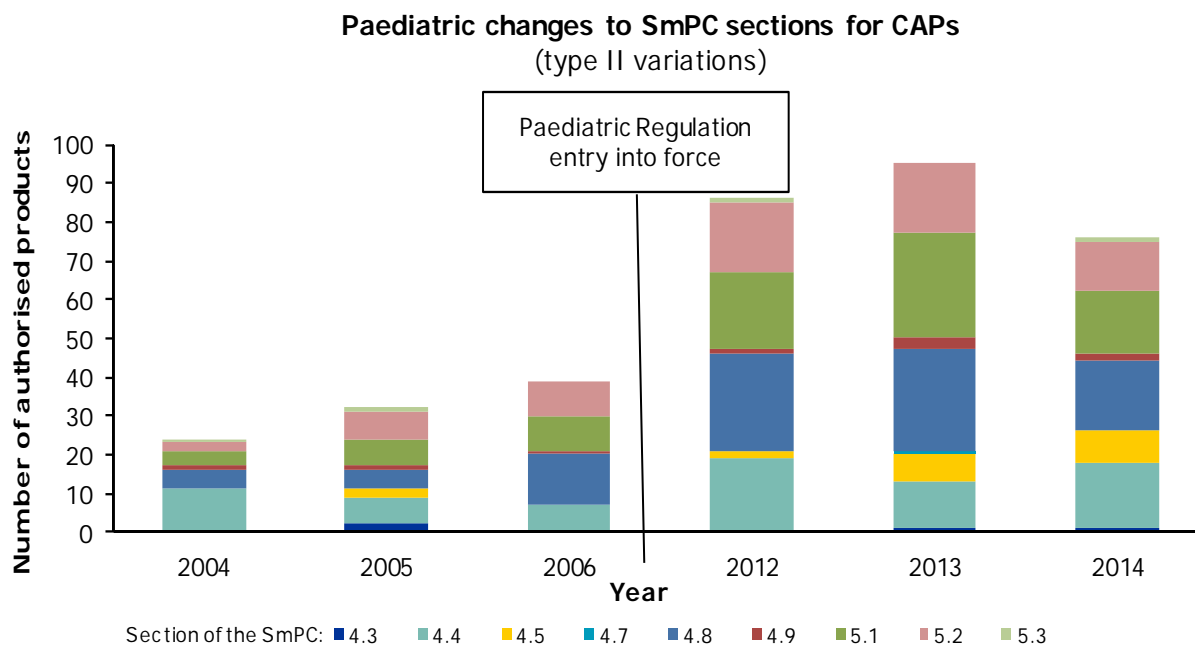
Figure 3. Number of centrally authorised products (CAPs) becoming available for children in 2004-2006 and 2012-2014 (new initial marketing authorisations, new paediatric indications (SmPC Section 4.1) or new posology information (SmPC Section 4.2) for already authorised products.



Source: EMA database (SIAMED)

The figure below provides a summary of the paediatric changes to other sections of the SmPCs – excluding new indications and posology - of authorised products in 2004-2006 and 2012-2014 (Figure 4.). Again, there was an increase from 2004-2006 to 2012-2014: in section 4.4 (Special warnings and precautions) from 25 to 48, in section 4.8 (Undesirable effects) from 23 to 69 and in section 5.1 (Pharmacodynamic properties) from 20 to 63 respectively.

Figure 4. Number of centrally authorised products (CAPs) with paediatric information updates in SmPC sections other than new indication or posology in 2004-2006 and 2012-2014



Note on SmPC sections:

4.3 Contraindications

4.4 Special warnings and precautions for use

4.5 Interaction with other medicinal products and other forms of interaction

4.7 Effects on ability to drive and use machines

4.8 Undesirable effects

4.9 Overdose

5.1 Pharmacodynamic properties

5.2 Pharmacokinetic properties

5.3 Preclinical safety data.

Source: EMA database (SIAMED), SmPCs of centrally authorised products.

It is clear that since the entry of the Paediatric Regulation into force in 2007 both the number of new medicines authorised for children in the European Union and the number of new paediatric indications for already authorised products (type II variations) have increased, and there is also more information available for clinicians on paediatric use especially with regard to safety information and clinical trial data.

1.3. Examples of achievements through the Paediatric Regulation

Rheumatology

Historically, authorised therapeutic options for children with rheumatologic diseases were extremely limited. This was mainly due to lack of funding and interest, because of expected low financial return. In recent years, following the inception of paediatric legislation in the US and EU, the development of new treatments for children with rheumatologic diseases has seen a significant surge (Ruperto N et al, 2013). Fourteen PIPs have been completed, so far leading to marketing authorisation of 8 new paediatric indications.

As an example, following PIP completion, new treatment options have been authorised for juvenile idiopathic arthritis (JIA) including canakinumab, abatacept, etanercept, and adalimumab.

Cardiovascular diseases

In the therapeutic area of cardiovascular diseases, several new treatments have been authorised on the basis of results from agreed PIPs, such as: angiotensin II receptor antagonists (valsartan, losartan) for the treatment of hypertension, and statins (rosuvastatin, atorvastatin, ezetimibe) for the treatment of hypercholesterolaemia.

Infectious diseases

Many medicines have become available after PIP completion for the treatment of infectious diseases. These new treatment options include: peginterferon alfa, ribaravin, and entecavir for the treatment of hepatitis C; atazanavir, darunavir, lopinavir/ritonavir, lamivudine/raltegravir and nevirapine for the treatment of HIV infection; voriconazole and caspofungin for the prevention and treatment of fungal infections, respectively, and several new antibiotics.

Paediatric oncology

Some new medicines for children with cancer were recently authorised based on data from studies in agreed PIPs (see section 2.12). For example, a new asparaginase (the first recombinant asparaginase) has become available for the treatment of acute lymphoblastic leukaemia, the most frequent cancer in children. The authorisation of dinutuximab is the first ever specifically for the treatment of neuroblastoma, the single most frequent solid tumour in children. The development was based on academic and publicly funded research, and ongoing studies are investigating less toxic administration schedules. These examples show innovations that have been brought to this patient group.

1.4. Article 29 procedures

For a coordinated and harmonised authorisation in national MAs of a new paediatric use across all Member States, a procedure based on Article 29 of the Paediatric Regulation may be triggered by a marketing authorisation holder of a national marketing authorisation when applying for a new indication, a new pharmaceutical form or a new route of administration for a medicinal product authorised under [Directive 2001/83/EC](#).

The application is assessed by the Committee for Medicinal Products for Human Use (CHMP), resulting in an opinion followed by a European Commission decision, and implementation at national level.

From 2007 to 2015, [nine procedures under Article 29](#) were completed for six active substances: anastrozole, irbesartan, valsartan, atorvastatin, latanoprost and rosuvastatin. Positive opinions on new paediatric indications and new pharmaceutical forms were obtained for all but anastrozole. The majority of these procedures took place in 2009 and 2010 (with only one, rosuvastatin, after 2010).

1.5. 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 protection (eight years of data exclusivity and two further years of market protection).

PIPs with a view of submitting a PUMA

Overall, 46 applications for a PIP have been received with a view of submitting a PUMA (as indicated in the PIP application form). Of these, 22 PIPs have been agreed. 24 applications are still ongoing or were withdrawn. Notwithstanding the above, the number of future PUMAs cannot be predicted accurately at the time of the PIP application, because any agreed PIP could potentially be used to apply for a PUMA when the medicine's patent has expired.

Twenty eight percent (13/46) of these medicines benefit from FP7 funded trials. Details can be found in Section 3.6.

Therapeutic areas

Of the 22 PIPs for potential PUMAs, most were in the areas of neonatology (five), neurology (four) and pain (three; one of which fits also in the area of neonatology). In the area of dermatology there were two agreed PIPs and one each in the areas of vaccines, gynaecology, anaesthesiology, infectious diseases, cardiovascular diseases, oncology, endocrinology/metabolic diseases and psychiatry.

Age groups

Out of the 22 PIPs, 11 included children from birth and in additional four, the youngest age group included infants ranging from one to four months. The entire paediatric age range (from birth to less than 18 years) was included in five PIPs and five were for neonates only.

Type of studies

Development of an age-appropriate formulation was included in 13 out of 22 PIPs. Safety/efficacy studies were included in 14 out of 22 PIPs, and 21 out of 22 included at least one safety study. Modelling and simulation studies or population PK studies were included in five PIPs. Placebo controlled trials were included in eight PIPs.

Further information about PIPs agreed with a view of a later PUMA submission can be found in the Annex.

Paediatric Use Marketing Authorisations (PUMAs)

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 for Buccolam (midazolam, oromucosal use). The second PUMA was authorised on 23 April 2014 for Hemangirol (propranolol hydrochloride, oral use) for the treatment of haemangioma. A third PUMA was authorised for Sialanar (glycopyrronium bromide, oral use) on 15 September 2016 for the treatment of sialorrhoea.

Although the Paediatric Regulation has led to increased research and development for paediatric medicines, the provisions to improve the information on and the development of the off-patent medicinal products in the paediatric population, have not been very effective.

For this group of medicinal products, the incentives such as data exclusivity, do not seem attractive enough. Trials are difficult to perform as these medicines are available on the market and often widely used off-label, and health professionals may not be motivated to study older medicines (Mukattash et al, 2011).

This may also be linked to varying pricing in Member States which may not recognise the added value of a PUMA in comparison to an unlicensed or extemporaneously prepared and possibly cheaper alternative, and may attach little value to older medicines even if they include a new age appropriate formulation/form.

1.6. Statements of compliance 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 also 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 in advance of the submission of the marketing authorisation application.

By the end of 2016, the PDCO had adopted positive opinions on final/full compliance for 131 agreed PIPs, which implies that the full paediatric programme was completed for these medicinal products. The number of compliance opinions has steadily increased over the years with peaks in 2014 and 2016 (Table 3.).

Table 3. Number of final/full compliance check opinions

Outcome of compliance procedure	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
Positive	5	8	9	9	4	16	31	17	32	131

Source: EMA database (PedRA).

Details of compliance opinions and medicinal products are listed in the Annex.

No NCA reported having checked compliance of a PIP. This may be because the NCAs have delegated the check to the EMA/PDCO, or because applicants/MAHs have obtained a PDCO opinion in advance of the regulatory procedure at the NCA.

Following the confirmation of compliance during an assessment and the inclusion of the results of the paediatric studies in the PIP, according to Article 28 (3) of the Paediatric Regulation, a compliance statement is added to the marketing authorisation. This was done for 30 centralised medicines and 35 nationally authorised medicines.

The compliance statement is intended for submission to patent offices to obtain the reward of Supplementary Protection Certificate (SPC) extensions. By the end of 2015, National Patent Offices (NPO) in 23 Member States reported as having granted or pending 322 six-month extensions of the SPC for 39 medicines (Article 36(1) of the Paediatric Regulation).

For details see Annex.

1.7. Comparison of EU with other regions

The objective of this analysis was to compare availability of paediatric medicines in regions which have paediatric legislation in place (EU and US) to those with no such provisions.

In the US, paediatric legislation predated the European Paediatric Regulation. US paediatric exclusivity provisions were established in 1997. This was followed by the introduction of the Best Pharmaceuticals for Children Act (BPCA) in 2002, and the Pediatric Research Equity Act (PREA) in 2003 (Bhatti et Sanders, 2011). No comparable legislation has been introduced in Canada (Rieder, 2011) but the voluntary submission of paediatric data leads to data protection extension. In Japan there is no regulation mandating paediatric studies. However, several measures to enhance paediatric drug development are in place (e.g. extension of exclusivity period, priority for scientific advice) (Tsukamoto et al, 2016).

Table 4. New paediatric medicines and indications per region (2007 to 2015)

Region	EU*	US	Japan	Canada
New paediatric medicines	80	76	12	38
New paediatric indications	141	173	38	107
Total	221	249	50	145

Note: The data provided by other regions included medicines that are not subjected to the obligations of the Paediatric Regulation. For the purposes of this analysis these medicines were excluded (e.g. generics, hybrid medicines, biosimilars etc.). * EU data include centrally authorised products and national/DCP/MRP products.

Source: EMA database (SIAMED), NCA questionnaire.

This analysis clearly demonstrates that in the regions with legislative provisions in place for the development of paediatric medicines (EU and US), a significantly higher number of new such medicines are available.

Distribution of paediatric medicines by therapeutic area is similar in different regions, with infectious diseases, vaccines, neurology and pneumology/allergology being the most common therapeutic areas with new paediatric indications.

2. Information on medicines for children

2.1. Articles 45 and 46

Articles 45 and 46 of the Paediatric Regulation require that existing and newly generated paediatric data, respectively, be submitted to Competent Authorities.

The CHMP has the responsibility for assessing paediatric studies of centrally authorised products, submitted under Articles 45 and 46.

The CMDh is the forum where paediatric studies of nationally authorised products, submitted under Articles 45 and 46, are discussed and where work sharing was agreed.

Variations following Article 45 or 46 submissions have been reported by 24 Member States (Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Hungary, Iceland, Italy, Ireland, Italy, Latvia, Malta, Norway, Poland, Portugal, Romania, Slovenia, Spain, Sweden, The Czech Republic, The Netherlands and United Kingdom) but medicines may not be authorised in all 30 Member States (Norway, Liechtenstein and Iceland participate in CMDh).

Table 5. Recommended SmPC changes related to Article 45 and 46 submissions (2008 to 2015)

	Article 45 centralised (EMA-CHMP)	Article 45 non- centralised (CMDh)	Article 46 centralised (EMA-CHMP)	Article 46 non- centralised (CMDh)
Active substances	62	219	280	80
Study reports	199	~19,000	429	479
Recommendations for SmPC changes* (e.g. addition of paediatric study information or safety data, clarification of paediatric information)	10	~124	~45	~28
New paediatric indications	2	14	2	1

Note: * Can be more than one change per SmPC.

Source: Procedural and work-sharing documentation of the CMDh, <http://www.hma.eu/cmdh.html>, using tracking sheet for 31 December 2015.

2.1.1. Recommendations following Article 45 submissions

Overall, for both nationally and centrally-approved medicines submitted under Article 45, paediatric data for 261 active substances have been submitted and assessed since 2008 resulting in approximately 140 recommendations to update the SmPC (and Package leaflets). Further details can be found in the Annex. As prior to 1995 when the centralised procedure came into operation all medicines were authorised nationally, most study reports relate to nationally authorised medicines.

For **centrally-authorised** medicinal products, by 2014 the CHMP had completed the assessment of all submitted data, covering 62 active substances. 199 assessment procedures were finalised by 2014. The SmPCs of 12 medicinal products were changed subsequent to the assessment. The publication of all assessment reports / outcomes of the assessment of studies submitted through Article 45 is included in the respective [EPAR web pages on the EMA website](#).

By the end of 2015, for medicinal products authorised through **national procedures** (MRP, DCP), more than 19,000 study reports had been made public for 219 active substances after completion by the CMDh of the [assessment of the submitted studies](#).

2.1.2. Recommendations following Article 46 submissions

Overall, for both nationally and centrally-approved medicines submitted under Article 46, paediatric data for 360 active substances have been submitted and assessed since 2008 resulting in approximately 82 recommendations to update the SmPC (and package leaflets).

For data submitted under article 46 for **centrally-authorised products**, 280 active substances had a completed assessment by the CHMP by 2015. The CHMP recommended over 50 changes to the product information for approximately 40 active substances.

By the end of 2015, 479 study reports for 80 active substances submitted under Article 46 for **nationally-authorised** medicinal products resulted in around 40 recommendations for SmPC changes one of which was a new paediatric indication for leuprorelin acetate (EL/W/0004/pdWS/001).

Details relating to nationally-authorised medicines can be found in the published assessment reports available on the [CMDh website](#).

2.2. Changes to product information

Increased information on paediatric medicines is achieved by adding paediatric information to the SmPC/PIL. This can be based on paediatric study results in particular from Article 45 or 46 assessment recommendations, or on other information that is relevant for children (e.g., non-clinical study results, findings from pharmacovigilance, or PDCO opinions). Table 6. summarises the paediatric-relevant changes to product information from 2007-2015 for centralised medicines.

Table 6. Increased information on centrally authorised medicines for paediatric use

	2007	2008	2009	2010	2011	2012	2013	2014	2015	Total
Dosing information for children added to SmPC (section 4.2)	14	14	16	15	20	27	16	20	15	157
Paediatric study data added to the SmPC (section 5.1)	11	12	11	23	20	20	27	16	13	153
Paediatric safety information added to the SmPC section 4.8	8	11	20	ND	28	25	26	18	12	148
Statements on deferral or waiver included or added to SmPC (section 5.1)*	0	0	2	28	31	55	75	53	58	302
Other paediatric information added to other sections of the SmPC (e.g., section 5.2)	7	13	15	12	19	41	42	42	27	218

Note: Figures exclude duplicates. * Counted twice if statement on both deferral and waiver included. ND = data not sufficient for analysis.

Sources: EMA database (SIAMED).

Table 7. summarises the paediatric-relevant changes to product information from 2007-2015 for nationally authorised medicines (including those authorised through the mutual recognition or decentralised procedures).

Table 7. Increased information on nationally (including MR and DC) authorised medicines for paediatric use.

	2007	2008	2009	2010	2011	2012	2013	2014	2015	Total
Dosing information for children added to SmPC (section 4.2)	15	12	14	8	26	25	20	25	14	159
Paediatric study data added to the SmPC (section 5.1)	NR	NR	NR	NR	NR	21	29	46	12	108
Paediatric safety information added to the SmPC section 4.8	NR	NR	NR	NR	NR	7	14	23	9	53
Statements on deferral or waiver included or added to SmPC (section 5.1)*	NR	NR	NR	NR	NR	11	20	41	34	106
Other paediatric information added to other sections of the SmPC (e.g., section 5.2)	NR	NR	NR	NR	NR	16	39	35	26	116

Note: The same information may be reported by more than one Member State in MRP or DCP medicines as these may be authorised in more than one country. The data reported are an approximation as not all Member States responded. * Counted twice if statement on both deferral and waiver included. NR = data not recorded.

Source: NCA questionnaire (simplified from 2014).

3. Paediatric research and development

3.1. Paediatric investigation plans

PIPs, waivers, modifications of an agreed PIP

The Paediatric Regulation requires applicants to provide a plan to deliver either the results of studies in compliance with an agreed PIP, or a waiver for such studies when filing for marketing authorisation (Article 7) or for certain variations/extensions of marketing authorisations (Article 8). Since the implementation of the Regulation, the PDCO has completed the assessment of a total of 2402 applications for PIPs or waivers. This required close collaboration between the Member States and the EMA as well as external experts and other stake holders such as patient organisations, the pharmaceutical industry and other regulatory authorities. This created an opportunity for exchange of ideas on matters relating to paediatric development, and joint efforts to overcome hurdles and prejudice associated with research in children. Paediatric drug development is now an integral part of adult development. The extremely valuable contribution of the European regulatory network to the success of the Paediatric Regulation is acknowledged. Assessors from the Member States have been involved as reviewers of applications, and provided their expertise in many other aspects concerning paediatrics (e.g. guidelines, workshops, Scientific Advice).

Table 8. Overview of outcomes of full waiver, PIP and modification requests by year

Request Type	Outcome	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
Full waiver	PIP agreed ¹		1									1
	Full waiver refused		1	11	6	2	2	2	1	3	3	31
	Full waiver granted	10	35	55	44	44	47	51	46	47	52	431
PIP	PIP agreed	1	81	123	202	107	87	96	91	71	90	949
	PIP refused		1	4	1	1	1	2	1		4	15
	Full waiver on PDCO's own motion		10	13	7	1		1	5	5	2	44
Modification	Modification refused				4	2	1	3	4	3	9	26
	Modification agreed		8	50	105	152	165	184	195	200	216	1275
	Full waiver granted				1			1	2	2	5	11
Total		11	137	256	370	309	303	340	345	331	381	2783

Note: ¹ A PIP was agreed instead of the initial waiver request.

Source: EMA database (PedRA)

PIPs by therapeutic area

Addressing previously unmet therapeutic needs with medicines that are researched and developed for use in children is a major goal of the Paediatric Regulation. PIPs are its main tool to ensure that the necessary data are generated to allow for a potential authorisation of a given medicine for an appropriate paediatric indication.

In this analysis 808 PIPs were included (duplicate PIPs, i.e. PIPs for identical products with marketing authorisations under different invented names, were excluded). The agreed conditions of each PIP were reviewed and each PIP was assigned to one therapeutic area. A high number of allergen PIPs were assessed in 2010-2011 due to a change in regulation in Germany. These are reported separately.

A total of 98 agreed PIPs from this analysis set had been completed and received a positive compliance check (12% of agreed PIPs) opinion by the PDCO (Table 9.).

Table 9. PIPs per therapeutic area (2007-2015)

Therapeutic area	Number of agreed PIPs	Number of completed PIPs	Completed/agreed PIPs	Number of authorisations of paediatric indications
Anaesthesiology	3	0	0%	0
Cardiovascular diseases	48	9	19%	6
Dermatology	33	5	15%	5
Diagnostics	13	2	15.4%	1
Gynaecology	12	3	25%	1
Endocrinology/metabolic diseases	70	7	10%	6
Gastroenterology/hepatology	33	5	15%	4
Haematology	46	3	6.5%	1
Transplantation	10	2	20%	1
Immunology/rheumatology	46	14	30.4%	8
Ophthalmology	17	2	12%	2
Vaccines	37	9	24.3%	9
Psychiatry	17	2	12%	2
Neurology	45	3	7%	2
Infectious diseases	96	14	15%	14
Neonatology/paediatric intensive care	16	1	6%	1
Oncology	83	7	10%	2
Pain	9	1	11%	0
Pneumonology/allergy	35*	7	20%	6
Uro-nephrology	16	1	6%	0
Orthopaedic diseases	9	1	11%	0
Allergens*	114	0	0%	0
Total	808	98	12%	71

Note: *Allergen PIPs assessed in 2010-2011 due to a change in regulation in Germany are listed separately here.

Source: EMA database (PedRA)

In the area of virology, a significant number of PIPs have been agreed, completed and led to authorisation of a paediatric indication. In particular, in the area of HIV infection, five out of 25 agreed PIPs have been completed leading to authorisation of five paediatric indications (20%). Other conditions with a high percentage of completed/agreed PIPs include: hepatitis C (16%), hypercholesterolemia (36%), acne (25%), contraception (28%) and type 1 diabetes mellitus (36%).

In contrast, a high number of agreed PIPs with a low number of completed PIPs were observed in the following conditions/therapeutic areas: multiple sclerosis (0%), type 2 diabetes (0%), ulcerative colitis and Crohn's disease (6%). Multiple sclerosis and type 2 diabetes are diseases of high need in adults. Developments for several medicines compete for the limited number of paediatric patients, which creates substantial difficulties for developers. However, as the conditions do exist in children, the PDCO does not grant waivers unless the needs are already covered by existing medicines, authorised for children.

Several variables impact on the duration and the timing of completion of a PIP. As medicine development is a lengthy process most completed PIPs are those submitted in the early years following the implementation of the Paediatric Regulation. Especially PIPs for rare diseases may face severe recruitment issues due to scarce patient populations, which may cause delays. Where other medicines are available, albeit off-label, recruitment of children to PIP programmes may also be hindered. If new treatments get authorised, completion of PIPs in related medicines can encounter problems due to the potential of off-label use of the medicine, which hinders the recruitment into clinical trials. However, as the PDCO cannot predict which products will obtain a marketing authorisation, PIPs for similar products are agreed.

Moreover, the timing of the PIP process relative to the overall development programme of a medicine needs to be considered. On many occasions PIPs have been submitted late in the overall development. This may lead to a PIP completion and subsequent paediatric marketing authorisation being unnecessarily delayed in relation to the marketing authorisation in adults. Delayed and non-completed PIPs may be indicative of the lack of willingness of some companies to develop medicines for children. For medicines that are developed exclusively for paediatric use the timing of submission of a PIP is not specified in the Regulation. Although in these situations it is also expected that the PIP is agreed early during the development, there have been cases when a PIP was submitted towards the end of the paediatric development programme, putting the committee in a difficult position and resulting in the potential loss of opportunities.

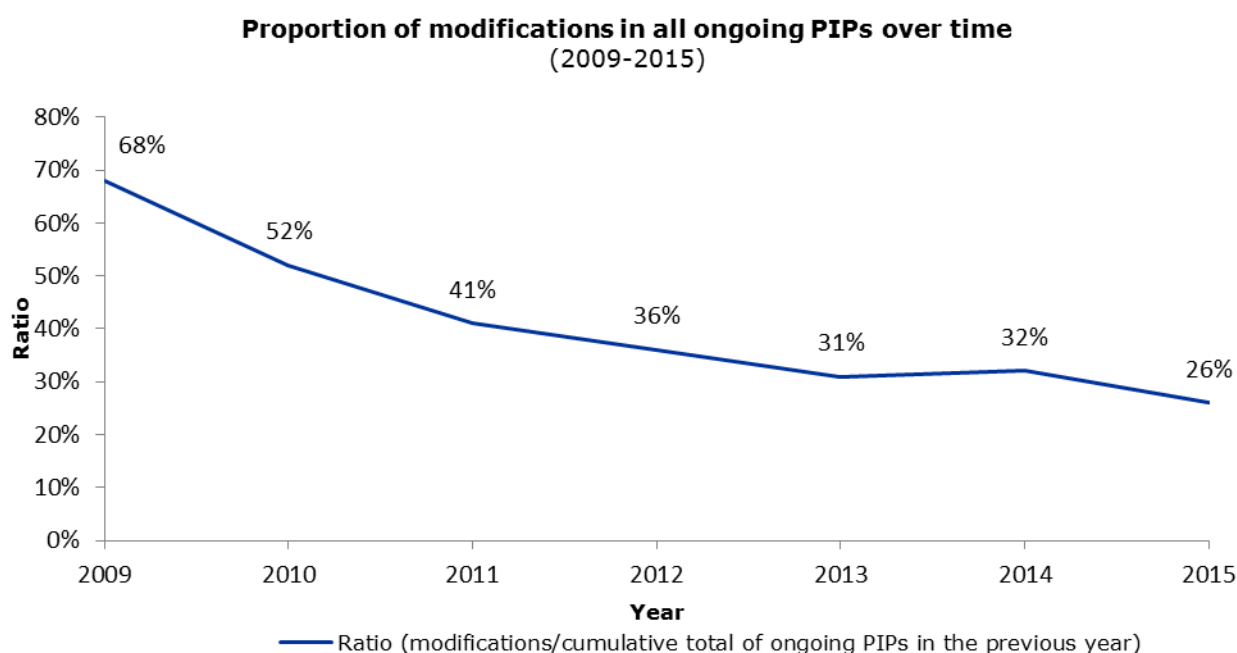
3.2. Modifications of agreed PIPs

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). A modification can only be initiated by the applicant, but not by the PDCO.

Many PIPs have been agreed and the absolute number of modifications is increasing. This is expected as modifications of plans are necessary to account for new data and evolving knowledge (e.g. adult and paediatric study results, changes in medical practice) during drug development. PIPs are part of the life cycle of a medicine.

However, the ratio of PIP modifications to ongoing PIPs is decreasing (Figure 5.). This may suggest improvements in the preparation and execution of PIPs and may also reflect efforts towards agreeing PIP opinions with clearer and simpler elements. Additionally, the revision of Commission guideline on the format and content of PIPs (2014/C 338/01) in September 2014 introduced measures to streamline the PIP process.

Figure 5. Proportion of modifications in all ongoing PIPs over time (2009-2015)



Source: EMA database (PedRA).

By the end of 2015, the PDCO had agreed 1059 modification opinions, while it had agreed 859 opinions on new PIPs in the same time period. The elements that were agreed to be modified were analysed in PIPs for 354 active substances with at least one modification. The most common major modifications involved changes to timelines (delays of completion of studies), followed by sample size reductions (Table 10.), reflecting possible consequences of other modifications, issues in the planning or conduct of studies, as well as the need to modify the number or design of studies which may lead to late submission of data and trials that are insufficiently powered.

Table 10. Changes to elements in modified PIPs by frequency

Major modification concerning	Frequency per agreed, modified PIP (%)
Timelines*	43
Sample size	14
Statistical plan	8
Deletion of study	8
Dosage or dosing rules	8
Secondary endpoint	7
Primary endpoint	7
Formulation	5
Non-clinical issues	3
Change in wording of condition	3
Removal of condition	2
Addition of condition	2
Pharmaceutical form for younger children	1
New full waiver on PDCO's own motion	1

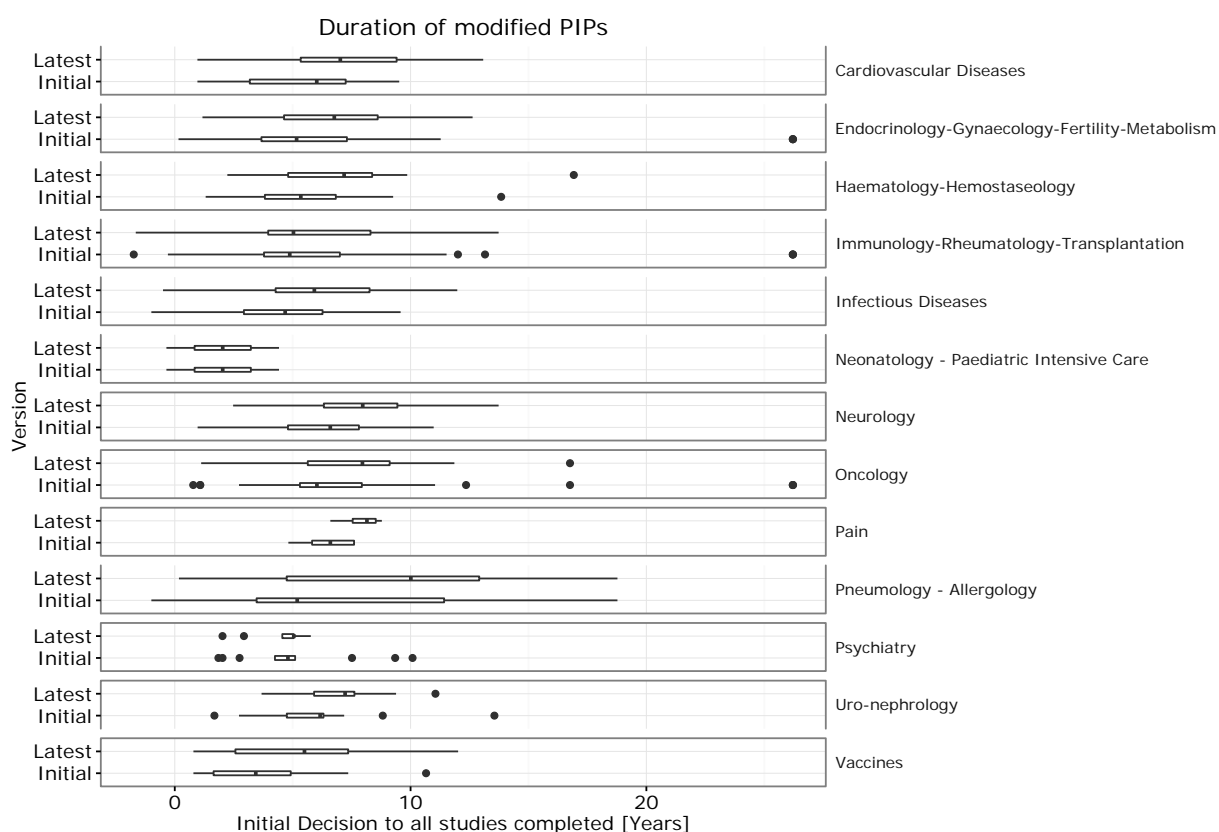
Note: Modifications were accumulated over all procedures. *Defined as 6 or more months.

Source: EMA database (PedRA extension).

With respect to all agreed PIPs, there is no clear relationship between the number of modifications and the therapeutic area(s) of the agreed PIP.

The consequences of modifications on the planned progress and completion of the studies in modified PIPs was further explored. Overall, the agreed modifications resulted in a median of 1.5 years delay in the planned completion of modified PIPs. Delays were compared across therapeutic areas. There is no strong pattern, and paediatric developments for infectious diseases and vaccines are similarly delayed as those for oncology; nevertheless, rheumatology and neonatology developments were not delayed apparently. The significant delays in pulmonology-allergy are due to allergy products whose developments are lengthy.

Figure 6. Comparison of development duration by therapeutic area among modified PIPs



Note: The central tendency and spread of PIP time lines is shown in box plots. The bold vertical bar within the box indicates the median of time lines, the left and right sides of the boxes correspond to the first and third quartiles of the time lines. The points represent outliers (more than one-and-a-half times the interquartile range away from the median [Tukey 1977]).

Source: EMA database (PedRA).

Product-specific waivers

By 31 December 2015, the PDCO had granted a total of 421 waivers where the PDCO did not deem the medicine to provide a benefit to the paediatric population (this could be for lack of safety/efficacy, the disease not occurring in the paediatric population, or due to lack of significant therapeutic benefit over existing treatments). Of these, the majority were in the therapeutic area of cardiovascular diseases (25%) and mainly represented fixed-dose combinations of antihypertensive medicines which in certain cases would not offer the flexibility of dosing required in children.

Many waivers were granted for medicines in the therapeutic area of endocrinology/gynaecology (13%). Most of these waivers were for fixed dose combination products for the treatment of type 2 diabetes mellitus, or for medicines for the treatment of infertility. Other therapeutic areas with a high number of waivers included oncology (9%), pain (6%) and ophthalmology (5%). The grounds for waiving a development in children were mostly lack of benefit (about 60% of developments) or that the condition occurred only in adults (30%). In addition, 46 and 27 waivers of a paediatric development were granted because the medicine was likely unsafe or ineffective in children, respectively.

The Paediatric Regulation has undoubtedly led to the development of many medicines for the treatment of paediatric diseases. However, the development of paediatric medicines is not necessarily driven by paediatric needs but rather by medicine development for the adult market. This is illustrated for example by a high number of completed PIPs in areas such as HIV infection where research and development are flourishing, and continuing neglect of areas such as paediatric oncology and neonatology.

Another example is diabetes mellitus, where many medicines are being developed for adult patients, due to the high prevalence of the disease and the relevance of the market. In particular for type 2 diabetes, many PIPs have been agreed despite the low number of children and adolescents with type 2 diabetes mellitus, because none of the products in the newer classes is authorised yet for children. This has exacerbated recruitment difficulties, due to many competing developments. At the same time, it is difficult for the PDCO to prioritise which medicines should be developed in children in such cases, given the limited information available on the potential safety and efficacy at the time the PIP is agreed, and the potential legal challenges associated with comparative evaluations. To address these issues, EMA has organised two workshops with invited experts, where innovative approaches were discussed, such as the use of non-competitive (platform) trials, where several products are compared to a single placebo (or standard treatment) group (see section 3.16.).

Comparison of PIPs and disease burden

Limited resources for research and development require establishing explicit criteria to guide prioritisation of medicine development according to disease burden (Catalá-López et al., 2010). Disability-adjusted-life-years (DALY) are widely used as a tool to quantify the burden of diseases. This time-based measure combines years of life lost due to premature mortality and years of life lost due to time lived in states of less than full health (from WHO methods and data sources for global burden of disease estimates 2000-2011).

The latest WHO data for children from birth to less than 15 years of age from 2012 indicate that the disease burden based on DALYs in the EU is highest for mental and behavioural disorders, neonatal conditions, congenital anomalies and respiratory diseases, which together cover almost 60% of the total disease burden. Disease burden compared to agreed PIPs as well as new authorised paediatric indications are presented by therapeutic area in Table 11.

Table 11. Comparison of disease burden for children younger than 15 years of age in the EU in 2012 and agreed PIPs/paediatric indications

Rank	Therapeutic area	Percentage of total DALYs	Percentage of agreed PIPs	Completed PIPs	New paediatric indications
1	Mental and behavioural disorders	20%	3%	2	2
2	Neonatal conditions	14%	2%	1	1
4	Respiratory diseases ^a	10%	5% ¹	7	6
5	Musculoskeletal diseases ^b	9%	1%	1 ^b	0
6	Endocrine, blood, immune disorders ^c	6%	20%	18	14
8	Neurological conditions	5%	7%	3	2
9	Infectious and parasitic diseases/respiratory infections ^d	5%	22%	23 ^e	23 ^e
10	Malignant neoplasms	5%	13%	5	2
11	Skin diseases	5%	5%	5	5
12	Digestive diseases	2%	5%	5	4
14	Cardiovascular diseases	2%	7%	9	6
13	Oral conditions	1%	-	-	-
14	Diabetes mellitus	1%	5%	5	1
15	Genitourinary diseases	0%	2%	1	0
17	Sense organ diseases	0%	3%	2	2
Total ²		100% (8,050)	100% (645)	87	68

Note: ¹ Allergen PIPs are not included in this analysis. ² Total numbers and percentages may not correspond to the totals of agreed PIPs/paediatric indications since some PIPs do not have a corresponding therapeutic area for the disease burden and vice versa. Not shown: nutritional deficiencies, other neoplasms, congenital abnormalities

a: Includes chronic obstructive pulmonary disease, asthma and other respiratory diseases

b: Includes rheumatoid arthritis, orthopaedic diseases, osteoarthritis, gout, back and neck pain, other musculoskeletal disorders

c: Includes endocrine and metabolic diseases, haematology and immunology/rheumatology.

d: Includes infectious diseases irrespective of affected organ.

e: Includes PIPs for vaccines.

Source: Global Health Estimates (GBE) for European Union Member States, 2012; World Health Organization Department of Health Statistics and Information Systems', May 2014. Accessible at http://www.who.int/healthinfo/global_burden_disease/estimates/en/index2.html

The data show that the paediatric development in terms of agreed PIPs does not necessarily correspond with the paediatric disease burden. While the highest burden exists for mental and behavioural disorders and neonatal conditions, only 3% and 2% of PIPs were agreed for these diseases. Conversely, the highest proportion of PIPs has been agreed for the areas of infectious diseases (21%) and malignant diseases (13%) which rank in 9th and 10th place, respectively in the disease burden index. The therapeutic areas used for the burden of disease and for the PIPs do not completely overlap, and the areas anaesthesiology, diagnostics, transplantation and pain, for which PIPs have been agreed, do not have a corresponding area in the WHO list of burden of disease. Additionally, in the therapeutic area of gynaecology, most agreed PIPs are for contraceptive medicinal products and not for treatment of diseases.

A discrepancy between disease burden and number of agreed PIPs is seen in various therapeutic areas. This discrepancy may indicate that paediatric medicine development is mainly driven by the adult development. Diseases that are unique to the paediatric population are still being neglected. EMA has also analysed pharmaceutical pipelines and approved medicines to identify the therapeutic areas and conditions where no pharmaceutical development is taking place (Papaluca et al, 2015).

Addressing unmet paediatric needs

List of needs for research and development

The former Paediatric Expert Group (PEG) at the EMA published in 2006 a [list of the needs](#) for research and development of medicinal products for children. After the Paediatric Regulation came into force, a survey was conducted in all EU Member States (Article 42) on all existing uses of medicinal products in the paediatric population (use of authorised medicinal products within the terms of the marketing authorisation, use of authorised medicinal products outside the terms of the marketing authorisation and of the SmPC – so-called off-label use, and use of unauthorised medicinal products). The analysis of the received data was published in 2010 and together with the list of needs from 2006 formed the basis for an inventory of therapeutic needs (Article 43) by therapeutic area. This inventory is continually being updated by the PDCO. It is accessible on the EMA's website and is aimed at identifying research priorities for medicinal products for children, either old (i.e. off patent) or new.

In addition to its benefits for industry, the inventory was also developed as a tool for the PDCO to evaluate the need for medicines and studies when assessing draft PIPs.

Since the survey of paediatric uses, PIPs have been agreed for a substantial proportion of medicines previously used off-label in the paediatric population (see Annex). 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. Hence there is still a risk of off-label use until the products in question are authorised for use in children based on the results of completed PIPs.

With the new Pharmacovigilance Regulation and Directive which came into effect in 2012 it is now required to not only report adverse reactions from the authorised use of a medicinal product but also from uses outside the terms of the marketing authorisation. Moreover, marketing authorisation holders are obliged to report any use of their medicinal product which is outside the terms of the marketing authorisation. This system may help to assess the extent of off-label use in children in the future.

An analysis of the therapeutic area of cardiovascular diseases, selected as an example, showed encouraging results. The assessment of paediatric needs in 2006 identified 60 medicinal products for cardiovascular diseases whose development in children was needed. Identified needs ranged from generation of pharmacokinetic, safety and efficacy data to the development of age appropriate formulations. Today 23 of these products hold a marketing authorisation in children. For 12 products a PIP has been agreed to cover the identified needs. Seven of these products with an agreed PIP have been authorised for use in the paediatric population or in a new subset of the paediatric population (Table 12.).

Table 12. PIPs agreed for paediatric needs identified in 2006 in cardiovascular diseases

Active substance	Indication	Age group authorised in 2006	Age group authorised in 2015	Paediatric need in 2006	PIP condition
Bosentan	Pulmonary arterial hypertension	> 12 years	> 2 years	Additional data on efficacy, safety and dose for children, especially < 3 years Age appropriate formulation	Treatment of pulmonary arterial hypertension (PAH)
Dobutamine	Cardiogenic shock, acute heart failure	Children (Spain, Germany)	0 < 18 years	Define the lower age limit based on data on efficacy and safety and investigate where needed. Age appropriate formulation	Treatment of neonatal circulatory failure
Dopamine	Cardiogenic shock, acute heart failure	Not authorised <18 years	Not authorised <18 years	Extension of indications to all age groups, including neonates (efficacy, safety data and dose) Age appropriate formulation	Treatment of vascular hypotension disorder
Sildenafil	Pulmonary hypertension	Not authorised <18 years	1 < 18 years	Extension of the indication (efficacy, long term safety data and dose) to all age groups Age appropriate formulation	Treatment of pulmonary arterial hypertension
Clopidogrel	Prevention of athero-thrombotic events	Not authorised <18 years	Not authorised <18 years	Extension of the indications to all age groups (efficacy, safety data and dose) Age appropriate formulation	Prevention of thromboembolic events

Active substance	Indication	Age group authorised in 2006	Age group authorised in 2015	Paediatric need in 2006	PIP condition
Captopril	Hypertension, heart failure	Not authorised <18 years	0 < 18 years of age	Re-analysis of the benefit/risk in children based on existing data Define lower age limit in both indications and investigate where needed. Age appropriate formulation	Treatment of heart failure
Enalapril	Hypertension, heart failure	Not authorised <18 years	28 days <18 years (limited clinical data; enalapril is not in children with glomerular filtration rate < 30 ml/min/1.73 m ² , as no data are available)	Re-analysis of the benefit/risk in children based on existing data Define lower age limit in both indications and investigate where needed Need for information on extemporaneous formulation in Summary of Product Characteristics	Treatment of hypertension Treatment of heart failure
Nifedipine	Hypertension	Not authorised <18 years	Not authorised <18 years	Extension of the indication to all age groups (efficacy, safety data and dose) Age appropriate formulation	Treatment of essential hypertension (Fixed dose combination nifedipine / candesartan)
Furosemide	Hypertension, heart failure, oedema	Children (for treatment of oedema in Sweden, hypertension in France)	Limitation: Difficulty to assess authorisation by MS	Indications for oedema and hypertension and age appropriate formulation to be made available in all Member States	Treatment of fluid retention
Valsartan	Hypertension	Not authorised <18 years	6 <18 years	Extension of the indication to all age groups (efficacy, safety data and dose) Age appropriate formulation	Treatment of hypertension

Active substance	Indication	Age group authorised in 2006	Age group authorised in 2015	Paediatric need in 2006	PIP condition
Atorvastatin	Dyslipidemia	Not authorised <18 years	>10 years	Extension of the indications to all age groups (efficacy, safety data and dose) Age appropriate formulation Data on efficacy, safety and dose in secondary dyslipidemia Lower age limit to be defined	Treatment of hypercholesterolaemia, combined (mixed) hyperlipidaemia Prevention of cardiovascular events
Colesevelam	Primary hypercholesterolaemia	Not authorised <18 years	Not authorised <18 years	Extension of the indications (efficacy, safety data and dose) Define lower age limit Age appropriate formulation	Treatment of heterozygous familial hypercholesterolaemia Treatment of homozygous familial hypercholesterolaemia

Source: Inventory of paediatric needs – cardiovascular products (2006), EMA databases

Examples of PDCO initiatives in areas of unmet medical need

The PDCO has acknowledged that unmet medical needs exist also in younger age groups or rare subtypes of diseases than those historically included in paediatric development programmes. Examples include:

- Juvenile idiopathic arthritis (JIA) and other auto-immune diseases (Ruperto et al., 2013)
- Cholesterol-lowering and anti-hypertensive medicines
- Diabetes mellitus (Karres et al., 2014; Tamborlane et al., 2016)
- Gaucher disease type 3.

For similar reasons and following evolving pathophysiological insights, development has recently been requested for less advanced and/or paediatric specific disease stages for selected products (such as for persistent pulmonary hypertension of the newborn).

For diseases which occur both in adults and children, such as haemophilia, the timing of (part of) the paediatric development is now being brought forward (i.e. before marketing authorisation in adults) in order to ensure that paediatric studies remain feasible and are conducted in the most appropriate time window, limiting the risk of off-label use.

3.3. Age-appropriate forms and formulations

Historically, paediatric use of many authorised medicines was prevented by the lack of age appropriate pharmaceutical forms or formulations.

Pharmaceutical quality-related studies in PIPs

All PIPs should address the need for specific forms suited to the targeted age group(s), and provide qualitative and quantitative information on the formulation proposed, with a thorough justification of its appropriateness. An expert PDCO Formulation Working Group (FWG) was established in February 2008 to review aspects of PIPs related to pharmaceutical quality and appropriateness of paediatric formulations. Issues commonly discussed by the FWG include size of tablets/capsules, dosing accuracy, acceptability/palatability studies, safety of excipients, and suitability of the pharmaceutical form (Quijano et al, 2013).

Table 13. provides an analysis of 849 agreed PIPs from 2007 to 2015 for which information on age-appropriate formulations has been recorded by therapeutic area.

Table 13. Number of PIPs with requests for development of age appropriate formulations by therapeutic area.

Therapeutic area	PIPs with study for age-appropriate form or formulation	All documented PIPs
Anaesthesiology	2	3
Cardiovascular diseases	24	40
Dermatology	13	42
Diagnostics	1	10
Endocrinology-gynaecology-fertility-metabolism	31	89
Gastroenterology-hepatology	19	38
Haematology-haemostaseology	24	50
Immunology-rheumatology-transplantation	27	76
Infectious diseases	76	105
Neonatology - paediatric intensive care	9	13
Neurology	24	47
Nutrition	0	2
Oncology	33	73
Ophthalmology	3	15
Other	9	29
Oto-rhino-laryngology	3	13
Pain	11	14
Pneumonology/allergology	16	114
Psychiatry	3	18
Uro-nephrology	17	19
Vaccines	8	39
Total	353	849

Source: EMA database (PedRA extension).

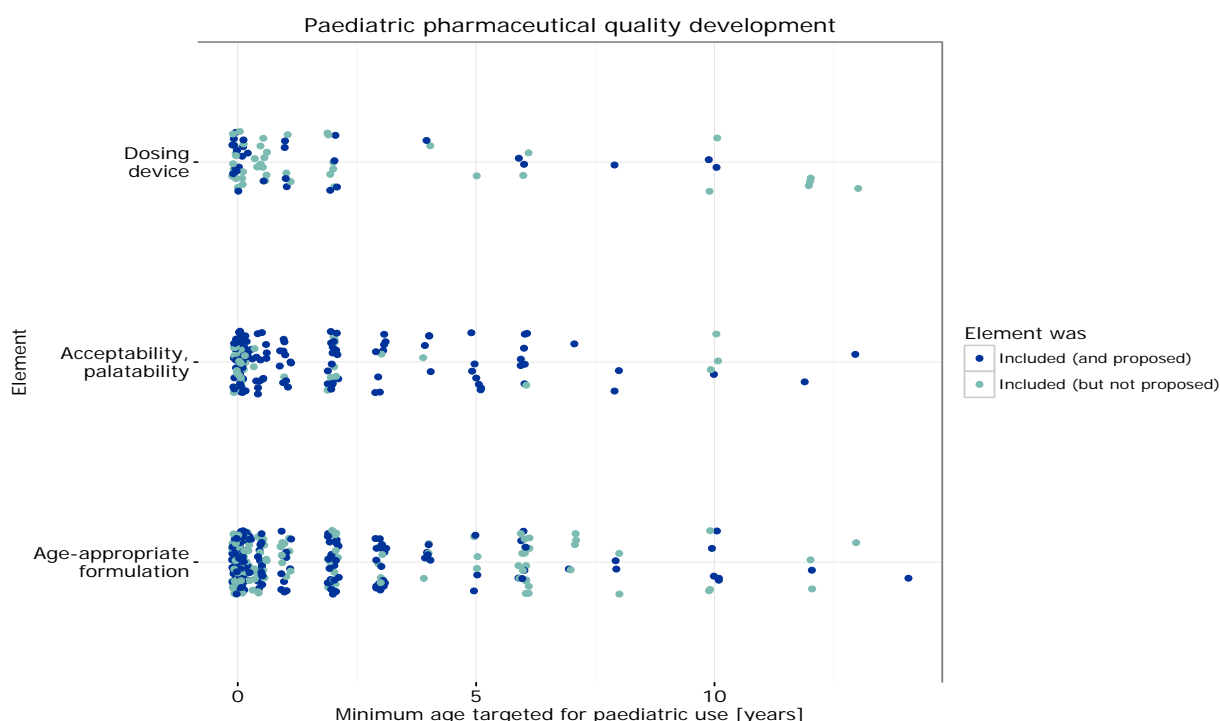
Approximately 40% of agreed PIPs include a specific measure to develop an age appropriate formulation and 10% included a request for a specific administration device. However, in many cases an age-appropriate form already existed, or the form for adults was also appropriate for the paediatric target age range.

In vaccines and other injectable medicines, the number of requests for age appropriate formulations is low. If it is required it would typically be for a specific strength of the formulation for paediatric use. In areas such as psychiatry, which affect mainly adolescents, again a low number of requests were made as the adult formulation is usually equally suitable.

As expected, in neonatology and diseases which affect children from birth, a high percentage of PIPs contained a request for specific age appropriate formulation(s).

The relation of paediatric target age range and need for pharmaceutical quality development is shown in Figure 7.

Figure 7. Proposals and requirements for pharmaceutical quality elements.



Note: Included (and proposed): element included in the PIP opinion as proposed by the applicant; included (but not proposed): element included in the PIP opinion as requested by the PDCO but not proposed by the applicant.

Source: EMA database (PedRA extension).

Acceptability and palatability testing is an integral part of medicine development for children. As shown in a survey (Participation of children and young people in PDCO activities, see 4.1.) poor palatability such as bad taste or after-taste is one of the main limiting factors for children accepting medicines. Furthermore, acceptability and palatability tests in adults can not usually be extrapolated to children. These tests can be conducted within the paediatric efficacy/safety trials or separately. Approximately 20% of all PIP opinions include explicit measures in this regard.

The '[Guideline on pharmaceutical development of medicines for paediatric use](#)', in the drafting of which several PDCO members were involved, provides recommendations to be considered when developing a paediatric formulation.

Excipients guideline review

The EMA, in collaboration with experts from NCAs, is currently revising the European Commission [‘Guideline on excipients in the label and package leaflet of medicinal products for human use \(CPMP/463/00 Rev. 1\)’](#), reviewing the literature and highlighting the gaps in knowledge for the paediatric population.

This revision is carried out by the Excipients Drafting Group (ExcpDG), which focuses its work on the scientific safety concerns of excipients used in medicines. In particular, the group has already finalised assessment of eight excipients (benzyl alcohol, benzoic acid and benzoates, benzalkonium chloride, gluten as a constituent of wheat starch, propylene glycol, cyclodextrins, sodium laurylsulfate and sodium) while work on 14 others is close to finalisation or ongoing.

3.4. Addressing needs of neonates

Medicine development for newborns presents additional challenges compared to the development for older children because they are the most vulnerable population, with the highest dependency on others to respect ethical principles, and because of specific disease characteristics.

Analysis by therapeutic areas

The classification system for PIPs and waivers uses “neonatology and paediatric intensive care” alongside the other established therapeutic areas. Usually these are determined within the submission by the applicant. As “neonatology” is defined by the age group, it follows that they are also included in other therapeutic areas. Table 14. shows the inclusion of the neonatal age group into paediatric development programmes (conditions) within PIPs.

Table 14. Inclusion of neonates in PIP development programmes (conditions) by therapeutic area.

Therapeutic area	Total number of PIP conditions	Including neonates	Including preterm neonates	Including term neonates	Neonates proposed- (requested) ¹	Not including neonates
Anaesthesiology	3	1 (33.3%)	0	1	1 (0)	2
Cardiovascular total	48	28 (58.3%)	7	25	17 (11)	20
• Cardiovascular diseases	46	26	5	23	15 (11)	20
• Neonatology cardiovascular	2	2	2	2	2 (0)	0
Dermatology	34	4 (11.8%)	0	4	3 (1)	30
Diagnostics	10	5 (50%)	1	5	3 (2)	5
Endocrinology-gynaecology-fertility-metabolism	91	15 (16.5%)	3	15	11 (4)	76
Gastroenterology-hepatology	37	6 (16.2%)	1	5	6 (0)	31
TOTAL						
• Gastroenterology-hepatology	36	5	0	5	5 (0)	31
• Neonatology gastroenterology	1	1	1	0	1 (0)	

Therapeutic area	Total number of PIP conditions	Including neonates	Including preterm neonates	Including term neonates	Neonates proposed- (requested) ¹	Not including neonates
Haematology-haemostaseology	48	25 (52.1%)	5	25	20 (5)	23
Immunology-rheumatology-transplantation total	67	6 (9.0%)	3	6	4 (2)	61
• Immunology-rheumatology-transplantation (ex neo)	66	5	2	5	4 (1)	61
• Neonatology immunology	1	1	1	1	0 (1)	
Infectious diseases total	122	46 (37.7%)	23	45	35 (11)	76
• Infectious diseases (ex neo)	117	41	19	41	30 (11)	76
• Neonatology infection (0- 3 Mo)	5	5	4	4	5 (0)	
Paediatric intensive care (1-18 yrs)	1	1 (100%)	0	1	0 (1)	0
Neurology TOTAL	57	20 (35.1%)	5	20	5 (15)	37
• Neurology	55	18	4	18	4 (14)	37
• Neonatology neurology	2	2	1	2	1 (1)	
Nutrition	2	2 (100%)	2	2	2 (0)	0
Oncology	79	19 (24.1%)	0	19	7 (12)	60
Ophthalmology total	18	3 (16.7%)	2	2	3 (0)	15
• Ophthalmology	17	2	1	2	2 (0)	15
• Neonatology ophthalmology	1	1	1	0	1 (0)	
Oto-rhino-laryngology	2	0	0	0		2
Pain	13	8 (61.5%)	5	8	6 (2)	5
Pneumology – allergology total	38	6 (15.8%)	3	4	4 (0)	32
• Pneumology - allergology	36	4	1	4	4 (0)	32
• Neonatology pulmonology	2	2	2	0	2 (0)	
Psychiatry	23	0	0	0		23
Uro-nephrology	21	0	0	0		21
Vaccines	42	4 (9.5%)	2	4	3 (1)	38
Total	756	199 (26.3%)	73	180	132 (67)	557

Note: ¹Proposed by applicant, requested by PDCO.

Source: EMA databases (PedRA, PedRA extension)

Neonates were included in 26.3% of all analysed development programmes, in 132 (17.4%) cases trials in neonates were already proposed by the applicant at the time of PIP submission, whereas in 67 (8.8%) cases the inclusion was requested by the PDCO. Neurology and oncology were the areas with the highest percentage of studies in neonates requested by the PDCO, 75% and 63.2%, respectively.

Some therapeutic areas, i.e. uro-nephrology, psychiatry and oto-rhino-laryngology do not include any studies with neonates. In other areas, such as nutrition and paediatric intensive care, every development programme included neonates in studies.

Over half of all programmes for cardiovascular diseases (58.3%) and haematology-haemostaseology (52.1%) included the neonatal population. About one third of all developments in anaesthesiology (33.3%), neurology (35.1%) and infectious diseases (37.7%), 24.1% in oncology, and under 20% in pneumonology (15.8%) and ophthalmology (16.7%) included neonates in studies. The smallest number of neonates was seen in developments related to immunology: dermatology (11.8%), immunology-rheumatology-transplantation (9.0%) and vaccines (9.5%).

Overall, most studies in neonates include 2.5 times more term than preterm newborns. Some areas, such as dermatology, oncology and anaesthesiology which also show low overall inclusion of neonates in studies include only term neonates.

The highest ratio of about 50% of programmes including preterm neonates was seen in the areas vaccines and infectious diseases.

Analysis by neonatal priorities

In 2015, the International Neonatal Consortium (INC) was launched. Under the auspices of the [Critical Path Institute](#), stakeholders involved in the area of neonatal medicines, i.e. parents, clinicians, researchers, industry and regulators, created working groups to develop more efficient regulatory pathways in the areas defined as highest priority.

The following overview includes PIPs in areas which have been identified by INC as priorities for the development of neonatal medicines. For the areas of neonatal gastrointestinal injury (e.g. NEC) and neonatal abstinence syndrome (NAS) no PIPs have been submitted.

Table 15. Agreed PIPs for prioritised conditions in neonatology

Condition	Neonates only	Neonates and children
Neonatal brain injury	<ul style="list-style-type: none"> Perinatal asphyxia: 2-iminobiotin 	Neonatal seizures: <ul style="list-style-type: none"> retigabine lacosamide carisbamate brivaracetam
Neonatal lung injury and circulatory failure	Bronchopulmonary dysplasia: <ul style="list-style-type: none"> budenoside azithromycin 	Pulmonary arterial hypertension/pulmonary hypertension of the newborn: <ul style="list-style-type: none"> treprostinil sildenafil tadalafil riociguat bosentan macitentan

Condition	Neonates only	Neonates and children
	Neonatal circulatory failure: <ul style="list-style-type: none"> • dobutamine 	Hypotension in the extremely low gestational age newborn: <ul style="list-style-type: none"> • dopamine
Neonatal ophthalmology	Retinopathy of prematurity: <ul style="list-style-type: none"> • ranibizumab 	
Perinatal/neonatal infections	Prevention <ul style="list-style-type: none"> • pagibaximab 	Treatment: <ul style="list-style-type: none"> • vancomycin • meropenem • eritoran • trombomodulin alfa • ceftriaxone/sulbactam • isavocunazonium • posaconazole • caspofungin

Source: EMA database (PedRA).

Table 16. Agreed PIPs for additional neonatal indications

Indication	Neonates only	Neonates and children
Pain	<ul style="list-style-type: none"> • paracetamol (moderate) 	<ul style="list-style-type: none"> • glucose (procedural) • tapentadol (acute-chron) • morphine (moderate, severe, prolonged) • fentanyl citrate (acute, pre-medication)
Nutrition	Prevention of growth retardation due to lack of bile-stimulated lipase in enteral nutrition: <ul style="list-style-type: none"> • bucelipase alfa 	Supplementation of amino-acids where parenteral nutrition is required: <ul style="list-style-type: none"> • Neoven (paediatric development discontinued)

Source: EMA database (PedRA).

3.5. 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 the development of medicines. EMA SA, which is open to pharmaceutical companies, academia and other parties developing medicines, is free of charge for paediatric questions (Article 26). SA may address paediatric matters only or combined paediatric and adult ones. Companies conducting their clinical developments in accordance with SA recommendations are more likely to be granted a marketing authorisation (Hofer et al, 2015).

The number of companies requesting paediatric SA is increasing every year. In 2007 only 7.6% of scientific advice was related to paediatric matters in comparison to 24.4% in 2016. The PDCO collaborates closely with EMA's Scientific Advice Working Party (SAWP) to address questions on pharmaceutical, non-clinical and clinical development.

As documented in Table 17. , PDCO members are systematically involved as experts in SA/protocol assistance (PA) procedures in which paediatric questions are concerned. Although PDCO members and alternates have contributed to SA since 2007, this has only been formally documented since 2009. The PDCO provided paediatric expertise most often on clinical development but also on pharmaceutical and non-clinical development.

The collaboration between SAWP and PDCO ensures optimisation of the paediatric development and a link to CHMP and the marketing authorisation process. It is of particular importance if innovative trial designs and extrapolation approaches (informed also by high quality data from adult studies) are used.

Table 17. CHMP Scientific Advice and Protocol Assistance (including follow-up)

Year	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
Total number of advice procedures (Scientific Advice and Protocol Assistance) ¹	277	321	388	400	433	420	473	551	510	582	4355
Number of paediatric-only and mixed (adult and paediatric development questions) advice procedures ¹	21	32	74	80	57	91	96	97 ³	109 ⁴	142 ⁴	799
Number of paediatric-only or mixed advice procedures that involved a PDCO member(s) ²	ND	ND	68	80	55	91	93	88	97	138	710

Note: ¹Year of advice letter; ²Year of start of procedure; ³Including qualification of biomarker procedures; ⁴Including qualification of biomarker procedures and HTA parallel scientific advice; ND = Not documented.

Source: EMA databases.

Scientific advice on paediatric matters is also provided at national level. According to data collected from 2010 until the end of 2016, more than 350 SA procedures on paediatric development were conducted by 10 Member States. Further details can be found in the [annual reports](#).

3.6. Paediatric research incentives

3.6.1. European Union funding

Article 40 refers to Community funding for research into off-patent medicinal products. The funding should cover the development of off-patent medicinal products with a view to the submission of a Paediatric Use Marketing Authorisation (PUMA).

In agreement with DG Research of the European Commission and in order to ensure that funds are directed to research of medicinal products with the highest needs in the paediatric population, the PDCO 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>).

The seventh call was the final call within Framework Programme 7 (FP7).

To date, 21 projects on at least 26 off-patent medicines (active substances) have received EU funding as part of the area HEALTH-(2007-2011)-4.2-1, and two investigator-driven clinical trials for off-patent medicines are funded as part of another area, HEALTH.2011.2.3.1-1 (Ruggieri et al., 2015).

The full list of projects is provided in the Annex.

Funding for off-patent medicines for paediatric use under FP 7 led to significant results in neglected areas. These projects are performing high-quality research and are progressing towards the increase of new paediatric medicines on the market (Ruggieri et al., 2015). Such research projects can still be funded within Horizon 2020, in particular those indicated for rare diseases, but have to compete with large non-paediatric projects. EU funding provisions specific to paediatrics are crucial to facilitate research and development projects in paediatrics, such as PUMA projects and new technologies.

3.6.2. National funding

Some initiatives have been taken at national level for funding research and development of medicinal products for paediatric use. From 2007 to 2015, feedback from the Member States has been received and collected in the annual reports to the EC. A summary of the feedback received is presented in the Annex.

3.7. Paediatric clinical trials

3.7.1. Clinical trials database and register

One of the achievements of the implementation of the Paediatric Regulation (Article 41) is the public availability of information on paediatric clinical trials. Protocol-related information from the European Clinical Trials Database (EudraCT) became publicly available via the European Clinical Trials Register (EU-CTR, <https://www.clinicaltrialsregister.eu/>) in March 2011. Posting and publication of results-related information became mandatory in July 2014. This achievement provides systematic disclosure of searchable information about ongoing and completed interventional clinical trials registered in the EU and interventional clinical trials which are included in an agreed PIP. It contributes to preventing selective reporting and provides a crucial information tool for patients, parents and clinicians to research data and potentially beneficial experimental therapies. Study features specific to paediatric trials have been implemented in the EudraCT results data model (e.g. number of children in the trial by age group(s), measures for protection of trial subjects).

In addition to ad-hoc consultations by public users the EU-CTR permits subscription to an automatic notification system so that interested parties can receive information, for example related to safety and the safeguarding of children, as soon as this information is made public.

3.7.2. Authorisation of paediatric clinical trials

Clinical trials in the EU are authorised by the Member States hosting trial sites. The National Competent Authorities (NCA) upload the clinical trial applications (protocol-related information) and the authorisation details to the European Clinical Trials Database (EudraCT). The data presented in this chapter were extracted from the protocol-related information in EudraCT. It is important to note that the completion of some data fields in EudraCT is not mandatory, including some that are relevant for paediatric information. While this may impact the quality of the data provided, it is expected that the data give a good approximation of the actual numbers. A description of EudraCT data filters used to create the analyses is provided in the Annex.

The total number of authorised paediatric trials planned to be initiated in a given year has remained fairly stable from 2006 to 2016. The proportion of new paediatric trials compared to all newly initiated trials has increased, from 9.3% in 2006 to 12.4% in 2016 (Table 18. , Figure 9.). However, the exact number is unknown as it is not mandatory to record this information in the database. As many paediatric studies in agreed PIPs are deferred until sufficient data on safety and efficacy are available in adults or older age-groups it is expected that they will only be recorded in EudraCT in the future.

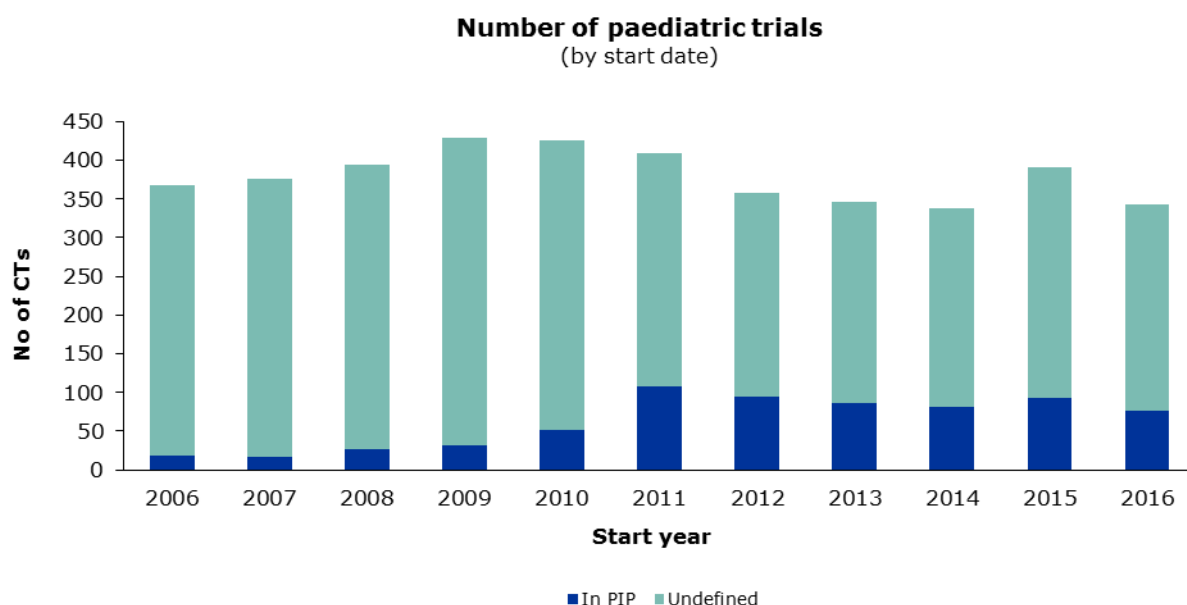
Table 18. Authorised paediatric clinical trials by start date¹

Trials	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Paediatric ² trials	368	375	394	428	425	408	357	346	338	390	343
Total number of trials	3938	4543	4371	4327	3903	3861	3539	3335	3324	3363	2763
Proportion of paediatric trials of all trials (%)	9.34	8.25	9.01	9.89	10.89	10.57	10.09	10.37	10.17	11.60	12.41
Paediatric trials marked as being included in agreed PIPs ³	18	16	26	32	51	107	95	87	81	93	77
Exclusively ⁴ paediatric trials	216	198	229	257	260	257	218	202	207	234	197

Note: ¹ Start date according to planned start of recruitment (if not available then according to NCA review date; if not available then according to upload date). ² A paediatric trial is a trial that includes at least one participant below 18 years of age. ³ It is not mandatory in the EudraCT database to state whether a trial is included in an agreed PIP. ⁴ An exclusively paediatric trial is a trial that includes only participants below 18 years of age.

Source: EudraCT database.

Figure 8. Absolute number of authorised paediatric clinical trials¹ by start date²

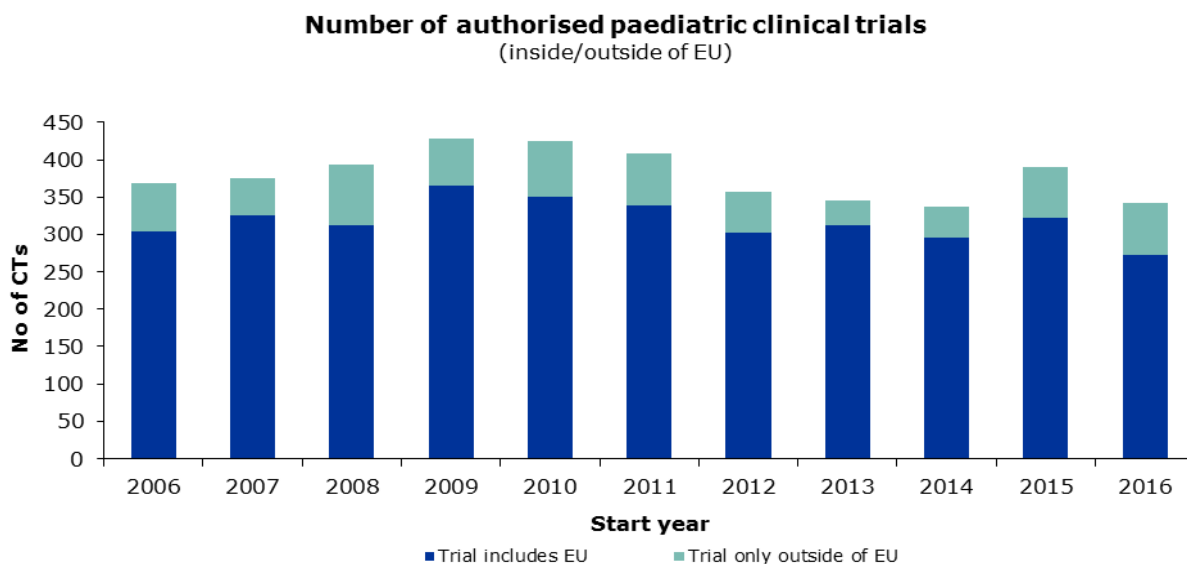


Note: ¹ A paediatric trial is a trial that includes at least one participant below 18 years of age. ² Start date according to planned start of recruitment (if not available then according to NCA review date; if not available then according to upload date).

Source: EudraCT database.

Some of the paediatric trials are conducted exclusively outside the European Union ("third-country trials") but are recorded in the database because they are part of an agreed PIP or in scope of Article 46 of the Paediatric Regulation (Figure 9.).

Figure 9. Number of authorised paediatric clinical trials¹ inside/outside of the EU, by start date²



Note: ¹A paediatric trial is a trial that includes at least one participant below 18 years of age. ²Start date according to planned start of recruitment (if not available then according to NCA review date; if not available then according to upload date).

Source: EudraCT database.

Based on data extracted from the EudraCT database, the planned number of study participants is presented in Table 19.

Table 19. Number of children planned to be enrolled in authorised clinical trials, by start date¹

Year	Preterm newborns	Newborns	Infants and toddlers	Children	Adolescents	Total
2006	1	901	19909	6641	4164	31616
2007	0	2	32293	5298	41191	78784
2008	226	181	23964	8196	4079	36646
2009	0	61	78514	14402	7945	100922
2010	39	104	22851	13388	7352	43734
2011	2659	1848	31081	59321	38590	133499
2012	1329	3069	22632	23326	21592	71948
2013	3190	770	14808	31375	21179	71322
2014	2574	1281	20425	26561	20838	71679
2015	2006	10394	28432	20042	19829	80703
2016	2844	830	8830	20248	14533	47285

Note: ¹Start date according to planned start of recruitment (if not available then according to NCA review date; if not available then according to upload date).

Source: EudraCT database.

Similar to the annual number of newly started paediatric trials, the number of paediatric study participants in clinical trials has not changed significantly from 216,352 in 2007-2009 to 199,667 in 2014-2016.

The number of neonates (preterm and term newborns) planned to be included in the trials loaded into the EudraCT database has increased by more than 40-fold between the two periods compared: from 470 in 2007-2009 to 19,929 in 2014-2016.

It is difficult to describe any further trends as the subject numbers are influenced by some trials that include high numbers of children (e.g. for vaccines); the initiation of these trials in a given year may significantly skew the data, as shown by the wide fluctuation in patient numbers.

The main design features of paediatric trials are presented in the Annex.

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).

An exploratory analysis of European paediatric trials was conducted aiming at identifying those trials that may contribute data for regulatory submissions targeting new indications, pharmaceutical forms, or routes of administration, i.e. those submissions which are in the remit of the Paediatric Regulation. The following categories of trials were identified as potential confounding factors and where therefore excluded:

- Extension- or follow-up studies;
- Trials that include adolescents as the only paediatric age-group and are primarily recruiting adults;
- Trials which are documented to be phase 4 because it is not clear if the categorisation as phase 4 is in relation to a paediatric or adult indication;
- Vaccine trials because the development of most vaccines even prior to the implementation of the Regulation included children;
- Trials conducted by non-commercial sponsors because in many cases they do not target regulatory submissions

When focusing on paediatric trials which are expected to contribute data for regulatory submissions in the scope of the Paediatric Regulation the number of studies conducted in Europe almost doubled from 96 in 2007-2009 to 164 in 2014-2016 (Table 20. , Figure 10.).

Table 20. Authorised paediatric clinical trials expected to contribute data for regulatory use¹, by start date²

Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Paediatric ³ trials	25	30	31	35	42	52	48	48	58	62	44

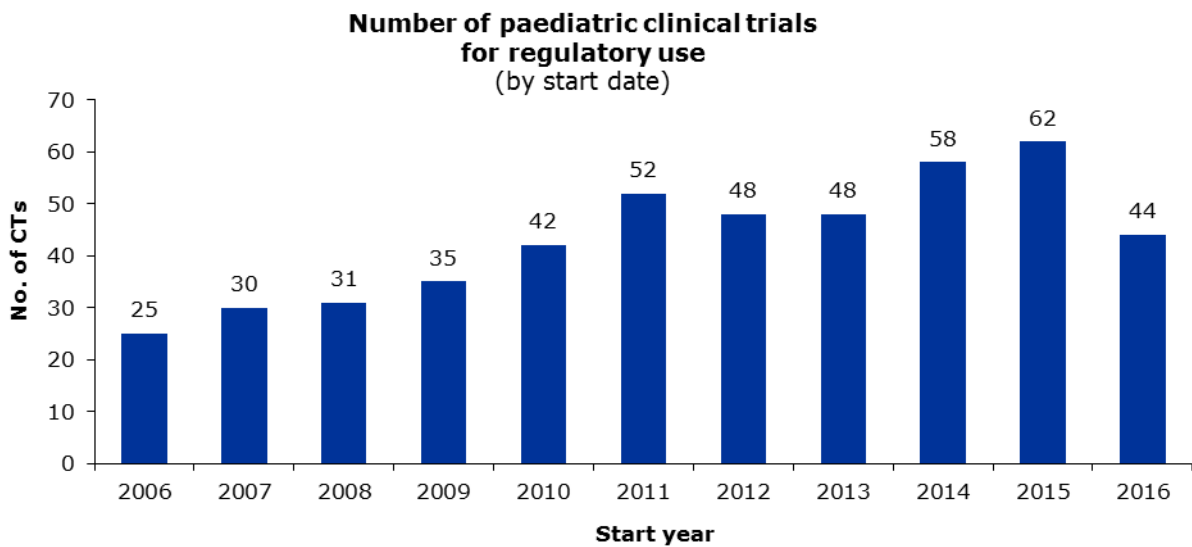
Note: ¹ Paediatric trials in this analysis meet the following criteria: at least one site in the EEA, a commercial sponsor (or part of PIP), more paediatric age-groups included than only adolescents, phase 1-3 (or part of PIP), not an extension or follow-up study or vaccine trial.

² Start date according to planned start of recruitment (if not available then according to NCA review date; if not available then according to upload date).

³ A paediatric trial is a trial that includes at least one participant below 18 years of age.

Source: EudraCT database.

Figure 10. Authorised paediatric clinical trials expected to contribute data for regulatory use



Source: EudraCT database.

The completeness and quality of data in EudraCT for the purpose of the analysis of trial details and design features are not exhaustive because completion of certain data fields is not mandatory; additionally, the EMA has no control over the quality and completeness of the records entered in the database.

Results-related information has been uploaded to EudraCT for more than 1,600 paediatric trials. However, no detailed analyses can be carried out to date. It is expected that functionality to report on results-related data in EudraCT will be implemented once the EU Clinical Trials Portal is launched as part of the implementation of the [Clinical Trial Regulation](#).

3.7.3. Difficulties in conducting and completing paediatric clinical trials

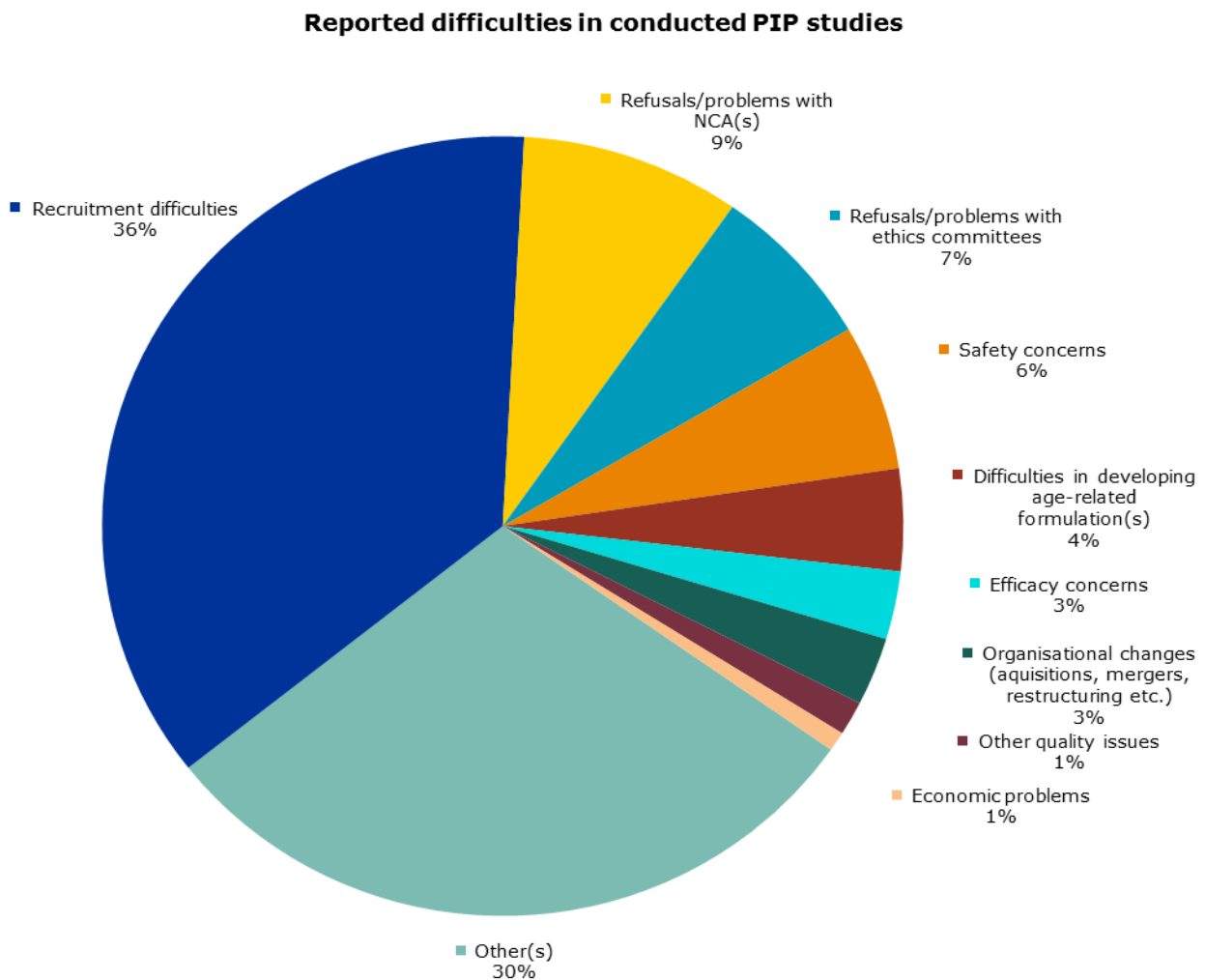
Once a medicinal product with a PIP obtains marketing authorisation in adults, the EMA receives annual reports on the paediatric measures/studies that have been deferred, i.e. that are allowed to be completed after marketing authorisation is obtained.

In these reports, companies are asked to comment on whether the PIP as a whole is progressing as planned or not; for all reports received up to 31/12/2015, the PIP was progressing as planned in 57% of the reports. For the 43% of PIPs not progressing as planned, specific reasons were reported, and are shown in Figure 11.

It can clearly be seen that the most frequent difficulties pertain to recruitment (36% of reports).

The analysis of the report data suffers from some limitations. First, once a product is authorised the reports are sent every year until the PIP is completed, therefore more than one report for the same product is included in the global analysis (at the same time, difficulties may change over time). Secondly, the obligation to submit annual reports only exists for products once they are authorised; therefore, the EMA does not receive data on the difficulties in conducting paediatric studies/measures before the product is authorised.

Figure 11. Reported difficulties in conducting PIP studies (2007-2015)

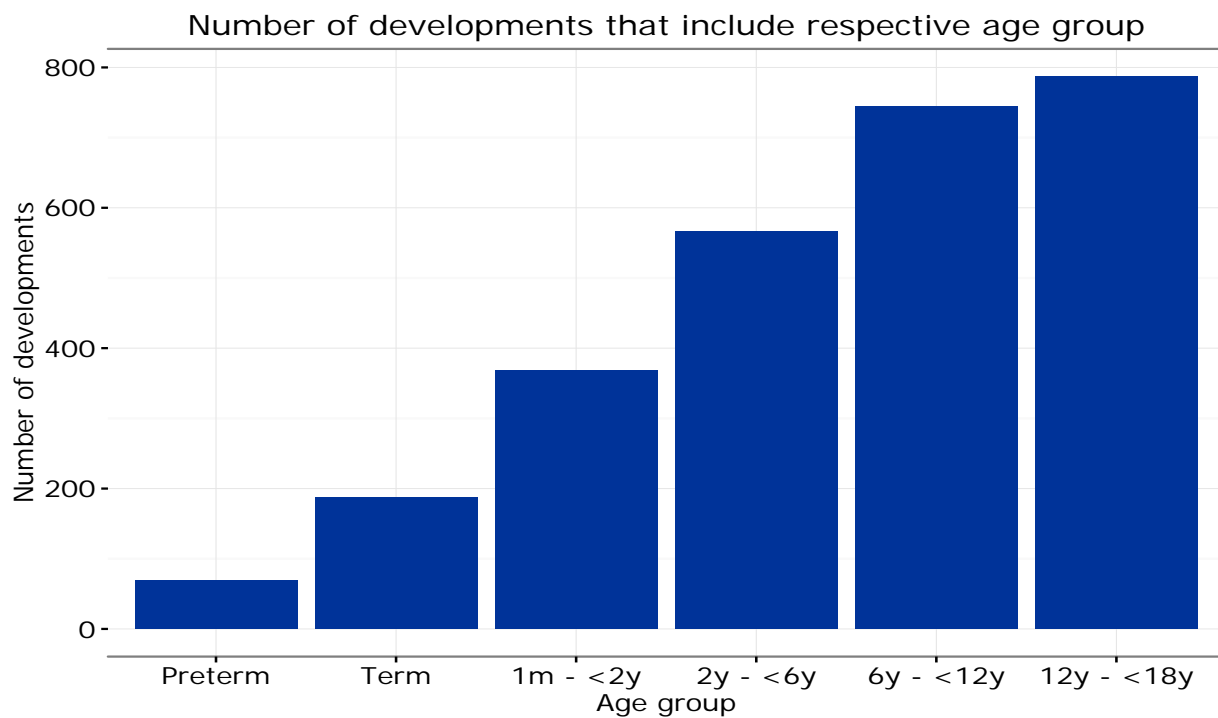


Source: EMA database (PedRA).

3.8. Inclusion of paediatric age groups in agreed PIP studies

The involvement of children in studies in agreed PIPs was analysed. It is clear that older children and adolescents are more often studied than younger children (Figure 12.). As medicine development is usually driven by adult needs, such medicines may be of more relevance to adolescent patients than to younger ones (e.g. medicines for type 2 diabetes, contraceptives, anti-psychotics). However, developments for diseases which are also of concern to young children (e.g. infections, asthma, juvenile idiopathic arthritis) include also the youngest age-groups.

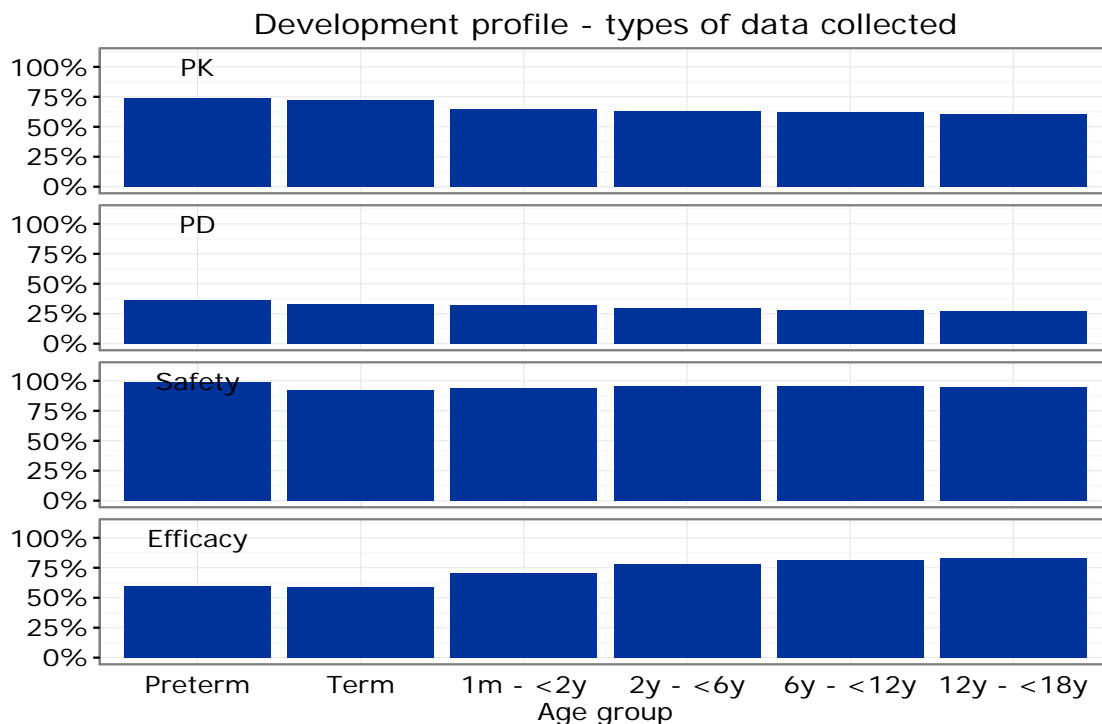
Figure 12. Number of developments including respective age groups.



Source: EMA database (PedRA extension).

An analysis of the type of data showed that pharmacokinetic data are to be collected in youngest age groups (less to 6 years of age) proportionally more often than in older age groups, and efficacy data less often (Figure 13.).

Figure 13. Proportion of developments by age group and type of study (pharmacokinetics (PK), pharmacodynamics (PD), safety and efficacy).



Source: EMA database (PedRA extension).

This analysis includes developments in agreed PIPs across all therapeutic areas, and this may mask more pronounced differences. Given the challenges of conducting clinical trials in the youngest age groups, data from older children and extrapolation and modelling approaches can be and are used to complement and strengthen the data, as described in section 2.10.

3.8.1. GCP Inspections

Regulatory authorities generally consider inclusion in clinical trials of vulnerable patients, such as children, as a factor that can trigger routine GCP inspections of trial sites. These inspections allow for a close scrutiny of GCP (Good Clinical Practice) compliance. Between 2007 and 2015, 70 GCP inspections of paediatric trial sites were coordinated by the EMA. These inspections were performed at the request of the CHMP for products undergoing the centralised marketing authorisation procedure. Therefore, the presented data are only a subset of the total number of inspections performed by EU and third country regulatory authorities of the countries where the clinical trials related to EU medicine development took place. The highest number of inspections was carried out in 2014 (19 sites), 2011, 2012, 2013 and 2015 (11 sites each, Table 21.). During the same period, the total number of site inspections coordinated by the EMA, including those involving trials conducted only in adults, was 529. Of note, inspections are counted by site, and several sites could relate to a single medicinal product.

The 70 paediatric sites inspected cover 29 medicinal products: eight vaccines, eight products used in diseases caused by inborn errors (e.g. adenosine deaminase deficiency (ADA-SCID), Duchenne muscular dystrophy, haemophilia, primary immunodeficiency, urea-cycle disorders and cystic fibrosis), four anti-viral drugs, four oncology products and five products intended to treat other diseases (malaria, growth hormone deficiency, severe veno-occlusive disease following haematopoietic stem cell transplantation, proliferating haemangioma and attention deficit hyperactivity disorder [ADHD]).

The GCP inspections identified 60 critical deficiencies, 434 major deficiencies and 498 minor deficiencies - on average 0.9 critical deficiencies and 6.2 major deficiencies per paediatric clinical trial site (Table 21.). Most of the 60 critical deficiencies (25) were related to inadequate trial management; in addition, eight deficiencies concerned lack of protocol compliance, seven inadequacies related to essential documents or standard operating procedures, five had to do with improper subject protection (safety and well-being, personal data and design of the trial), five concerned failures related to the product manufacturing and accountability, two were related to informed consent procedures and two with Institutional Review Boards/Institutional Ethics Committees. The subjects responsible for the major deficiencies identified were the sponsor (n=34; 57%), the investigator (n=4; 7%), multiple subjects (n=21; 35%) or an external laboratory (n=1; 2%). A comparison of GCP inspections between paediatric and all trials indicates that the number of critical and major findings per inspected site is similar when considering all trials or paediatric trials only (Table 21. and Table 22.). The grading of inspection findings and the duties and responsibilities of inspectors are outlined in the [Procedure for reporting of GCP inspections requested by the Committee for Medicinal Products for Human Use \(CHMP\)](#). No significant trends were identified in relation to time or to deficiency type.

It is the responsibility of the inspectors not only to grade the findings in an inspection, but also to measure to what extent the findings affect the overall compliance with GCP standards of the conduct of the trial, and comment on the reliability of the data generated in the clinical trials submitted in support of a marketing authorisation application. For inspections requested by the CHMP, critical findings in clinical trials with the paediatric population represented around 6% of the total number of findings, the same percentage as in all trials (adult and paediatric). Moreover, it should be clarified that even where critical findings were reported the overall conduct of the clinical trial was classified as GCP compliant and the data were judged reliable for use in the evaluation procedure in the majority of cases. It should also be taken into account that some deficiencies have only relevance to or may have a higher impact on children (for example, deficiencies relating to informed consent/assent) and may therefore be reported only in paediatric clinical trials.

Table 21. Deficiencies identified in 70 GCP inspections of paediatric clinical trial sites

Deficiencies by year	Critical	Major	Minor	Total	No. Insp. sites	Crit. per insp. site	Major per insp. site
2007	3	5	5	13	1	3.0	5.0
2008	0	0	0	0	0	0	0
2009	3	13	24	40	4	0.8	3.3
2010	0	11	10	21	2	0.0	5.5
2011	13	83	135	231	11	1.2	7.5
2012	7	58	62	127	11	0.6	5.3
2013	5	102	73	180	11	0.5	9.3
2014	22	108	118	248	19	1.2	5.7
2015	7	54	71	132	11	0.6	4.9
TOTAL	60	434	498	992	70	0.9	6.2

Note: In 2008 no inspections of paediatric clinical trials took place.

Source: EMA database (Corporate GxP).

Table 22. Deficiencies identified in 529 GCP inspections of clinical trial sites

Deficiencies by year	Critical	Major	Minor	Total	No. Insp. sites	Crit. per insp. site	Major per insp. site
2007	47	265	180	492	32	1.5	8.3
2008	45	329	272	646	52	0.9	6.3
2009	56	294	302	652	45	1.2	6.5
2010	66	465	538	1069	69	1.0	6.7
2011	32	254	364	650	45	0.7	5.6
2012	37	391	488	916	71	0.5	5.5
2013	64	429	559	1052	83	0.8	5.2
2014	30	290	353	673	57	0.5	5.1
2015	106	449	357	912	75	1.4	6.0
TOTAL	483	3166	3413	7062	529	0.9	6.0

Source: EMA database (Corporate GxP).

3.8.2. 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 23. shows that there was no increase 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.

Table 23. Paediatric trials which were prematurely terminated or temporarily halted

Number of trials ¹	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Any reason	24	23	37	37	38	31	23	17	14	7
Reason IMP quality	0	0	0	0	1	0	1	0	0	0
Reason lack of efficacy	1	1	2	4	1	3	2	1	0	1
Reason not commenced	4	7	9	8	5	6	5	10	0	1
Reason safety	3	3	2	3	2	1	3	1	2	1
Reason other	23	20	32	31	27	19	13	5	9	4

Note: ¹The analysis may include paediatric trials that were terminated/halted due to signals in a related adult trial.
Source: EudraCT database.

3.9. Interactions with ethics committees

Ethical review of paediatric clinical trial protocols before trial authorisation is of utmost importance to safeguarding children who may participate in such research. However, since implementation of the Paediatric Regulation it has become apparent that historical reservations about clinical research involving children and a lack of awareness of the aims of the Paediatric Regulation still persist among researchers or ethics committee members, which may in turn lead to the rejection of paediatric protocols. Therefore, an interaction and exchange of information with ethics committees had to be built. The EMA and PDCO put efforts into developing relationships with ethics committees through workshops and guideline development.

A [workshop](#) with ethics committees took place at the EMA in 2011. This meeting brought together 25 ethics committee members representing 15 Member States, European regulators, members of paediatric research networks and clinical researchers, as well as representatives of pharmaceutical companies. It strengthened the relationship of all groups involved and highlighted the shared ethical responsibilities for progress in science and health of children.

In addition, many PDCO members were involved in individual interactions with ethics committees. A questionnaire regarding interactions with ethics committees was sent to all active PDCO members and alternates. The questions intended to capture interactions on general topics relating to paediatric clinical research and on specific issues relating to paediatric clinical trials included in PIPs between January 2007 and December 2015.

Responses were received from 38 PDCO members (38/66, 58%). Of these, seven (7/38; 18%) are or were members of ethics committees themselves. Four members (4/38; 10%) participated in congresses addressed to ethics committees in the years immediately following the entering into force of the Paediatric Regulation, specifically in 2008 and 2009, to present the Paediatric Regulation and its objectives as well as to discuss specific issues related to the conduct of paediatric clinical trials (e.g., trial design, inclusion/exclusion criteria, use of placebo). Four members (4/38; 10%) attended regular ethics committee meetings, and three members (3/38; 8%) had been invited by ethics committees as representatives of the PDCO on at least one occasion. In one case a PDCO member took part in ethic committee discussions about a paediatric clinical trial included in an agreed PIP.

Finally, an analysis of EudraCT data has identified 98 instances of clinical trial applications for studies including children, which have received a refusal from an ethics committee in the EU. Fifteen of these were reported as being included in a PIP; however, for 48 instances no information about inclusion in a PIP was available. The reasons stated for the refusal are reported in Table 24. ; of note, in more than half of the cases no reason was reported (or is marked as "other" or "not specified").

Table 24. Negative opinions from national ethics committees

Reason for refusal	Total	Trial part of PIP?		
		No	Not answered	Yes
(left unanswered)	53	19	28	6
Other	16	5	7	4
Evaluation of the anticipated benefits and risks	13	10	0	3
Patient Information Sheet and consent form and procedure	13	5	7	1
Protocol	11	0	10	1
Control Group	10	4	1	5
Relevance of the Clinical Trial	6	6	0	0
Not specified	4	0	4	0
Clinical data	3	0	3	
Compliance with GCP	3	1	0	2
Inclusion of persons incapable of giving informed consent or other vulnerable populations	3	2	0	1
Compensations to investigators	2	2	0	0
Inclusion and exclusion criteria	2	2	0	0
Measures to minimise pain, discomfort and fear	2	2	0	0
Compensations to subjects	1	1	0	0
Data Protection and Confidentiality	1	1	0	0
Non-clinical pharmacology and toxicology data	1	0	1	0
Total	98	35	48	15

Source: EudraCT database.

The Paediatric Regulation has brought ethics committees and regulators closer together, recognising their shared responsibility for the progress of paediatric clinical research whilst safeguarding the children involved.

3.10. Extrapolation, modelling and simulation in PIPs

Clinical research in children should be conducted utilising the least number of children required to yield robust and meaningful results. Additionally, paediatric research often faces challenges due to the rarity of many paediatric diseases, heterogeneity of children with respect to age, development, and co-morbidity, and issues around consent to study participation. For these reasons, it is often not possible to generate a full data set in the paediatric population according to the usual regulatory standards.

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 PDCO actively contributes to facilitating the development and use of such means, including non-conventional trial designs.

Extrapolation is defined as extending information and conclusions available from studies in one or more subgroups of the patient population (source population(s), or in related conditions or with related medicinal products, to make inferences for another subgroup of the population (target population), or condition or product, thus reducing the need to generate additional information (types of studies, design modifications, number of patients required) to reach conclusions for the target population, or condition or medicinal product.

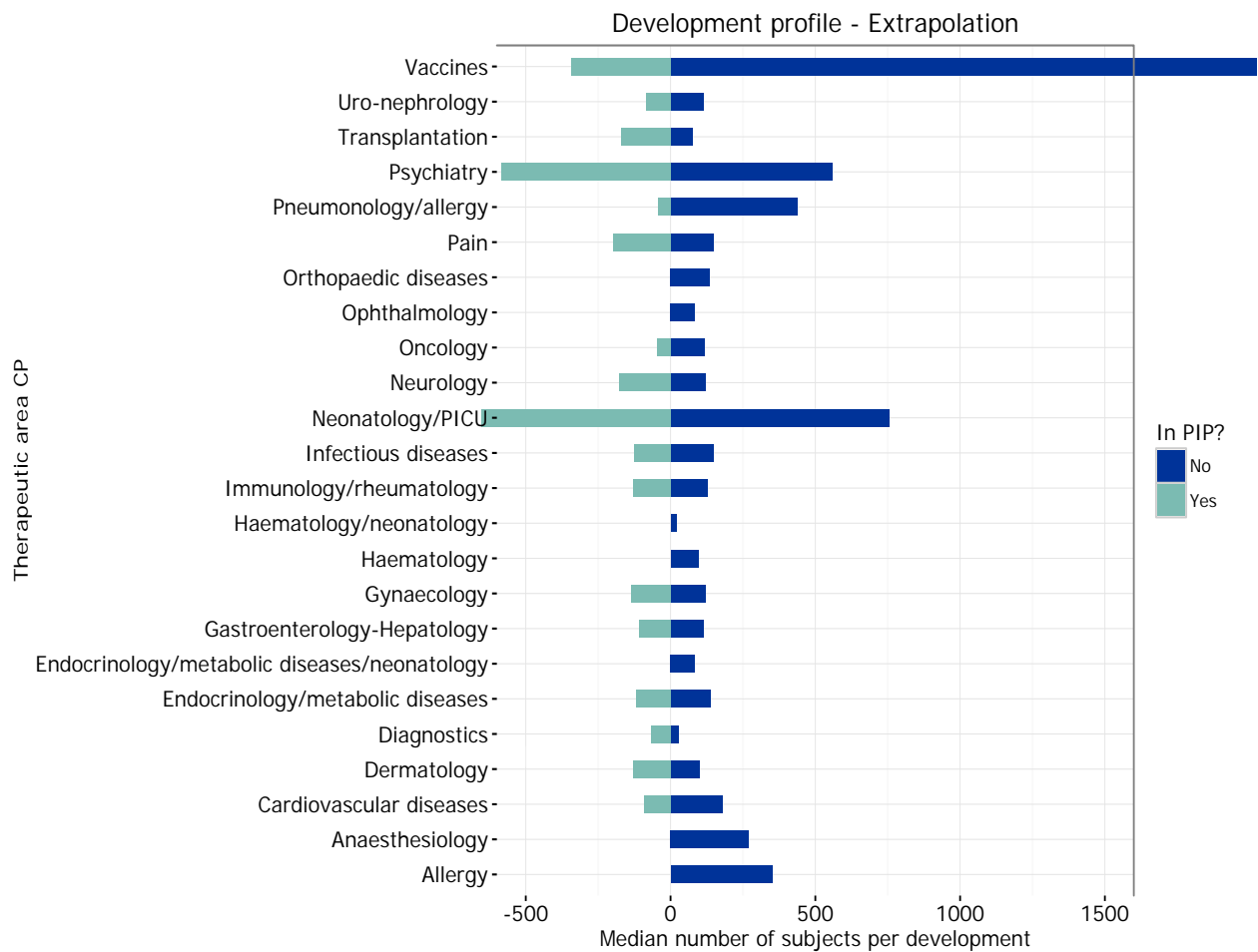
The EMA established an extrapolation expert group including clinicians, pharmacologists, pharmacometricians and statisticians from the EMA, NCAs and from academia.

In 2013, the [concept paper on extrapolation of efficacy and safety in medicine development](#) was published and a reflection paper is being developed. The aim of the reflection paper is to propose a framework that supports an explicit and systematic approach to extrapolation as basis for regulatory decision making in paediatric development across committees.

To date, 52 PIPs including explicit extrapolation measures have been agreed. Generally, extrapolation is limited to efficacy data; evaluation of safety requires studies in the target population due to differences in safety profiles between adults and children. An analysis according to therapeutic area showed that extrapolation of efficacy is most commonly part of the development of medicines for infectious diseases and oncology (about 20% of developments, respectively) and rarely part of the development of medicines in the areas of pneumonology/allergology and neurology as well as of vaccines. The anticipated impact of using extrapolation in PIPs was further analysed. For example, the median total number of paediatric subjects is generally lower when extrapolation is part of the development plan; however, the impact varies by therapeutic area and may not always lead to reduced sample sizes (Figure 14.). This is in line with the understanding that measures to extrapolate efficacy are relevant to strengthen the development and the interpretation of paediatric data; only as a consequence, the sample size may be reduced in some cases.

With the publication of the reflection paper in 2016, it is anticipated that the number of PIPs with extrapolation measures will increase. However even if the framework might not necessarily reduce the actual number of paediatric studies, it is anticipated that it should lead to an overall reduction in the number of children enrolled in paediatric studies, or at least minimise the number of subjects who are randomised to a sub-optimal dose, including placebo.

Figure 14. Impact of acceptability of extrapolation on sample size planning



Source: EMA database (PedRA extension).

In 2013, the EMA Modelling and Simulation Working Group (MSWG) was established in order to provide specialist scientific support on modelling and simulation to the SAWP, PDCO and CHMP. Models with covariates to account for growth and maturation are used to characterise and extend the PK/PD relationship from adults to children or between different paediatric age groups. Based on the projected PK/PD in children and taking into account the clinical context, decisions are made on paediatric doses and on the potential need for further clinical investigations, such as PK/PD and efficacy/safety studies, if uncertainties on the benefit-risk balance remain.

Whilst in the beginning most referrals to the MSWG came from the SAWP (56 out of 85 by December 2014 compared to 24 from the PDCO), in 2015 most referrals came from the PDCO (47 out of 90). This shows that modelling and simulation is increasingly becoming an important element of PIPs.

3.11. Innovation in PIPs

Since the adoption of ICH E11, guideline on "[Clinical Investigation of medicinal products in the paediatric population \(CPMP/ICH/2711/99\)](#)" in 2000, medicines development has evolved, regulatory requirements have changed, new infrastructure for complex paediatric trials has become available, and innovative therapies have emerged.

Several workshops have taken place to promote use of modelling and simulation in paediatric medicine development, such as:

- [Workshop on modelling in paediatric medicines \(2008\)](#);
- European Medicines Agency-European Federation of Pharmaceutical Industries and Associations modelling and simulation workshop (2011);
- European Medicines Agency/European Federation of Pharmaceutical Industries and Associations workshop on the importance of dose finding and dose selection for the successful development, licensing and lifecycle management of medicinal products (2014).

Under the FP7 Call – Health projects the EU has funded three international multidisciplinary research consortia aiming at the efficient assessment of the safety and/or efficacy of a treatment for small population groups including drug development for children.

The projects [ASTERIX](#) (Advances in small trials design for regulatory innovation and excellence), [IDEAL](#) (Integrated design and analysis of small population group trials), [InSPiRe](#) (Innovative methodology for small population research) were initiated in 2014. All three projects have created networks of clinical trial experts involving all relevant stakeholders such as academia, industry, regulators and patient advocacy groups. The aim of these projects is to identify the difficulties in clinical research in small populations and identify promising approaches to efficiently overcome them.

This cultural shift towards more innovative approaches in paediatric medicine development informs the current review of the addendum to ICH E11. The guideline aims to provide a harmonised approach within the member regions addressing topics such as novel methodologies (e.g. extrapolation, modelling and simulation, innovative trial designs).

Examples of innovative approaches

The PDCO seeks to promote recent scientific and clinical developments in PIPs with the aim to make medicines available for diseases without satisfactory therapeutic options. The collection of case examples provides a qualitative indicator of the introduction of some innovative elements into paediatric research and development by the PDCO.

Reflection of scientific or clinical advances and potential therapeutic advances:

- Inherited immune deficiency disorders: the PDCO approved development plans to investigate novel genetically modified T cells.
- Rare genetic disorders: the PDCO approved development plans for rare genetic disorders that, so far, had unsatisfactory therapeutic options such as metachromatic leukodystrophy, Wiskott-Aldrich Syndrome, osteogenesis imperfecta, adrenoleukodystrophy.
- Allergic conditions: the PDCO approved development plans for novel treatment options which represent innovations in their field such as peanut extracts or synthetic peptide immuno-regulatory epitopes.

- Diagnosis of tuberculosis: the PDCO approved a PIP for an innovative diagnostic tool for tuberculosis.
- Hepatitis C: the PDCO deprioritised when relevant development plans that included regimens with peginterferon to reflect recent therapeutic advances in direct antiviral therapy.

3.12. Animal studies for safer paediatric research

Non-clinical studies are conducted to support the development of medicinal products to be used in paediatric patients. The safety and efficacy profiles of a medicine can be different in adults and children, and non-clinical studies can help with identifying such differences. Serious adverse reactions that may be irreversible are of particular concern. Standard non-clinical studies on adult animals, or safety information from adult humans, cannot always adequately predict these differences in safety profiles for all paediatric age groups, especially effects on immature organs. There are several examples of medicinal products that have different safety profiles in adult compared with paediatric patients. Such differences might be qualitative and/or quantitative, immediate and/or delayed. They might be caused by pharmacokinetic/dynamic differences, developmental differences in growth, maturation and function of target organs/systems.

Studies in juvenile animals might be warranted even if animal data or adult human data have already predicted adverse reactions on developing organ(s), where there is a need to further address a specific concern or to study reversibility or possible worsening of the expected findings, as well as to establish safety factors.

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 facilitate a systematic approach to PIP evaluation. The group reviews the non-clinical strategy proposed by the applicant (including but not restricted to pharmacology, toxicology, pharmacokinetics/toxicokinetics) and suggests to PDCO which additional elements may be needed to support the development of paediatric medicines, including the need to perform juvenile toxicity studies on a case by case basis in compliance with existing guidelines. In keeping with the 3R principle (“refine, reduce, replace”) the NcWG may also recommend to not conduct a juvenile animal study proposed by the applicant if it is not considered necessary.

Juvenile animal studies included in PIPs

Eight hundred and eighty one conditions from agreed PIPs were reviewed (a PIP may contain more than one condition, i.e. more than one development programme). Juvenile animal studies were included in 232 PIP conditions (26%).

Of the PIPs containing juvenile animal studies, 71% were intended for a target population of children two years of age or younger and 43% of these PIPs included neonates (Table 25.).

Even though some of the PIPs contained more than one juvenile animal study, the majority (80%) contained only one juvenile study. Seventy-six percent were in the rat, 6% in the mouse, 8% in the dog and 10% in the monkey. About 4% of PIPs contained juvenile studies in more than one species.

Table 25. Overview of PIPs containing at least one juvenile animal study (JAS), by therapeutic area and age range (neonates, children below 2 years of age)

Therapeutic area	Number of PIPs with at least one JAS (% of all PIPs in therapeutic area)	Number of PIPs for children < 2 years of age, with at least one JAS	Number of PIPs for neonates, with at least one JAS
Cardiovascular diseases	19 (40%)	18	11
Dermatology	5 (15%)	3	3
Endocrinology - gynaecology-fertility - metabolism	30 (37%)	13	8
Gastroenterology - hepatology	9 (27%)	7	4
Haematology - haemostaseology	4(9%)	4	0
Immunology - rheumatology-transplantation	14 (25%)	9	3
Infectious diseases	40 (42%)	35	25
Neurology	31 (69%)	21	16
Oncology	24 (29%)	21	8
Pain	7 (78%)	7	5
Pneumology - allergology	10 (29%)	6	5
Psychiatry	10 (59%)	1	1
Uro-nephrology	7 (44%)	4	2
Other	22	16	8
Total	232	165 (71%)	99 (43%)

Source: EMA databases (PedRA, PedRA extension).

Are juvenile animal data predictive of the paediatric clinical situation?

A case example

Toxicology studies in juvenile animal studies can be predictive of the clinical safety profile in children (Bailey and Marien, 2011). As a consequence, the implementation of clinical precautions after the occurrence of pre-clinical safety findings makes it difficult to obtain definitive data on the predictive value of such findings from juvenile animal studies for the paediatric clinical situation; for example, precautions may entail exclusion of certain paediatric age subsets from clinical trials or specific monitoring and stopping rules.

Kalydeco (ivacaftor) is a very important example of the usefulness (predictive value) of juvenile animal data in paediatric medicines development.

Kalydeco (ivacaftor) was approved in 2012 for cystic fibrosis for adults and for children from six years of age. Cataracts had been observed in juvenile rats dosed from postnatal day seven to 35 with dose levels of 10 mg/kg/day and higher (resulting in exposures 0.22 times the human exposure at the maximum recommended human dose). Such findings had not been observed in the standard adult toxicology studies. The results of this juvenile animal study therefore prompted the inclusion of ophthalmological monitoring throughout the paediatric clinical trials. Indeed, cases of non-congenital lens opacities (cataract) were subsequently reported in some children receiving ivacaftor. Given that lens opacities (cataracts) observed in the juvenile rat toxicity study were considered ivacaftor-related, there is a plausible causal relationship. These adverse ophthalmological events might have been missed in children, had specific monitoring not been included in the trials, as vision was not impaired at early stages. This demonstrates that juvenile animal data can be of great relevance for the safety of children in clinical trials.

The clinical and regulatory consequences of these findings were: recommendations for baseline and follow-up ophthalmological examinations in children starting ivacaftor treatment, and update of Section 4.4 of the SmPC, "Special warnings and precautions for use" (i.e. inclusion of the risk of cataracts in paediatric patients treated with ivacaftor).

Clinical and regulatory consequences of juvenile animal study outcomes

By December 2015, the PDCO had agreed 46 full waivers (5% of all agreed PIP/waiver opinions) and 83 partial waivers (9% of all agreed PIP/waiver opinions) based on safety grounds. Seventeen percent of the full and 22% of the partial waivers were based to a significant extent on juvenile animal data.

Twenty-four percent of the full waivers based on safety grounds resulted in a switch from initial PIP application to a waiver in the course of the PDCO evaluation. The majority of these (91%) were full waivers on PDCO's own motion.

Table 26. displays the full and partial waivers based on safety grounds by therapeutic area and waiver age range. Furthermore, the table indicates the number of cases where juvenile animal results contributed to the waivers.

Table 26. Full and partial product-specific waivers based on safety grounds

Therapeutic area	Full waiver	Partial waiver	Waiver						
			< 1m	< 6m	< 1y	< 2y	< 4y	< 6y	< 12y
Anaesthesiology	-	2	-	-	-	2	-	-	-
Cardiovascular diseases	1	7 (4)	1	-	1 (1)	3 (2)	-	2 (1)	-
Dermatology	2 [1]	6	1	-	-	-	3	2	-
Endocrinology – gynaecology – fertility - metabolism	14 [6]	8 (3)	1	-	-	4 (2)	1	1	1 (1)
Gastroenterology - hepatology	3	9 (1)	-	3 (1)	-	1	5	-	-
Haematology - haemostaseology	-	3	-	2	1	-	-	-	-
Immunology – rheumatology - transplantation	7 (6)	5 (1)	-	-	-	2	2	-	1 (1)

Infectious diseases	2 (1)	15 (3)	3	2	-	1	2 (2)	4	3 (1)
Neurology	1	4 (1)	1	-	-	2	-	1 (1)	-
Oncology	1	9 (2)	1	4	2 (2)	2	-	-	-
Ophthalmology		2	-	-	-	-	-	1	1
Pain	6 (1) [1]	1	-	-	-	1	-	-	-
Pneumology - allergology	1 [1]	-	-	-	-	-	-	-	-
Psychiatry	4 [1]	2 (1)	-	-	-	-	-	2 (1)	-
Uro-nephrology	2 [1]	3	-	1	1	1	-	-	-
Vaccines	1	4	-	1	1	2	-	-	-
Other	1	3 (2)	-		1 (1)	-	-	1 (1)	1
Total	46 (8) [11]	83 (18)	8	13 (1)	7 (4)	21 (4)	13 (2)	14 (4)	7 (3)

Note: Numbers in the table represent total numbers of full and partial waivers based on safety grounds. Out of 881 conditions in total, 129 contained either full or partial waivers based on safety grounds. In case of (multiple) modifications, each PIP/condition was only counted once. () = number of waivers which were based (also) on results from juvenile animal toxicity studies. [] = number of switches from initial PIP applications to full waivers based on safety concerns (most of these were full waivers on PDCOs own motion).

Source: EMA databases (DREAM, PedRA).

Juvenile animal studies for anti-cancer medicines

At the initiative of the EMA, the results of juvenile animal toxicity studies in agreed PIPs of 19 anti-cancer medicines were assessed by a group of non-clinical experts, in collaboration with clinical experts. Of these medicines, 14 were targeted therapies. Pharmaceutical companies had already initiated or completed a juvenile study or proposed such study as part of the PIP in 7 cases. The expert group concluded that in four of the 14 anti-cancer medicines, juvenile animal studies should be completed before administering the medicine in a trial to patients in the youngest age group, which ranged from one to eight year-olds, to identify any potential toxicities or dosing rules. In these cases, based on the existing data, administration to older children was considered appropriate. In two cases, the safety concerns were such that it was considered necessary to complete juvenile animal studies before initiating any paediatric clinical trial. In three further cases, juvenile studies were required to be completed early during the paediatric development, while paediatric patients of all ages could already receive the medicine in the trial.

For 9 anti-cancer medicines, the results ruled out that the safety concern triggering the juvenile study had relevance for administering the medicine to youngest children. In 8 cases, however, new target organ toxicities were detected (growth, behaviour, bone, brain, eye, heart, kidney, lung, nasal cavity, reproduction organs, spleen, thymus). Notably, 3 out of these 8 anti-cancer medicines resulted in serious, juvenile-specific safety issues that may severely impact the youngest patient population. As a consequence, for some of the later anti-cancer medicines, trials were waived in youngest, and likely affected children, and for most medicines, the monitoring of risks and toxicities in paediatric trials was required to be specifically adapted (e.g. assessments, preventive measures, stopping rules).

The juvenile animal toxicity studies with anti-cancer medicines have brought new information such as previously unknown toxicities (new target organ toxicities), cases with toxicities that could seriously harm younger patients and toxicities not previously encountered by paediatric oncologists. In contrast, some animal studies supported the administration of an anti-cancer medicine in a clinical trial to youngest patients, disproving the safety concern which led to conducting the animal study. It was also found that it took only 6 to 9 months to conduct the animal studies, and the latter could run in parallel with the preparations of the paediatric clinical trials of the PIP. Therefore, juvenile animal studies did not delay paediatric trials, but safeguarded children against potential serious age-specific adverse reactions.

Robust non-clinical evaluation (including non-juvenile studies where necessary) could lead to an earlier initiation of paediatric clinical trials, as fewer safety data from adults would be needed. This could be particularly relevant for paediatric indications (i.e. tumour types) which are different from those studied in adults. For the first paediatric trials of a given medicine, international paediatric oncology networks systematically exclude patients of less than 1 year of age. In PIPs, approaches to include younger patients in trials were tailored to the case, avoiding unnecessary staggering and delay of inclusion of the youngest patients. Moreover, safety data from non-clinical research in addition to clinical efficacy data are useful in selecting and prioritising anti-cancer medicines (Pearson et al, 2016).

Reduction of unnecessary use of animals (“3 Rs”)

The need to perform juvenile toxicity studies is reviewed for each PIP in compliance with existing guidelines. During this review the NcWG also highlights those juvenile studies proposed by the applicant that are deemed unnecessary or whose requirements could be reduced (e.g. sample size, duration, endpoints). Table 27. highlights case examples of PIPs where the NcWG review contributed to a reduced use of animals as compared to the initial proposal by the applicant.

Table 27. Case examples resulting in reduced use of animals

Condition	NcWG/PDCO recommendations resulting in reduced use of animals
Diabetes	Deletion of certain endpoints (sexual maturation, reproduction) from juvenile animal study
Clostridium difficile infection	Proposed reproduction toxicity studies not deemed necessary
Juvenile idiopathic arthritis	Only a single dose in ePPND study deemed necessary
Non-infectious uveitis	Proposed juvenile animal study in rats not deemed necessary
Antiseptic	Proposed juvenile animal study in rats not deemed necessary
Systemic lupus erythematosus	Proposed repeat-dose toxicity study in juvenile monkeys not deemed necessary
Bacterial infection	Proposed juvenile animal study in rats not deemed necessary
Chronic kidney disease	Deletion of certain endpoints (ophthalmoscopy and behavioural evaluations) from juvenile animal study

Source: EMA databases (DREAM, PedRA).

3.13. Medicines for children with cancer

About 15,000 children less than 15 years of age (and 20,000 teenagers and young adults from 15 to less than 24 years) are newly-diagnosed with cancer in the EU per year (Ferlay et al. 2008). While more than 3 out of 4 children can be cured, their treatment burden and long-term sequelae are significant. Every year, almost 100,000 children die from cancer, more than 90% of them in resource-limited countries (Sullivan 2013) and about 6,000 in the EU.

In the [5-year Report to the European Commission](#), paediatric oncology has been identified as a neglected therapeutic area as little progress has been made with new and better treatments for childhood cancers, and this was attributed in part to the difference in clinical conditions between adults and children. Cancers that concern children are biologically different from those concerning adults, and therefore any medicine's mechanism of action needs to be used to guide investigating treatments of the paediatric malignancies and to address the unmet therapeutic needs in paediatric oncology. Consequently, the development should be driven by the potential paediatric use, i.e. by the data (existing or to be generated as part of a PIP) on the mechanism of action, or on the target of the anti-cancer medicine where the anti-cancer adult indication is under development.

3.13.1. PIPs for anti-cancer medicines

There are overall 89 oncology PIPs⁵ (89 / 935 = 10% of all PIP decisions as of December 2016), and these are for 73 anti-cancer medicines. These 73 anti-cancer medicines represent more than 35 different mechanisms of action (based on the ATC code and the scientific assessment by the PDCO). The main cancer types being studied in 43 out of the 73 PIPs for anti-cancer medicines are those which primarily affect paediatric patients (e.g. acute lymphoblastic leukaemia, Ewing sarcoma, medulloblastoma, neuroblastoma, rhabdomyosarcoma). In fact, 15 out of these 43 PIPs are intended to identify and to investigate a childhood cancer as therapeutic target for the medicines' mechanism of action (see also Table 29. below).

Based on compliance opinions issued by the PDCO for anti-cancer medicines, 9 developments in PIPs have been completed (9 / 73 = 12%). These are: ipilimumab, vandetanib, bevacizumab (high-grade glioma), bevacizumab (rhabdomyosarcoma), recombinant asparaginase, everolimus (astrocytoma), imatinib (acute lymphoblastic leukaemia), nilotinib, dinutuximab. Two more PIPs for anti-cancer medicines should have been completed at the time of this report, but applicants have not requested a compliance check (docetaxel, mercaptopurine).

A number of anti-cancer medicine developments were discontinued (teprotumumab, cediranib, cilengitide, cyclophosphamide, elacytarabine, enzastaurin, ombrabulin, evofosdamide), mostly due to findings in adult clinical trials.

3.13.2. Authorisations of anti-cancer medicines

In total, six new anti-cancer medicines were authorised for children since the Paediatric Regulation came into force (after July 2008; as the assessment may take two years, authorisations were expected from 2010 onwards) (Table 28.).

Table 28. Active substances of centrally authorised medicines for paediatric oncology indications.

Authorised before 2007	Authorised from 2008 onwards
Busulfan ^{IND}	Asparaginase (recombinant) ^{PIP NEW}
Clofarabine ^{NEW}	Daunorubicin ^{IND}
Nelarabine ^{NEW}	Dinutuximab ^{PIP NEW}
	Etoposide ^{IND}
-	Everolimus ^{IND PIP}
-	Idarubicin ^{IND}
-	Imatinib ^{IND PIP}

5

http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fpip_search.jsp&mid=WCOb01ac058001d129&searchkwByEnter=false&alreadyLoaded=true&isNewQuery=true&keyword=Enter+keywords&searchType=Invented+name&taxonomyPath=&treeNumber=¤tCategory=Oncology

Authorised before 2007	Authorised from 2008 onwards
-	Mercaptopurine** NEW
-	Mifamurtide NEW
-	Pegaspargase * NEW
-	Temozolomide IND
-	Thiotepa** NEW
-	Vandetanib IND PIP

Note: NEW = newly authorised including for paediatric use. PIP= authorised based on studies in an agreed PIP. IND = new paediatric indication for already authorised medicine. * Pegaspargase was previously nationally authorised. In 2015 it was authorised via the centralised procedure. ** PIP agreed. However, authorisation based on well-established use.

Source: EMA website.

In total (that is, for both adults and children), 58 anti-cancer medicines have been authorised via the centralised procedure after the Paediatric Regulation came into force.⁶ Thirty-five out of these 58 (60%) received an initial marketing authorisation for a condition for which paediatric studies had been waived (product-specific waiver or class waiver). Despite having a waiver, for 7 out of these 35 new anti-cancer medicines, the pharmaceutical companies also proposed PIPs (see also next section). The remaining 23 out of the 58 (40%) medicines had an agreed PIP to cover the initial marketing authorisation.

3.13.3. Voluntary PIPs for anti-cancer medicines

Most cancers in children are biologically different from cancers that occur in adults. Therefore, studies are required where medicines target the biological features specific to the childhood cancer. This is a principle of medicine development that is similarly used in adult oncology. It is sometimes referred to as mechanism of action (Pearson et al. 2016) or pharmacodynamic audit trail (Sarker 2009).

Proposed and agreed PIPs for anti-cancer medicines follow this principle. When a medicine is proposed for authorisation to treat a cancer that only occurs in adults, waivers of paediatric studies are usually requested, and in the current framework have to be granted, in relation to the "adult" cancer condition. This section provides an analysis of cases where even though a waiver could have been granted as the specific "adult" cancer does not occur in children, applicants actually proposed a PIP, based on the mechanism of action for treatment of cancers that occur in children.

These PIPs include initial studies with children who have cancer types with a biological rationale for anti-cancer activity. In such studies, biological changes reflecting the mechanism of action of the medicine are measured. Later studies may then be for a particular cancer from this range or for biologically defined cancers. In any case, the medicine would not be studied, or not only be studied, in the cancer for which the medicine is used in adults. Currently 15 PIPs fit this description (Table 29.).

⁶ Marketing authorisations applications for anti-cancer medicines that were subject to article 7 of the paediatric regulation; http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByKey&alreadyLoaded=true&isNewQuery=true&status=Authorised&status=Withdrawn&status=Suspended&status=Refused&keyword=L01&keywordSearch=Submit&searchType=atc&taxonomyPath=Diseases.Cancer&treeNumber=&searchGenericType=generics

Table 29. Overview of "voluntary" PIPs that were agreed to target a treatment of a paediatric solid malignant tumour

No.	PIP number	Active substance (INN)	Authorised use in adults (Condition)	Marketing authorisation submitted and validated (Date)	PIP agreed (Date)
1	117	Ipilimumab	Melanoma	05/2010	11/2008
2	389	Linifanib	None	-	07/2009
3	458	Ridaforolimus	Soft tissue sarcoma, bone sarcoma	08/2011	01/2010
4	1143	Cabozantinib	Thyroid carcinoma	11/2012	07/2012
5	1147	Dabrafenib	Melanoma	08/2012	01/2012
6	1177	Trametinib	Melanoma	02/2013	02/2012
7	1178	Regorafenib	Intestinal carcinoma	03/2013	10/2012
8	1251	Talimogene laherparepvec	Melanoma	09/2014	03/2013
9	1308	Nano particle albumin bound paxcitaxel	Breast cancer	09/2006	04/2013
10	1407	Nivolumab	Melanoma, lung cancer	09/2014	03/2014
11	1425	Cobimetinib	Melanoma	09/2014	01/2014
12	1474	Pembrolizumab	Melanoma	06/2015	03/2014
13	1489	Idasanutlin	None	-	10/2014
14	1638	Atezolizumab	None	-	04/2015
15	1757	Copanlisib	None	-	10/2016

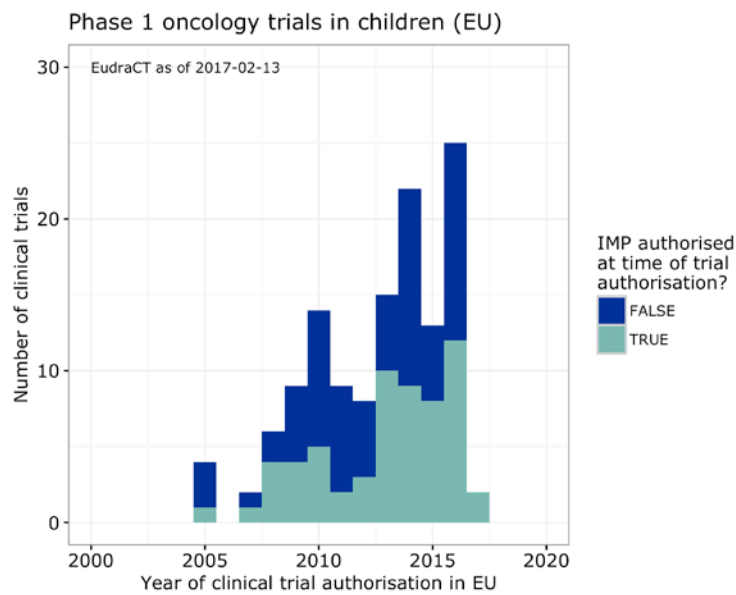
Source: EMA website.

3.13.4. Early phase paediatric oncology trials

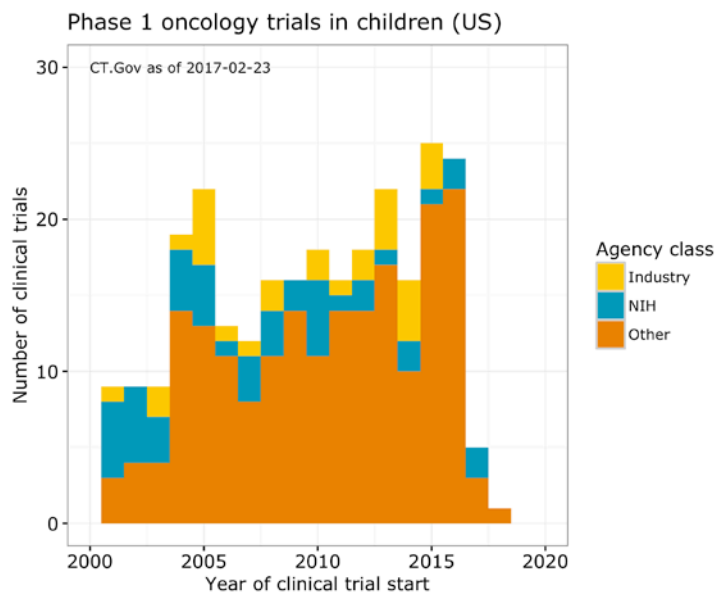
Given the limited relevance to children of information from adult trials of anti-cancer medicines, there is interest in conducting early phase trials in children based on biological rationale and animal toxicology and efficacy data, rather than on adult trials (see also [Addendum on Paediatric Oncology, EMA 2003](#)). Such trials may show signals of anti-tumour activity in paediatric cancers not seen in adult trials.

Overall, the number of new phase 1 paediatric oncology trials seems limited in the EU compared to the U.S., with an average of about 10 per year. Only about half of these are trials for a medicine that was not yet authorised at the time the trial was started. In comparison with the number of new medicines authorised to treat a cancer in adults (about 10 per year, many of which would be relevant to children), the number of paediatric early trials is small. In addition, some anti-cancer medicines that fail in mid- or late clinical development in adults may still be relevant to treat a cancer that is specific to children. In the US more of early phase trials are conducted in children. This could be due to the fact that traditionally paediatric oncology clinical study groups or the National Cancer Institute (NCI) act as sponsors for paediatric oncology trials, including for trials of unauthorised medicines and in collaboration with pharmaceutical industry. The documentation in ClinicalTrials.Gov does not include information on whether the medicine was authorised or not.

Figure 15. Number of phase 1 oncology trials newly started by year in the EU and US



Source: EudraCT database.



Source: ClinicalTrials.gov.

Overall, the number of phase 1 paediatric oncology trials registered in the US is significantly higher also in recent years, after the Paediatric Regulation came into force in the EU. Nevertheless, it needs to be taken into account that a number of oncology PIPs include paediatric trials conducted outside the EU, such as in the US.

3.14. Class waiver revisions

When a medical condition does not occur in children and a pharmaceutical company requests a waiver for this reason, the PDCO grants such a waiver based on Article 11 (b) of the Paediatric Regulation. To avoid unnecessary administrative procedures, the committee had adopted a list of 39 condition waivers, in 2008 and 2009. By the end of 2016 the committee handled 606 requests to confirm the applicability of a class waiver to a development; most of these (66%) concerned oncology developments of anti-cancer medicines.

The committee subsequently reviewed its experience with class waivers, PIPs and product-specific waivers. It was concluded that the existing class waiver list limited the opportunities to discuss with applicants and consider the potential benefits and use of some new medicines for children. In fact, some medicines with novel pharmacological properties and unprecedented benefits in terms of efficacy in life-threatening diseases (such as reviewed by Masters et al. 2015) were being developed for adults only but the potential use in children could not be assessed.

The PDCO adopted a [review of the class waiver list](#) on 23 July 2015. In its review, the PDCO assessed the characteristics of the medicines and available evidence for their possible use in children; results of paediatric trials were assessed to decide whether paediatric trials of the class of medicinal products were necessary. The outcome of the scientific review resulted in revocation of 8 condition waivers (including 2 cancers), restriction of 28 condition waivers, and confirmation of 9 class waivers (Table 30.).

Table 30. Outcome of class waiver review

Paediatric development waived	Previous class waiver CW/1/2011	Revised class waiver CW/0001/2015
For any medicine within a certain condition	<ul style="list-style-type: none"> 44 conditions (including 22 cancers) 	<ul style="list-style-type: none"> 8 conditions (no cancer)
For specific classes of medicines within a certain condition	<ul style="list-style-type: none"> 2 classes of medicines that are likely unsafe in children and that are used to treat 1 condition in adults 	<ul style="list-style-type: none"> 2 classes of medicines that are likely unsafe in children and that are used to treat 1 condition in adults 8 classes of medicines that are likely ineffective in children and that are used to treat 9 conditions (cancers) in adults 10 classes of medicines for which further studies in children are not justified and that are used to treat 14 conditions (including 11 cancers) in adults

Source: EMA website.

It is anticipated that a higher number of new medicines and developments will have to be submitted to the PDCO for product-specific discussions and it is hoped that the class waiver revision will encourage companies to develop more new medicines for use in children.

By 2015, no changes are evident in the numbers of requests for product-specific waivers, for confirmation of class waiver applicability, or for PIP applications in the therapeutic area of oncology, which was most affected by the changes of the class waiver list.

However, in 2016, the number of applications for granting of a full product-specific waiver in oncology increased to a record high of 12, from an average of about 7 in the preceding five years, and there was no increase in the number of applications for agreement of an oncology PIP.

The anticipated positive effects have not born out, at least not until the end of 2016, taking into account the transitional period (the revision from July 2015 will only come into effect for marketing authorisation or variation applications in July 2018 (Article 14.3 of the Paediatric Regulation)).

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

The European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) was launched in 2009 as a network of research networks, investigators and centres with recognised expertise in performing clinical studies in children (Ruperto et al, 2012).

Enpr-EMA's mission is to facilitate studies to increase the availability of medicines authorised for use in the paediatric population. To achieve this, Enpr-EMA aims to:

- Establish a European paediatric research network of national and European specialist networks, investigators and centres with expertise in performing paediatric clinical trials to foster high quality ethical research on the safety and effectiveness of medicines for children;
- Provide efficient inter-network and stakeholder collaboration, to build up the necessary competences at European Union level, and to avoid unnecessary duplication of studies;
- Raise awareness among healthcare professionals, parents, carers, children and young people on the need and support for paediatric clinical trials;
- Assist and enter into dialogue with Ethics Committees on issues relevant to research and clinical trials in children;
- And finally facilitate the development of Paediatric Investigation Plans (PIPs) for applicants by considering early consultation with Enpr-EMA members when preparing the application for a PIP (EU Guideline on the format and content of PIP and waiver applications).

The Enpr-EMA paediatric networks are composed of:

- National networks (e.g. NIHR Clinical Research Network: Children in the UK);
- Paediatric 'sub-speciality' networks at European level and beyond, which group centres working in the same therapeutic area, generally benefiting from public funding (e.g. ECFS- Clinical Trial Network);
- Age-related networks (e.g. neonatal network, Neo-Circulation);
- Activity or structure-related networks (e.g. community-practitioners networks, hospital-based dedicated clinical-research centres linked by a common structure, pharmacovigilance networks: FIMP-MCRN);
- European networks publicly funded (e.g. TEDDY);
- Paediatric and other relevant learned societies (e.g. ESPGHAN).

Besides, other interested stakeholders, who are not paediatric networks, are included within Enpr-EMA: patient organisations (e.g. International Patient Organisation for Primary Immunodeficiencies (IPOPI)), Paediatric Committee (PDCO) members, observers from healthcare professional organisations (e.g. European Academy of Paediatrics (EAP)), and observers from Industry representing EFPIA and EUCOPE.

To date, 39 networks are listed in the fully searchable [Enpr-EMA database](#) with 21 networks registered as category 1 networks. Detailed information is provided in the Annex.

A survey was conducted among all registered Enpr-EMA networks regarding their involvement in the setting up of paediatric clinical trials which are included in PIPs. Thirteen networks responded (Table 31.).

Table 31. Involvement of Enpr-EMA networks in paediatric trials which are part of agreed PIPs

Network	Involvement in paediatric PIP trials (number of trials)*	Other involvement
SwissPedNet (Swiss Research Network of Clinical Paediatric Hubs)	12	--
EAP (European Academy of Paediatrics)	--	--
PRINTO (Paediatric Rheumatology International Trials Organisation)	12	--
Juvenile scleroderma network	--	Advice given regarding PIP implementation
TEDDY (Task-force in Europe for Drug Development for the Young)	8	--
FP-MCRN (Family Pediatricians Medicines for Children Research Network)	--	2 projects by Italian Competent Authority
NIHR CRN-Children (National Institute for Health Research - Medicines for Children Clinical Research Network)	335	--
NEO-CIRC (Neocirculation)	1	--
ECFS-CTN (European Cystic Fibrosis Society - Clinical Trials Network)	18	--
FINPEDMED (Finnish Investigators Network for Pediatric Medicines)	21	--
MCRN-NL (Dutch Medicines for Children Research Network)	21	--
PENTA-ID (Paediatric European Network for Treatment of AIDS)	6	--
RIPPs (Réseau d'Investigation Pédiatrique des Produits de Santé)	40	--

Note: *It cannot be excluded that some of the reported studies are duplicates.

Source: Enpr-EMA survey 2015.

Responding networks were involved in a total of 474 paediatric trials, including 17 FP7 studies.

The networks' input ranged from advising pharmaceutical companies in their paediatric drug development strategies, and study protocol developments to identification of suitable study centres, and active involvement in trial management and patient enrolment. Further details on the results of the survey can be found in the Annex.

The establishment of Enpr-EMA has been a significant achievement. It has expanded beyond Europe, with the registration of American, Canadian and Japanese national and multispeciality networks. With Enpr-EMA's support new speciality networks have been established in therapeutic areas with previously no European paediatric network. This was the case in the area of diabetes and endocrinology (EUCADET - European Children and Adolescent Diabetes and Endocrinology Trials network) and gastroenterology (PEDDCReN - Paediatric European Digestive Diseases Clinical Research Network).

Existing European young person's advisory groups within Enpr-EMA networks linked up with established North American ones into a communicating international network for worldwide involvement of young people in research, and participated in the first international summit of the International Children's' Advisory Network ([iCAN](#)).

Enpr-EMA networks with existing young people advisory groups provided training and practical tips on strategies and guidance on the involvement of young people and families in the activities of Enpr-EMA.

Ad-hoc working groups have been established, including networks and industry representatives, tasked with addressing the most important needs identified. For example, the differing requirements for consent / assent in the Member States were identified as one of the greatest challenges in achieving ethical approval across countries. The group developed an [overview table of the requirements regarding consent of children](#) in all Member States, including legislative backgrounds. The table has been published on the Enpr-EMA website.

Enpr-EMA has been successfully implemented as a platform for sharing good practices among paediatric clinical trial networks, and as a pan-European voice for promoting research into medicines for children (Lepola et al. 2016). Enpr-EMA is able to provide assurance on the quality of networks being recognised as its members, and to ensure that networks contacted in parallel for one specific study communicate and collaborate with each other, thus avoiding potential duplication of studies.

3.16. External experts, workshops and scientific guidelines

Expert meetings and workshops

Several scientific and regulatory workshops and expert meetings at the Agency were held to address critical issues related to paediatric drug development and PIPs. The EMA has organised 23 meetings including external experts and 20 workshops within the regulatory network which targeted specific questions on the development of medicines for children. Some of them were conducted in co-operation with the FDA or other regulatory authorities as well as patient-organisation representatives. Information on demographics, biology and treatments as well as on the relationship between paediatric and adult population subsets, and between different disease conditions was also discussed. The outcomes of expert meetings and workshops are published on the EMA website (currently 34 of them), and where appropriate, included in EMA scientific guidelines.

The collaboration with industry and experts during these meetings has provided a platform for exchange of ideas, improvement of understanding between stakeholders on current clinical practice and needs, with the aim to collaboratively foster the progress in paediatric drug development, from PIP to marketing authorisation.

Further details can be found in the Annex.

External experts involved in PIP/waiver assessments

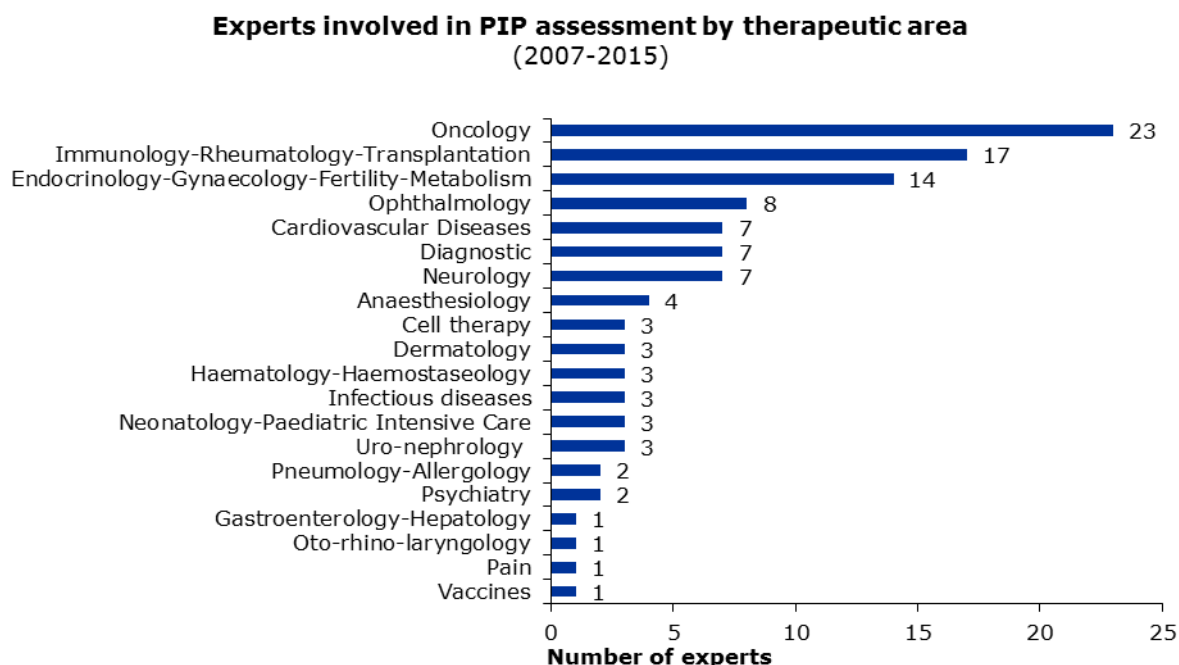
External experts are consulted by the PDCO in order to ensure that paediatric development programmes are in line with up to date clinical practice and scientific knowledge.

Since the entry into force of the Paediatric Regulation, 113 external experts have been involved in discussions of PDCO paediatric investigation plans or waivers; in some cases the expert was involved in more than one procedure or more than one expert was involved in the same procedure. In addition to ad-hoc involvement of external experts by the PDCO, some NCAs have set up working groups of experts for specific paediatric issues.

External experts were mainly involved in assessment of oncology applications, followed by immunology-rheumatology-transplantation and endocrinology-gynaecology-fertility-metabolism (Figure 16.), which probably reflects the very active development of medicinal products in these areas.

The involvement of external experts has been requested on fewer occasions in more recent years. In particular, external experts were involved in 23 and 29 PIP or waiver assessments in 2008 and 2009, respectively, compared to 8 and 7 assessments in 2012 and 2013, respectively. This may reflect that the PDCO has progressively acquired additional experience in assessing PIPs and is building a scientific memory, that more paediatric guidance has been provided and is used in applications as well as that paediatric medicine development has been discussed in a number of scientific workshops and public meetings.

Figure 16. Number of external experts involved in PIP assessments by therapeutic area from 2007 to 2015.



Note: some experts have been involved in several PIP assessments.

Source: EMA records.

Guidelines

The PDCO has been actively involved in revising existing guidelines, as well as initiating new guidelines to improve development of medicinal products for use in children (Table 32.). These guidelines address various aspects of paediatric drug development, such as age group involvement, study design, endpoints, comparators, safety follow-up. All guidelines are published and made available to stakeholders via the EMA website. By the end of 2015, a total of 24 guidelines including contributions of the PDCO had been published. Twenty two further guidelines were in the process of being drafted with PDCO contributions. The list of guidelines is included in the Annex.

Table 32. Guidelines for paediatric medicines development

Number	2009	2010	2011	2012	2013	2014	2015	Total
New or revised guidelines	3	5	6	3	1	1	5	24

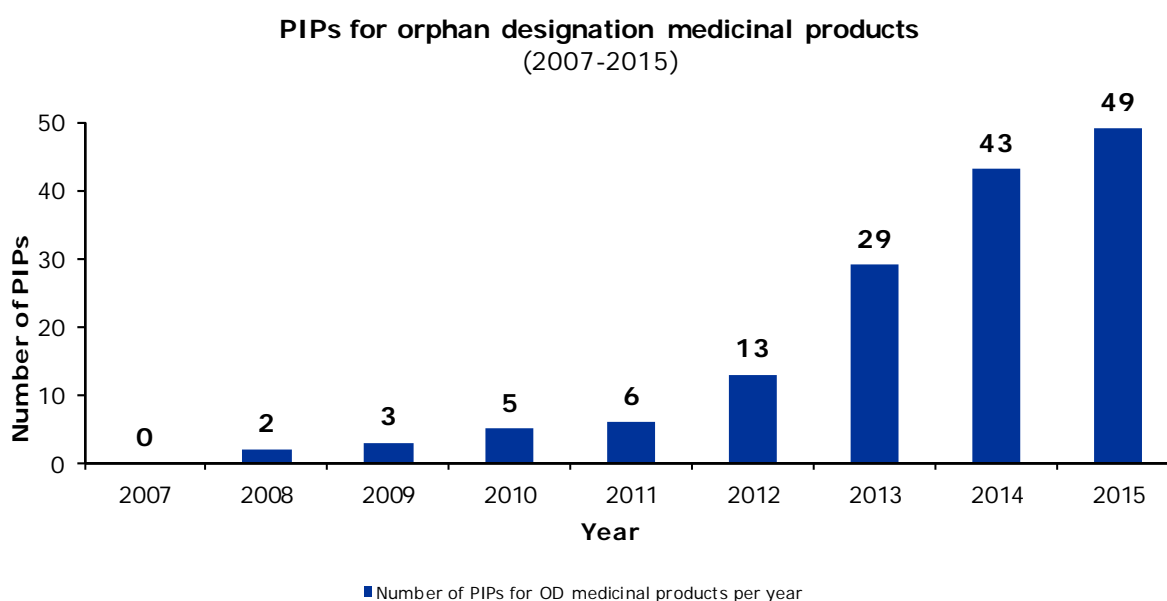
Source: EMA internal data.

3.17. PIPs for orphan medicines

The Paediatric Regulation and the Orphan Regulation have the common objective to promote and incentivise the development of medical products for otherwise neglected populations with unmet medical needs, namely children and patients with rare diseases.

Since the entry into force of the Paediatric Regulation a total of 150 PIPs (Figure 17.) have been agreed for medicinal products which have also received an orphan designation (an additional 19 PIPs for orphan medicines were agreed in 2016). The results indicate that there is a progressive increase in the number of PIPs proposed for paediatric diseases which are also rare diseases. PIPs for medicinal products whose orphan designation was withdrawn, or whose market exclusivity expired were excluded from the analysis, as well as those PIPs whose development was discontinued.

Figure 17. Number of PIPs agreed per year for medicinal products with orphan designation



Note: Medicines whose orphan designation was withdrawn, or whose market exclusivity expired were excluded from the analysis, as well as those medicines whose development was discontinued.

Source: EMA database (PedRA, Orphan database).

The highest number of agreed PIPs is for the oncology therapeutic area (33, 22%) followed by endocrinology/metabolic diseases (22, 14%) and haematology (18, 12%). To date eight PIPs agreed for medicinal products with an orphan designation have been completed, and paediatric indications authorised.

Table 33. Number of PIPs agreed by therapeutic area for medicinal products with orphan designation

Therapeutic area	Number of agreed PIPs	Number of completed PIPs	Number of authorisations of paediatric indications
Anaesthesiology	0	0	0
Cardiovascular disease	10	0	1
Dermatology	8	0	0
Diagnostics	1	0	0
Endocrinology/Metabolic diseases	22	2	2
Gastroenterology-Hepatology	6	0	0
Gynaecology	0	0	0
Haematology	18	1	0
Infectious diseases	11	1	1
Immunology/Rheumatology	4	2	2
Neonatology/PICU	1	0	0
Neurology	13	0	0
Oncology	33	2	1
Ophthalmology	7	0	0
Orthopaedic diseases	3	0	0
Pain	0	0	0
Pneumonology/allergy	9	0	2
Psychiatry	0	0	0
Transplantation	3	0	0
Uro-nephrology	1	0	0
Vaccines	0	0	0
Total	150	8	9

Source: EMA database (PedRA, Orphan database).

3.18. Timely planning and conduct of paediatric development

To ensure that the development of medicines for children is appropriate and in line with paediatric needs and to avoid any delays in marketing authorisation for adults by integrating the paediatric development at an early stage of medicine development, the Paediatric Regulation 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 and before phase 2 in adults commences.

From 2007 to 2009, as the Regulation came into force when most developments were already beyond this stage, most applications were submitted later than the required deadline. Since 2010, compliance with this requirement is monitored by the EMA and reported in the Commission annual report by measuring the time lag between the submission date (first PIP or Waiver) and the declared date of completion of PK studies in adults. In cases where submission is delayed, companies are asked to provide a justification which is considered by the PDCO.

The timing of PIP applications has improved in 2013 and 2014 (Table 34.). The EMA / PDCO have recently launched early interaction meetings to assist with timely submission of the PIPs and appropriate development according to paediatric needs. 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 34. 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)	2010	2011	2012	2013	2014	2015
Number of delayed PIP applications	65 (75%)	44 (59%)	34 (39%)	18 (20%)	12* (13%)	14* (18%)
Reference: number of all PIP applications	88	74	87	91	92	76
Time lag in months, median (range)	22	35 (9-159)	35 (9-241)	28 (9-66)	29 (7-52)	26.5 (10-87)
Number of delayed applications for full waiver	26 (59%)	13 (42%)	11 (23.5%)	6 (11%)	5* (10%)	7* (15%)
Reference: number of all applications for full waiver	44	31	47	56	47	46
Time lag in months for delayed full waiver applications, median (range)	18	35 (9-137)	61 (19-179)	33 (14-60)	31 (10-41)	79.5 (10-123)

Note: * In 2014 and 2015 only applications considered unjustified are reported.

Source: EMA database (PedRA).

Missed and realised opportunities

In more than 20% (64) of the paediatric development programmes that were submitted late for agreement (295 documented in the PedRA extension), at least one missed opportunity for relevant interaction was identified in the scientific discussion (Table 35.).

Table 35. Missed opportunities in PIPs related to timing of submission

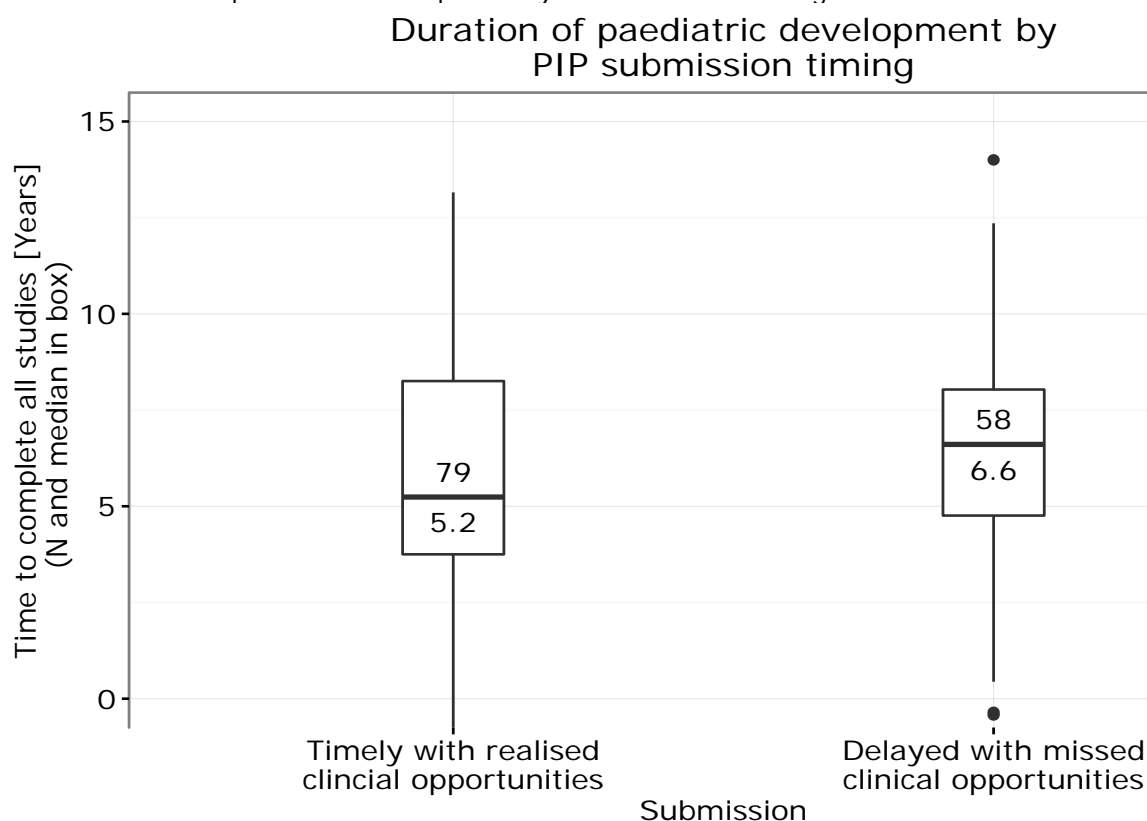
Missed opportunity	Number and proportion among late submissions (N=295)
Formulation	17 (6%)
Nonclinical	17 (6%)
Clinical	57 (19%)
Modelling/Simulation	2 (1%)
Joint paediatric adult trials	6 (2%)
Any opportunity as listed above	64 (22%)

Source: EMA database (PedRA, PedRA extension).

Notably, missed opportunities most often concerned the paediatric clinical part of development (57/64 cases), and in 6/64 cases there was a missed opportunity to conduct studies jointly in adult and paediatric populations.

There seems to be an association of late submissions and missed clinical opportunities with longer development duration (Figure 18.); this seems to support that early discussions of paediatric medicine development can help to seize opportunities for improving paediatric clinical development, which might include starting trials earlier, having seamless designs, optimising the number of subjects or making studies more feasible.

Figure 18. Duration of paediatric development by PIP submission timing



Note: The central tendency and spread of PIP time lines is shown in a box plot for each of the two categories. In the box, the number of developments and the median duration are given. The bold horizontal bar within the box indicates the median of time lines, the boxes' lower and upper sides correspond to the first and third quartiles of the time lines. The points represent outliers (more than one-and-a-half times the interquartile range away from the median [Tukey 1977]).

Source: EMA database (PedRA, PedRA extension).

4. Other initiatives

4.1. Participation of children and young people in PDCO activities

In addition to the participation of three patients' representatives (families) as members of the PDCO (with three alternates), there is a recognised need to involve patients (children) and their families in the planning of clinical research and the development of medicines to meet their needs. This is even mentioned in the Charter of Fundamental Rights of the European Union.

Based on this provision, and supported by the Universal Declaration of Human Rights and the Convention on the Rights of the Child, the EMA and PDCO have facilitated the direct participation of children and young people of different cultures and backgrounds in PDCO activities, in an age-appropriate manner. Patients are also represented in scientific advice procedures, and at CHMP.

Supported by Enpr-EMA, a worldwide consortium of children's advisory groups was established in 2014, linking established European young persons' advisory groups with North American ones into the International Children's Advisory Network ([iCAN](#)) for young people involved in clinical research. The first international summit of iCAN took place shortly thereafter with participants from several Enpr-EMA networks. As Enpr-EMA networks are becoming more and more involved in advising industry and the PDCO on the planning and setting up of paediatric clinical trials, close collaboration and exchange between Enpr-EMA and iCAN is instrumental in making children's voices heard.

Children and adolescents from the Scottish clinical research network accepted an invitation by the PDCO and presented in 2015 to the committee their hopes and concerns regarding clinical research. This was the first opportunity for the committee as a whole as well as for staff of the Paediatric Office at the EMA to share ideas with, and learn from the young people involved in clinical research. As a consequence, it was agreed to set up a young people's working group as part of the EMA's Patients' and Consumers' Working Party. This group will be working together with the PDCO in order to provide guidance on how to best involve young patients in the activities of the Agency and its committees.

At national level, children, families and/or patients' organisations have already been involved in paediatric activities in many ways. A survey among all 28 NCAs (19 respondents) found that 8 NCAs involved children, families or patients' organisations in activities related to paediatric medicine development.

Children, families and patients' organisations were involved in clinical trial authorisations (e.g. assessment of patient information sheet and informed consent, procedures foreseen in the study protocol such as the number of blood extractions), during national SA procedures (e.g. relevance of patient reported outcomes), during the assessment of new paediatric indications and pharmacovigilance activities (reporting of ADRs). Input from these groups was also taken into account for the development of paediatric guidelines (e.g. paediatric formulations) and drug priority lists, or during the elaboration of new regulatory policies.

The main therapeutic areas in which children, families and patients' organisations were involved at national level were oncology and rare diseases, and also epilepsy, psychiatry and vaccines.

Potential areas for development were cited in the survey: communication around safety of paediatric medicines, access to paediatric medicines (e.g. compassionate use programmes, reimbursement decisions).

Eleven NCAs did not involve children, families and/or patients' organisations in activities related to paediatric medicines, for reasons of lack of resources or time (8 NCAs), or because it was not deemed necessary (cited by four NCAs).

In order to collect children's opinions and to provide a basis for further improvements of ethical paediatric clinical research and development a survey was conducted in 2015 among European children (Vornanen et al. 2016). Responses were received from around 900 children from 8 Member States (Finland, Germany, Sweden, Spain, Hungary, France, Luxembourg, UK). Respondents ranged from primary school children to adolescents with the majority being between 13 and 17 years old. Sixty-three percent were affected by a chronic health condition. As expected, most children considered medicines such as creams/liquids easy to take and injections the most difficult. To the question "why do you find some medicines difficult to take?" the most frequent answer was "I don't like the taste" (37.2%) with "it hurts to take the medicine" the next most frequent answer (18.9%). Even though only nine percent of the respondents had participated in a clinical trial the majority had good understanding of what a medical research study is (55%). To the question "what would be your reasons for agreeing to take part in a medical research study?" 42% responded "if the new medicine might help others" and 31% "if the new medicine might make me better". The most common reason why young people would refuse to take part was the potential for the medicine to harm them (37%) and blood tests/hospital visits (18%).

The results of the survey showed that children are willing to participate in clinical research, especially if there were a direct benefit for them, and if it would help others. However, practical aspects such as frequent hospital visits or painful procedures cause them concern.

4.2. International activities

Paediatric cluster with Australia, Canada, Japan, US

The paediatric cluster, which is a forum for exchange of information mainly via teleconferences, was formed as early as in 2007. Members of the EMA's Paediatric Office, and the US Food and Drug Administration (FDA) Office of Pediatric Therapeutics (OPT) as well as of the FDA divisions participate on a monthly basis in these cluster teleconferences; PDCO rapporteurs and peer reviewers are also invited and participate as needed. During these teleconferences, contents of PIPs, studies mandated under the US Paediatric Research Equity Act and studies in Written Requests issued by the FDA are discussed. General questions are also addressed, such as types of paediatric studies applicable to certain paediatric therapeutic areas, extrapolation of efficacy and choice of endpoints. Where relevant, the discussions in the teleconferences are reflected in EMA / PDCO Summary Reports. By December 2015, more than 500 products/topics had been discussed.

A review on waivers compared PDCO's decisions with FDA's Pediatric Review Committee (PeRC) recommendations for all product-specific paediatric full waiver applications submitted to EMA from January 2007 to December 2013. Despite the different legal frameworks, criteria, and processes of determination, the outcome was the same in the majority of cases. For single active substance products, PDCO and PeRC came to the same outcome in 42 out of 49 indications (86%). For fixed dose combinations, PDCO and PeRC had the same outcome in 24 out of 31 indications (77%); this lower percentage reflects the consideration by the PDCO that association of two or more active substances in combination did not seem to provide a significant benefit over the existing products (Egger et al. 2016, in press).

In 2012, the inflammatory bowel disease working group was established for in-depth discussion of issues identified by the paediatric cluster such as the lack of scientific consensus on efficacy endpoints/disease outcome assessments, which present a hurdle for global drug development in paediatric inflammatory bowel disease. The outcome of the joint discussions on endpoints and study design were published in two joint manuscripts in 2014 (Sun H et al. 2014, part 1 and 2).

In 2013 a new tool, so-called common commentaries, was launched to inform sponsors of products discussed at the paediatric cluster. These documents provide informal, non-binding comments to sponsors on paediatric development plans that have been submitted to both FDA and EMA, which are under review by both agencies and have been discussed at the cluster. By the end of 2015 a total of 16 common commentaries had been sent to sponsors.

In 2014 the [joint document](#) summarising the agreed collaborative approach for developing innovative paediatric medicines for Gaucher disease, a rare disease, was published on both Agencies' websites.

The Pharmaceuticals and Medical Devices Agency (PMDA) Japan joined the paediatric cluster in 2009, followed by Health Canada in 2010. Most recently, in 2014, Therapeutic Goods Administration (TGA) Australia joined as an observer.

Other exchanges with FDA

Since the end of 2009, FDA colleagues regularly participate in the virtual meetings of the PDCO Non-Clinical Working Group and the PDCO Formulation Working Group. In addition, staff exchanges included visits of 5 EMA Paediatric Medicine staff members to the FDA, where they were given the opportunity to observe the FDA Pediatric Review Committee (PeRC) meetings, as well as visits of several FDA OPT staff to observe some activities of the EMA, including PDCO meetings. The EMA has provided remote access to FDA colleagues to its Paediatric database.

WHO

The EMA is chairing the [Paediatric Medicines Regulators' Network \(PmRN\)](#) of the World Health Organization (WHO) and their initiative "Better Medicines for Children". This network was set up with representatives from national medicines regulatory authorities from all regions, aiming to provide a forum for discussion and to facilitate collaboration around paediatric medicines regulatory considerations.

International Council for Harmonization

Representatives of the PDCO have been closely involved in the ongoing drafting and review of ICH guidelines concerning the paediatric population.

- Review of ICH E11 'Clinical Investigation of Medicinal Products in the Paediatric Population'
- Drafting of ICH S11 'Nonclinical Safety Testing in Support of Development of Paediatric Medicines'.

4.3. Paediatric Pharmacovigilance

The Paediatric Regulation reinforced the post-authorisation requirements, adapting pharmacovigilance mechanisms to meet the specific challenges of safety monitoring in the paediatric population. Such provisions include data collection on potential long-term effects and further requirements (Article 34), such as the obligation to detail measures to ensure efficacy and safety follow-up regarding paediatric use in all applications for marketing authorisation that include a paediatric indication.

Art 34 in the Paediatric Regulation specifies the concept of a risk management system to be set up and of specific post-marketing studies to be performed and submitted for review specifically for the paediatric population.

These concepts were taken further by the new pharmacovigilance legislation (Regulation (EU) No 1235/2010 and Directive 2010/84/EU amending existing pharmacovigilance provisions contained in Directive 2001/83/EC and Regulation (EC) No. 726/2004) which came into force in July 2012. Collaboration with the Pharmacovigilance Risk Assessment Committee (PRAC) was established. Paediatric aspects were included in the guidelines on good pharmacovigilance practices (GVP), which provide practical measures to facilitate pharmacovigilance

This has led to a change in the medical environment for a safer use of medicines in the paediatric population in the EU.

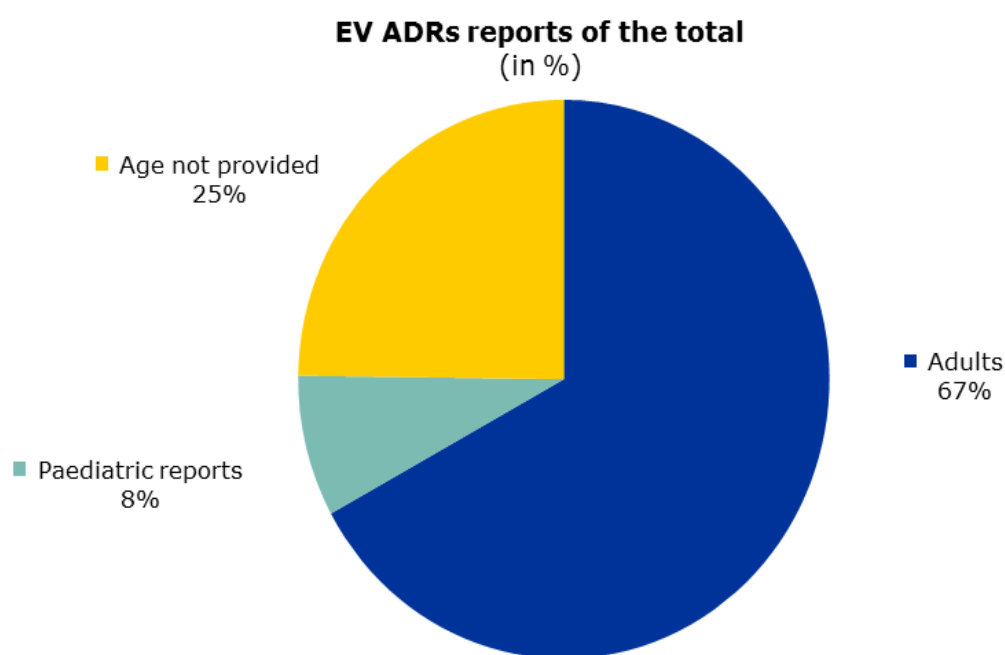
EudraVigilance and safety signals

The Agency proactively analyses the safety information within the large numbers of reports of adverse drug reactions submitted to its EudraVigilance database.

The Agency has introduced new tools for the detection of adverse drug reactions (ADRs) involving the paediatric population within all the data reported to EudraVigilance (Blake KV et al, 2014). Reports of ADRs in children were found to differ from those in adults, not only in terms of reactions and drugs involved, but they were also relying on more limited sets of reaction types and drugs.

EudraVigilance (from 1 January 1995 to 11 June 2015) contained 4,271,180 spontaneous reports, for 75% included the age of the patient; 10.9% of these were paediatric reports (Figure 19.) (Blake KV et al, 2016).

Figure 19. Eudravigilance (EV) paediatric reports (January 1995 to 11 June 2015)



Source: Eudravigilance database.

Furthermore, new filters to obtain data from EudraVigilance have been designed in order to support the assessment of PIPs.

Communication has been established between PDCO and PRAC to facilitate exchange of information regarding new pharmacovigilance signals in the paediatric population. This led to formal consultation between the two committees in the majority of cases (at least 12 different occasions out of 18 in total) when safety issues of paediatric interest were under discussion by PRAC from 2012 to 2015. Such interaction has shown cohesion of the system and a plurality of views introduced into the assessment, and best use of expertise of the EU network.

Following these assessments, risk minimisation measures were recommended, ranging from revisions of the product information (SmPC and PL), to restriction of the use of the medicine to specific subsets of the paediatric population, or the requirement to conduct further studies or develop new formulations. For example, for codeine-containing medicines for pain relief the PRAC recommended [restrictions of use in children](#) following consultation with the PDCO.

Risk Management Plans (RMPs)

In accordance with the Paediatric Regulation the PDCO highlights potential long-term safety or efficacy issues in relation to paediatric use in PIP opinions, when deemed necessary. This supports setting up RMPs and other pharmacovigilance activities and long-term follow-up plans.

From the establishment of the PRAC in July 2012 to December 2015 such long-term concerns in relation to paediatric use were considered in the RMP of at least 40 paediatric medicines as part of new marketing authorisations or extensions thereof.

This confirms that a link between pre-authorisation and post-authorisation settings has been established, and suggests that the conditions to continue monitoring of specific concerns for the paediatric population have been put in place. This is particularly important for maturing organs in children, and effects on development need to be followed up beyond the completion of the paediatric trials required for marketing authorisation.

Post-authorisation safety studies (PASSs)

Post-authorisation safety studies (PASS) are usually non-interventional studies, defined as any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.

Since the establishment of the PRAC protocols of 19 paediatric PASS have been assessed by the PRAC. For 15 of these studies a corresponding concern on long-term safety had been expressed in the respective PIP opinions. This confirms that dedicated paediatric PASSs are being initiated.

Paediatric pharmacovigilance Guideline and Workshop

In 2014 the EMA convened a first one-day workshop on the needs and priorities for pharmacovigilance in the paediatric population (EMA/288486/2014 Human Medicines Research & Development Support Division Report on the EMA workshop of pharmacovigilance in the paediatric population 28 April 2014).

This workshop led to increased co-operation between the PDCO and PRAC, which has resulted in the creation of a joint PDCO/PRAC working group, and triggered the revision of the 'Guideline on conduct of pharmacovigilance for medicines used by the paediatric population.

4.4. Meetings with stakeholders/applicants

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

EMA-industry stakeholders platform meetings

The EMA hosts annual meetings between regulators and representatives of industry stakeholder organisations. This aims to provide an opportunity for both general updates and more focused discussions on specific processes or issues to support continuous improvement, and generally to foster a constructive dialogue with industry stakeholders. Two such meetings relating to paediatric medicine development have taken place to date.

Business pipeline meetings

Business pipeline meetings were launched in 2003 at the EMA aiming to discuss with pharmaceutical companies their portfolio of medicines. This is an activity of business intelligence and forecast of applications.

During the reporting period (up to end of 2015) more than 110 such meetings took place. Questions and issues on paediatric development are steadily rising, and members of the paediatric medicines office have been increasingly part of such meetings. Currently, almost 80% of business pipeline meetings have some relevance to paediatrics.

Early paediatric interaction meetings

Early paediatric interaction meetings were launched in June 2015. The aim of these meetings is to guide companies at very early stages in the development, certainly much earlier than the timing of the PIP as foreseen by the regulation, on matters relating to strategy of the paediatric development programme.

Pharmaceutical companies have responded well to this initiative showing increasing interest. It is too early, however, to provide data and conclusions on the early paediatric interaction meetings.

Pre-submission meetings

Since 2009, the paediatric medicines office holds pre-submission meetings with applicants before the submission of applications for PIP and / or waivers, or before applications for requests for modification of agreed PIPs. These are generally intended to discuss validation issues in order to ensure a smooth validation process, or in conjunction with participation of PDCO members to discuss scientific issues related to the development.

SME meetings

As part of the activities of the SME office to support small and medium-sized companies with less regulatory experience, EMA held pre-submission meetings to discuss paediatric matters for 19 medicines (during the period 2009-2015).

PRIME

PRIME (PRiority MEDicines) scheme was launched in March 2016 with the aim to enhance interaction and early dialogue with medicine developers, and bring promising innovative medicines to patients faster by optimising and supporting medicines development. It is anticipated that PDCO will be closely involved in PRIME application procedures for paediatric medicines.

4.5. Streamlining the handling of applications

The EMA and the PDCO are conscious of the resource implications of submitting applications in compliance with the requirements of the Paediatric Regulation, and are constantly working on administrative simplification and streamlining of the procedure. Changes are implemented after receiving feedback from various stakeholders, including Industry, during ad-hoc meetings and other events.

The 5 year report already mentioned the electronic workflow introduced in 2007, which allows applicants to re-use previous submission data. Since then, EMA has completed several other initiatives, to ensure most efficient handling of applications for PIP/waivers/compliance checks. These have included:

- Simplification of Opinions: the content of the Opinions was optimised and simplified, by the creation and use of the Key elements form, which applicants are invited to pre-populate with the proposed list of key elements for the measures in the PIP Opinion. This form, published in 2010, was revised in 2015. The exercise has helped in reducing the need for modifications of agreed PIPs, as evidenced by the data reported in the EMA annual report (2014) to the European Commission.
- Possibility to submit study reports even if they are not full/final. This improvement addressed the issue of study extensions, not included in the PIP, which prevented applicants from being able to submit a final/full study report (as the study was not technically completed). As above, the improvement was based on modifications in the revised EC Guideline on the Format and Content of Applications, published in September 2014.
- Updated and reorganised procedural advice on the [Paediatric Medicines section of the EMA website](#). While this is a continuous activity, a major overhaul was introduced at the beginning of 2015.
- A new document is now published for every Decision on PIP and waivers, the Summary of the PDCO evaluation of the PIP/waiver application. This Summary provides information on the role of the PDCO in shaping the initial proposal from the applicant, to arrive to a final agreed Opinion on the Paediatric Investigation Plan (or waiver). These Summaries, published since June 2014, also provide guidance for applicants of similar products, or aimed at similar conditions.

In January 2016 the Internal Audit Service (IAS) of the European Commission conducted an audit of the Paediatric Regulation procedures. An interim report from the IAS states that “the EMA deploys and uses adequate systems for the management and control of the procedures, which facilitates robust scientific, procedural and administrative support to the PDCO, and that necessary expertise is employed in the evaluation. A strong emphasis on internal effectiveness and compliance with legal deadlines contributes to meeting the objectives of timely delivery of high quality opinions and decisions and in compliance with the Paediatric Regulation. Finally, the EMA ensures legal soundness of the final opinions and decisions by involving legal and regulatory experts in the process.”

Standard PIPs

The European Medicines Agency’s Paediatric Committee has developed a number of standard PIPs. These are documents which provide recommendations for the key binding elements to be included into the PIP opinion with the aim to assist applicants with the agreement of PIPs on specific types or classes of medicines.

A particularly challenging project was the drafting of the standard PIP for the Tetanus-diphtheria-pertussis (DTaP) vaccines, due to the complexity of vaccination programmes and differences across Member States: “Expected key elements and requirements for a new DTaP containing combination vaccine seeking marketing authorisation ([EMA/82701/2015](#))”.

The PDCO has defined, in collaboration with the European Centre for Disease Prevention and Control (ECDC) and European public health vaccinology experts, the schedule that should be evaluated during clinical trials in children when developing a new DTaP containing combination vaccine. The proposed schedule has been defined as the one producing data that can cover the various vaccination schedules in the individual European Member States, through extrapolation of results to immunologically less challenging schedules.

The following [standard PIPs](#) have been published on the EMA website:

- Tetanus-diphtheria-pertussis vaccines;
- H1N1 pandemic-influenza vaccines;
- Allergen extracts for immunotherapy;
- Acute myeloid leukaemia;
- Rhabdomyosarcoma.

Publication of PDCO decisions and lay summaries

The PDCO decisions on agreed PIPs and waivers are publicly available [on the EMA website](#). This enables interested stakeholders (such as pharmaceutical companies and patients) to obtain information on medicines being developed for the paediatric population. It also provides an insight on current PDCO requirements. Furthermore, since 2014, lay summaries for each PDCO evaluation of a PIP or waiver are published. The summaries describe the proposal from the applicant for the development of their medicine in children, the PDCO's conclusion on the potential use of the medicine in the paediatric population, the plan agreed between the committee and the applicant at the completion of the procedure (including any partial waivers or deferrals) and the next steps.

4.6. Publications relating to the Paediatric Regulation

PDCO and the Paediatric Office at EMA have published 97 peer-reviewed articles from 2007 to 2015 in order to raise awareness of the Paediatric Regulation, highlight paediatric medical research needs as well as challenges in drug development for children. These publications do not only aim at sparking interest and understanding in stakeholders, principally health care professionals and the academic community, in the benefits of the Paediatric Regulation, but also critically reflect on its shortcomings and potential improvements. In any case, these proactive publications have vastly increased transparency of the processes and outcomes (e.g., availability of medicines and formulations relevant for paediatric medical care), in order to allow public scrutiny and to build up trust in the regulatory system. They have also enabled public stakeholders to provide feedback and collaboration regarding paediatric guidelines, the list of paediatric needs and research priorities (e.g. as external expert or investigator).

Additionally, 152 articles by external stakeholders looking into the successes and challenges of the Regulation have been identified.

A list of publications relating to the Paediatric Regulation is included in the Annex.

4.7. Training courses on the Paediatric Regulation

Training courses of the regulatory network

In order to collect data on the dissemination of the scientific work of the PDCO and EMA to the general public, healthcare professionals, industry, paediatric patients and their families through training and other external activities, a questionnaire was sent to the NCAs of all 28 Member States, asking them to report relevant activities that have taken place between January 2007 and December 2015.

Responses were received from 19 NCAs (68%).

Of these, over half (10/19; 53%) reported involvement in EU university training programmes on paediatric medicines, paediatric drug development and/or the Paediatric Regulation.

NCAs also reported a high level of involvement in activities reaching out to the general public with 12/19 responders (63%) reporting external activities to inform the general public about paediatric medicines, paediatric drug development, the Paediatric Regulation and/or other aspects relevant to the use of medicines in children. These activities are diverse and include press releases, articles and interviews in newspapers and magazines, posters in paediatricians' offices, interviews on television, webportals, conferences for patient organisations etc.

In addition, 74% of the responders (14/19) also reported training activities involving Healthcare professionals, such as lectures given at meetings and conferences, articles or interviews in specialist publications, newsletters etc. It has to be noted that this was not directly asked in the questionnaire and hence may be under-reported.

This high level of involvement is also reflected in the European Medicines Agency's Paediatric Medicines Office, of which 37% of current Scientific Officers reported involvement in University programmes.

EU Network Training Centre

In February 2014, the EMA and the Heads of Medicines Agencies (HMA) initiated a project to establish an EU Network Training Centre (EU NTC), a central online platform for the exchange of regulatory and scientific training across the EU network. This initiative aims to provide for continuous professional development of national competent authorities and EMA staff, thus improving the quality, consistency and efficiency of the work and promote harmonised application of the regulatory framework and guidelines.

The EU NTC continued to build its framework in 2015 with the launch of the EU NTC interim platform including a catalogue of more than 100 training events across the EU.

In addition the EU NTC mandate also includes the creation of a set of curricula to harmonise and enhance scientific expertise across the network. One of the 7 key scientific and regulatory areas agreed as key priorities to develop training curricula for the EU regulatory experts of the network is paediatrics.

Global Research in Paediatrics (GRiP)

GRiP is a Network of Excellence, supported by a consortium that received funding from the EU FP7 to establish a training programme on paediatric pharmacology and clinical trials.

One of GRiP's main goals is to address the lack of development and safe use of medicines in children by adequately educating current and future generations of health professionals to be able to conduct robust paediatric clinical trials aimed to ensure marketing authorisation with specific paediatric therapeutic indications. EMA with its PDCO is a partner of GRiP, and has have been involved in the development and running of a Master of Science (MSc) Programme in "[Paediatric Medicines Development and Evaluation](#)", targeting health professionals with work experience in the field. This is a two-year programme with an MSc awarded by the University of Rome 'Tor Vergata'. The great majority of the programme is offered online through a virtual learning environment. The first class of students started the Master programme in November 2014. As of 2016, this MSc is developed as a Joint Degree with four universities (Rome, Paris, Rotterdam, and Basel) and supervision is ensured by EMA staff.

EMA as a partner has also contributed regulatory and scientific knowledge to other work packages of GRiP, including on paediatric formulations, safety pharmacoepidemiology on the use of medicines in children, outcome measures, methodology, and neonatology.

5. Involvement of Member States and EMA

The successful implementation and operation of the Paediatric Regulation requires continuous extensive scientific, regulatory, and financial resources from the EMA and the European network of National Competent Authorities.

5.1. NCA resources

Paediatric Committee members, assessors and national experts provide significant time and expertise to the work of the Committee. Rapporteurships from 2007 to 2015 by Member States are provided in Table 36. In addition, significant resources are invested by NCAs to support the PDCO (chairpersons from Belgium (2007-2013) and Germany (2013 until present), and various working groups related to paediatric matters, chaired by PDCO members from Belgium (NcWG), Norway / Ireland (FWG), Norway (MSWG).

Table 36. Number of contributions (rapporteurships/peer reviews) for initial applications, modification and compliance checks from 2007 to 2015 by Member State or representatives

MS/organisation	Number of initial applications	Number of PIP modifications	Number of compliance checks
Austria	143	112	10
Belgium	144	76	9
Bulgaria	55	26	5
Croatia	1	3	0
Cyprus	2	0	0
Czech Republic	87	54	7
Denmark	146	148	16
Estonia	50	83	22
Finland	67	57	2
France	268	207	37
Germany	435	311	64
Greece	10	2	0
Hungary	78	68	10
Iceland	14	16	1
Ireland	115	53	6
Italy	149	136	43
Latvia	34	14	0
Lithuania	18	12	0
Luxembourg	102	67	12
Malta	69	30	6
Norway	52	27	4
Poland	132	83	11
Portugal	446	159	17
Romania	84	22	6
Slovakia	8	0	0
Slovenia	89	34	5
Spain	211	185	28
Sweden	186	113	41

MS/organisation	Number of initial applications	Number of PIP modifications	Number of compliance checks
The Netherlands	236	179	31
United Kingdom	266	118	27
Healthcare and academia representatives	132	81	8
Patient associations representatives	70	34	2

Source: EMA database (PedRA).

In addition to PDCO activities, NCAs contribute to the following activities relating to paediatrics:

- Approval of paediatric clinical trials performed in their regions and uploading information to the EudraCT database;
- Involvement in national and EU paediatric scientific advice;
- Assessment of Article 45 and Article 46 procedures, compliance checks and updates of SmPCs for paediatric data relating to nationally approved products;
- Contribution to the CMDh paediatric subgroup which was established to coordinate paediatric activities and regulatory procedures;
- Contribution to the collection of data for the annual reports, and reporting on companies who benefit from or infringed the Paediatric Regulation (in collaboration with their Patent Offices);
- Assessors training in paediatric matters.

5.2. EMA resources

The European Medicines Agency has also contributed significant resources to support paediatric activities, including:

- Support to the PDCO and its activities (including FWG, NcWG, MSWG, extrapolation expert group);
- Support to the CMDh paediatric subgroup;
- Scientific evaluation of PIPs and waivers;
- Input to paediatric scientific advice;
- Input to CHMP assessments on paediatric indications;
- Contribution to and coordination of scientific guideline review;
- Input to PRAC assessments;
- Input to CAT assessments;
- Contribution to paediatric monthly cluster (FDA, PMDA, HC, TGA);
- Coordination of paediatric matters in COMP procedures;
- Provision of the Enpr-EMA secretariat;
- Regulatory and legal support on paediatric matters;
- Training of assessors;
- Organisation of workshops and expert meetings;
- Analysis of the data from Member States and EMA databases to produce annual reports for the European Commission.

6. Lessons learned

The implementation of the Paediatric Regulation by the European regulatory network in the last nine years has been a complex process. The Regulation has led to successful changes in the development and authorisation process of medicines and brought about a major increase in awareness of paediatric needs in regulatory interactions. Its implementation involved challenges in particular due to scientific complexities, which the EMA, its Paediatric Committee (PDCO) and the EU regulatory network have had to identify and address. This included the need to develop and support new scientific approaches to drug development such as modelling and simulation or extrapolation.

The data in this report confirm that the objectives of the Paediatric Regulation are being achieved. There is clear evidence of increased and better research, more clinical trials in children, and increased availability of paediatric medicines and age-appropriate information.

Nine years after the entry into force of the Regulation, it is still necessary to address challenges, difficulties and consequences in order to achieve the objectives more efficiently, and to progress regulatory science on paediatric medicine development.

The positive impact of the EU Paediatric Regulation, introducing a balance of obligations and rewards to develop medicines for children was first recognised in the 5-year Report to the European Parliament. Independent assessments of similar US legislation have further confirmed that legislative measures are a necessary and effective instrument to correct the market forces that had historically led to unacceptable inequalities in the standards and practices relating to access to safe and effective medicines for children compared to adults.

After the experience gained during the implementation and as elaborated in this section the following issues need particular attention:

- Legislative measures are necessary to correct the inequalities in the standards and practices relating to access to safe and effective medicines for children compared to adults. The system of obligations and rewards of the EU Paediatric Regulation has stimulated paediatric development of medicines.
- In spite of that success, once the marketing authorisation for adults is granted, deferred paediatric studies may be delayed or not initiated. This is due to the fact that once the product becomes authorised, the most significant deterrent of the Regulation, non-validation of the marketing authorisation application, is not applicable. This leaves the regulatory network without the means to enforce the PIP completion once the product is authorised. Additionally, once the medicine is authorised in adults and thus available for off-label use in children, it becomes more difficult to recruit children into clinical trials.
- The principles underpinning the definition of rewards for orphan medicines do not foresee the circumstances where the orphan medicinal product is patent protected. This creates the need for companies to choose between rewards derived from the PIP or Orphan designation, many times to the detriment of the framework created for orphan medicinal products.
- The lack of research infrastructure has been identified by EnprEMA as the major hurdle to sustainable paediatric research. A common infrastructure to support the existing networks and allow them to collaborate effectively and offer high quality services to industry when developing medicines for children would be a valuable addition for the EU.

- Even when a new medicinal product is approved for use in children this does not necessarily imply that children have access to the medicinal product. The improvement of availability and access means to medicines would greatly benefit the paediatric population and improve consistently the tangible effect of the Paediatric Regulation.
- EU coordinated action in the area of research in paediatric drug development would facilitate and increase the research activity in paediatrics and would be a key enabler for stimulating the development of better medicines for children.
- The regulation links the adult indication to the obligation to have a paediatric investigation plan; therefore, matching the adult condition with the one in children is a determinant factor. This factor needs to be addressed if the therapeutic interest is to be considered a major driver for development of medicines for children. An EU structured, scientific, prospective and agreed identification of paediatric needs could provide predictability to the pharmaceutical industry. In addition where competition in drug development is a bottleneck, prioritisation of drug developments for the most promising substance(s) at EU level could be promoted in a multi-stakeholder approach.

6.1. Balance of obligations and rewards

The EU Paediatric Regulation contains a system of obligations and rewards which has proven to be effective in stimulating paediatric development of medicines.

In the EU legislation, most rewards are linked to the obligations, whereas these are separate in the US (where legislation entered into force earlier); this is in fact one of the major differences between the two regions. However, experience from the US and other regions suggests that a system including both obligations and rewards is appropriate and necessary to achieve results with a public health impact.

Japan, Australia and Canada have no obligations to develop paediatric medicines and have seen limited progress in this area (Council of Canadian Academies, 2014), see section 1.7. The same was the case in the EU before implementation of the Paediatric Regulation despite having guidelines in place (CPMP guideline since 1995, ICH E11 since 2001).

6.1.1. Obligations

As mentioned, experience from the EU, the US and other regions conclusively shows that a system based exclusively or primarily on voluntary initiatives from developers, or solely on incentives, does not result in development of medicines that address satisfactorily the public health needs of children.

Guidelines and recommendations alone are not sufficient to stimulate and ensure adequate development of good medicines for children, as demonstrated by the insufficient paediatric medicines development prior to the Paediatric Regulation despite the existence of such documents.

The EMA also experienced the lack of voluntary development in areas of high unmet paediatric needs but little commercial interest, such as paediatric oncology. An analysis was made by the EMA on requests by pharmaceutical companies to confirm the applicability of a class waiver to their medicinal product. In these procedures, the PDCO of the EMA identified a potential paediatric interest for some of these medicines in disease(s) different from the disease(s) initially intended to be targeted by the applicant, and thus encouraged a voluntary paediatric development that would support paediatric indication(s). Between 2011 and 2014, the Agency confirmed the applicability of the class waiver in 73 cases and identified a potential paediatric interest for 50 of them (68%). Unfortunately, the suggestion to submit a PIP application to cover a new paediatric development was accepted only in a single case, suggesting that rewards without obligations have some limitations in fostering the development of paediatric medicines.

Conversely, the obligations of paediatric development introduced by the Paediatric Regulation have proved successful considering the high number of new paediatric medicines and indications granted since the implementation of the Regulation, many of which have fulfilled previously unmet paediatric needs (e.g. new medicines in rheumatology).

For example, measures and studies whose completion is not deferred and need to be completed before marketing authorisation application tend to be completed in time and in compliance with the agreed PIP. This is ensured by checking compliance at the time of the marketing authorisation application as non-compliance would prevent validating the application. On the contrary, once the marketing authorisation for adults is approved, deferred studies may be delayed. The PDCO sees many requests to postpone completion, or requests for changes of critical elements of the studies that substantially reduce the scope and quality of the development in children. Once the product becomes authorised, the most significant deterrent of the Regulation, i.e. non-validation of the marketing authorisation application, is not applicable.

Finally, some categories of marketing authorisation applications are exempt from the obligations of the Paediatric Regulation, which has occasionally led to unsatisfactory outcomes. For example, generic and biosimilar medicinal products (Articles 10(1) and 10(4) of Directive 2001/83/EC) are exempt from the requirements of Article 7 and 8. This means that a generic or biosimilar medicinal product does not need to maintain a paediatric indication or a paediatric age-appropriate pharmaceutical formulation that was authorised for the originator. In such cases, a potential public health problem may occur if the (potentially unsuitable) generic or biosimilar product is prescribed for children (off-label) and/or without the age-appropriate formulation (risk of medication errors). It should also be noted that hybrid applications (Article 10(3) of Directive 2001/83/EC) are exempt from paediatric obligations even if these applications may cover a new indication that may be of relevance for the paediatric population.

6.1.2. Rewards and incentives

SPC extension

Annual questionnaires to the National Patent Offices identified that by the end of 2015, 23 Member States had reported as granted or pending 322 six-month (national) extensions of the Supplementary Protection Certificate (SPC) for 39 medicines even though 99 PIPs have been completed.

Two Paediatric Use Marketing Authorisations (PUMA) have been granted so far (as of December 2015), which benefit from the 10-year period of protection.

Three orphan medicinal products have obtained a two-year extension of the market exclusivity period.

For certain medicines the obligations of the Regulation, i.e. to obtain a PIP or waiver apply without the opportunity to obtain the reward (for example active substances which are not eligible for an SPC/patent that qualifies for an SPC, such as some vaccines). In addition, requesting the reward is cumbersome in comparison to other rewards in the regulatory field (e.g. data protection or market exclusivity, which are automatically applied), as applications must be made in each Member State where an SPC exists

Moreover, some completed PIPs did not lead to a reward if the paediatric development was completed after the two-year advance notice period which is required to apply for the SPC extension. The two-year notice is intended to provide due warning to manufacturers of generic medicinal products, but it effectively prevents the possibility of granting the reward to the company having performed the development in some cases.

Orphan product incentive

The Paediatric Regulation foresees two additional years of market exclusivity as a potential reward for orphan medicines.

The paediatric legislation was developed when about 60% of the orphan-designated products were off-patent (2003-2004). However, over time this has substantially changed, and in the years 2013 to 2016 (September) 95% of the orphan-designated products which obtained marketing authorisation are covered by a patent (41/43). As a consequence, the orphan reward (2 additional years of market exclusivity) appears less interesting to developers, unless there is no SPC, or it cannot be extended.

The fact that the two rewards are mutually incompatible can be seen as unfair, as developing for a rare disease in children is doubly difficult. Considering this change of paradigm that a substantial number of orphan medicinal products are covered by a patent the adequacy and the proportionality of the reward for orphan medicinal products might be discussed.

Paediatric Use Marketing Authorisation (PUMA)

The granting of only three PUMAs demonstrates the lack of appeal of the data exclusivity and market protection reward to developers. The lack of interest in PUMAs is probably associated with the lack of other incentives in addition to the above periods of market protection such as specific pricing schemes or other measures to minimise the off-label use of available generic medicines not authorised in the paediatric population or not benefiting from an age-appropriate formulation. Challenges to develop such medicines are the result of complex factors which include but are not limited to data protection and pricing. All steps of the chain would need to be addressed to observe significant changes.

6.2. Availability of paediatric medicines

Even when a medicine is authorised for use in children this does not necessarily imply that children have access to the medicinal product, despite specific obligations being imposed on marketing authorisation holders which have benefited from the paediatric rewards (Article 33 of Regulation (EC) No 1901/2006). This is an important issue which requires consideration from all stakeholders in order to make appropriately studied and authorised medicines available to children. Actual availability and accessibility depend on further arrangements for placing on the market such as reimbursement and sufficient pricing, which have to be agreed in each Member State.

6.3. Research in neglected areas and populations

Neonates represent a particularly neglected population, with high unmet medical needs. Clinical trials in neonates are increasingly proposed by applicants and requested, wherever appropriate, by the PDCO. Twenty-six percent of all agreed PIPs include studies in neonates. However, based on the desire

to protect neonates, neonatal studies were very often deferred until experience has been gained with other age groups. These deferrals have led to continuing off-label use as neonatal trials are difficult and always performed last.

The issue is currently being discussed and general understanding seems to support significantly earlier conduct of neonatal studies, considering the limited relevance of evidence obtained in older age groups to protect this group.

Another neglected area that had been identified in the 5-year Report is paediatric oncology.

There is an ongoing debate on the progress achieved in medicine development for children with cancer (unite2cure, 2016). Clearly, a number of new medicines have become available for these patients (section 3.13.). Perhaps more importantly, a high number of paediatric developments of novel medicines is ongoing and now results of first paediatric trials are emerging. However, only a fraction of medicines that recently became available for adults were presented by pharmaceutical companies for discussion of the potential relevance for children with cancer, and this cannot be improved through regulatory obligations in the current framework. For such medicines, the revocation of the list of class waivers was envisaged to stimulate paediatric discussions, but this remains to be followed-up.

From the perspective of patient care, 7 novel medicines were presented in a recent review to demonstrate the progress in treatments for children with cancer (Saletta et al. 2014). However, only 2 of these 7 medicines have a PIP (3 have a Written Request), and for 2 additional medicines early-phase paediatric studies were submitted for assessment (Article 45 or 46). This points out to the gap between paediatric oncology research and development and the medicines that reach the regulatory networks. Reducing and closing this gap is a necessity from the patient perspective (unite2cure, 2016).

6.4. Role of EnprEMA

The Agency has developed a European network of research networks in accordance with Article 44 (1) of the Paediatric Regulation, investigators and centres with recognised expertise in performing clinical studies in children (Enpr-EMA). Enpr-EMA was mentioned by the European Commission as one of the successes of the Paediatric Regulation (European Commission, 2013).

The lack of sustained core funding for reusable research infrastructure at site level as well as for coordination of research activities at network level has been identified by Enpr-EMA as the major hurdle to paediatric research. A recently conducted survey among Enpr-EMA networks and industry (Lepola et al. 2016) detected lack of consistency and uniformity, and limited resources of networks as a general problem. Regular funding and staffing (administrative and scientific) have proven to be crucial factors for effective networks with strong operational status.

Differences in national legislations, ethics procedures, and healthcare organisation have an impact on the services and practice for the networks' capabilities. Consequently, contributions to core funding of networks from national healthcare systems, as they are linked to the local infrastructures, could help to scale up the networks' and sites' capacity.

There is also a need for standardising not only the processes related to the execution of clinical trials but for developing common training curricula, quality standards and performance measures to improve operational site capacity and to allow them to collaborate effectively and offer high quality services to both academic consortia and industry when developing medicines for children.

In addition, many networks in Europe are still virtually unknown to industry with respect to therapeutic areas, competence, expertise, and contact information. This lack of awareness and insufficient communication has caused suboptimal collaboration and challenges for paediatric clinical trial networks and industry. In order to address industry needs for more information, a publicly accessible and

searchable [Enpr-EMA Network Database](#) has been developed with links and contacts to paediatric clinical trial networks. Networks, themselves, should provide clear information on their websites, including identification of therapeutic areas, contact details, possibility to obtain expert advice, and response timelines.

6.5. Research into off-patent products for children

Funding for off-patent medicines for paediatric use under FP 7 led to high-quality research projects which are progressing towards the increase of new paediatric medicines on the market (Ruggieri et al., 2015). Such research projects can still be funded within Horizon 2020, in particular those indicated for rare diseases, but have to compete with large non-paediatric projects. EU funding provisions specific to paediatrics are crucial to facilitate research and development.

There is currently no dedicated EU funding to respond to the Paediatric Regulation provision on funding the development of off-patent products for paediatric use, “through the Community Framework Programmes for Research, Technological Development and Demonstration Activities or any other Community initiatives for the funding of research” (Article 40).

EU coordinated action in this area would facilitate and increase the research activity in paediatrics and would be a key enabler for stimulating the development of better medicines for children.

6.6. Scope of PIPs and waivers

Classifications of diseases and conditions are mainly based on organ or system pathologies. As the characteristics and the biology of the diseases are better known and now the main basis for medicine development, the limitations of the application of these classifications to medicine development are apparent.

This also applies to those systems specifically developed for regulatory purposes. Modern day drug development builds on molecular pathology, cell biology, and, increasingly, systems biology, rather than on anatomic systems based on organ pathology. The PIP condition is linked to the adult indication. As a consequence, promising products with a mechanism of action shared between adult and paediatric pathologies but a different anatomic classification may not be developed for children.

The PDCO has to determine the condition (target) for which a new medicinal product is to be used and developed, to identify the scope of the PIP opinion, the indication proposed by the applicant being the starting point. In cases where the paediatric need differs from that in adults, the additional requirements for companies may create difficulties and result in the need for additional scientific and financial resources that in the absence of additional incentives may be a burden on drug development.

Another issue identified is that some diseases/conditions are common in adults but relatively rare in children, and several medicines are developed in parallel and compete for the same and limited paediatric patient pool. This creates substantial difficulties for developers. Areas where there is extensive development in adults but few children are affected are for example type 2 diabetes, hypertension, melanoma and osteoporosis.

The regulation links the adult indication to the obligation to have a paediatric investigation plan; therefore, a match of the adult condition with the condition in children is a determinant factor. This does not correspond to the interest of the product from a pharmacological activity and therapeutic interest point of view. This area needs to be addressed if the therapeutic interest is to be considered a major driver for development of medicines for children. The approach would require setting up an EU structured, scientific, prospective and agreed identification of paediatric needs to provide predictability to the pharmaceutical industry.

Finally it should be noted that as result of the adoption of PIPs for the same condition several medicines are developed in and in competition for the same and limited paediatric patient pool, which has created substantial difficulties. The prioritisation of drug developments for the most promising substance(s) in areas where there is extensive development in adults but few children with the disease, requires discussion at EU level in a multi-stakeholder approach.

6.7. PIPs and their life-cycle

The development of a medicinal product is a dynamic process, continuously influenced by the results of ongoing studies.

Most agreed PIPs have been modified after the first EMA decision, sometimes in a significant number of cases (eight or more modifications in a few cases). Modifications are expected and necessary as part of the PIP life-cycle; still, multiple modifications and multiple PIPs per medicine can result in administrative burden for all stakeholders and in delays in completion of paediatric clinical trials. As the level of detail in the key elements of PIP opinions has been reduced after the first years, the number of modification requests per PIP has decreased. Whereas specific requirements aim at high quality paediatric development, excess level of details in PIP opinions may result in lack of flexibility. Changes have already been undertaken to address the issue within the limits of the current legislation, in the revised EC Guideline and at the implementation level.

Applicants are required to submit PIPs not later than upon completion of human pharmacokinetic studies in adults. Although this creates an opportunity for discussion of paediatric matters early on during the development, it is challenging to consider all aspects of medicine development for children at a time when important characteristics even of the adult development are not yet known. PIP opinions which are too detailed at such an early stage can be difficult to agree and counterproductive because emerging data will inevitably lead to changes. Given the fact that currently only applicants are allowed to request a modification of the agreed PIP, a submission at an early stage of the product development prompts the PDCO to include all the necessary details in the original PIP opinion; otherwise the developed plan would be less than comprehensive. Considering a life cycle approach of the PIP in line with the development progress with additional time points for interaction on PIP refinement could be given consideration as an area for improvement.

In some cases changes to study protocols are implemented by companies directly without prior discussion with the PDCO. In these cases the PDCO can only assess changes retrospectively, sometimes at very late stages of the development programmes, putting the committee in a difficult position.

6.8. Paediatric expertise and committees

Following significant efforts and resources of Member States, the PDCO and EMA, paediatric expertise has been provided to EMA committees and working parties on paediatric questions. MSs provide their support to these activities according to their respective resources and capacities. The collaboration between CHMP, SAWP and PDCO has been ensured by substantial effort of the EMA Offices and Departments involved and through members of the Committees, through regular interaction processes, and cross-committee involvement of EMA scientific officers.

What has proved to be of significant added value in any case, is to have dedicated paediatric expertise within the regulatory system. This has ensured that the scientific complexity of the paediatric development is taken into account, that new development approaches are optimising the involvement of children, i.e. allowing generation of relevant data without performing unnecessary trials

(extrapolation, innovative approaches on modelling and simulation, etc.) and that the trials are requested to address unmet paediatric needs.

The complexity of paediatric development has highlighted the importance that the Paediatric Committee, or any other scientific body involved in the procedures of the Paediatric Regulation, includes substantial representation of clinical experts in paediatric conditions, on top of the other expertise listed in Article 4 of the Regulation. In the first 9 years of the Regulation, the composition of the PDCO has been optimised through the identification by the European Commission of appropriate nominated members, in full collaboration with the EMA and the patients' and healthcare providers' association. This has allowed strengthening the expertise of the committee in specific areas, such as for example quality of form and formulation aspects, paediatric endpoints, paediatric oncology, neonatology, ethics and statistics.

Among the current criteria for the composition of the PDCO there is the requirement that five members, with their alternates, must be also CHMP members, to be appointed by the CHMP. This requirement has caused a number of substantial difficulties, listed below.

- Substantial workload and travel burden for the joint CHMP-PDCO members, who need to attend two, three or four-day meetings in London every month, and work on more procedures. The PDCO procedures are not being financially compensated. As a consequence, the CHMP has met with serious difficulties in identifying the required number of joint members, and PDCO attendance of the joint members has been very poor.
- Problems arise when a joint member at the CHMP/PDCO resigns. In that situation, the Member State that appointed that CHMP/PDCO member is not allowed to nominate directly a PDCO member. The Member State may only appoint a new CHMP member, while the decision of whether to appoint the CHMP member also in the PDCO rests with the CHMP itself. This has led to the absence of the Member State (previously holding the joint position) in the PDCO for a considerable amount of time (only four CHMP/PDCO member/alternate teams present since 2010).

In conclusion, the added value of having specific paediatric expertise in a committee is obvious and evidence based to avoid missing paediatric specific aspects and ensure the best outcomes on paediatric medicines development and evaluation. The importance of systematic collaboration between committees to maximise the use of expertise has also been demonstrated.

6.9. Funding of paediatric regulatory activities

One of the difficulties of the implementation of the Paediatric Regulation has been that paediatric procedures do not attract fees and Committee members are not compensated for this highly complex work. This has been challenging, also in relation to the work-sharing evaluation of the large number of studies submitted according to Article 45, which is still ongoing. The difficulty of assigning resources to numerous procedures without fees is high and may require changes in the approach.

6.10. Appropriate use of authorised medicinal products

Off-label use has traditionally been widespread clinical practice mainly because of the limited treatment options for children. A change of habits is necessary to encourage health care professionals to use new appropriately studied and authorised medicines. Medical schools and specialist training programmes have a joint responsibility to further increase awareness of the potential risks of off-label prescribing for vulnerable patient groups when an authorised product is available.

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8. Glossary/Abbreviations

Abbreviation/term	Explanation
Adolescents	Children between initiation of puberty and 18 years of age (often simplified as from 12 to less than 18 years of age)
ADR	Adverse drug reactions
ATMP	Advanced therapy medicinal product
BPCA	Best Pharmaceuticals for Children Act (U.S. legislation)
CAP	Centrally Authorised Product (medicine authorised by the European Commission, after scientific evaluation by EMA)
CAT	Committee for Advanced Therapies at EMA
Children	Term often used to define the paediatric population from 2 years to less than 12 years of age
CHMP	Committee for Medicinal Products for Human Use at EMA
CPMP	Committee for Proprietary Medicinal Products at EMA (predecessor of CHMP)
CMDh	Co-ordination group for Mutual Recognition and Decentralised Procedures – human (A committee of the National Competent Authorities, hosted by EMA for their meetings)
COMP	Committee for Orphan Medicinal Products at EMA
CT	Clinical trial as defined in Directive 2001/20/EC
DALY	Disability-adjusted life year (a measure of disease burden)
DCP	Decentralised Procedure (a non-centralised procedure for authorisation of medicinal products)
DIA	Drug Information Association
DREAM	Document Records Electronic Archive Management at EMA
EC	European Commission
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
Enpr-EMA	European Network of Paediatric Research at the European Medicines Agency
EPAR	European Public Assessment Report
ePPND study	Enhanced pre- and postnatal development study
EU	European Union
EUCOPE	European Confederation of Pharmaceutical Entrepreneurs
EU-CTR	European Clinical Trials Register
EudraCT	European Union Drug Regulating Authorities' Clinical Trials Database: https://www.clinicaltrialsregister.eu/
FDA	U.S. Food and Drug Administration
FP7	Framework Programme 7, an EU funding programme (2007-2013). Its successor is Horizon 2020.
FWG	Formulation Working Group (an informal subgroup that assists the PDCO on issues regarding formulations and pharmaceutical forms for children)
GCP	Good Clinical Practice
GRIP	Global Research in Paediatrics (scientific network, funded by FP7)
HEALTH	An EC funding programme on off-patent medicines
HC	Health Canada (Regulatory body for medicines in Canada)
HIV	Human immunodeficiency virus
iCAN	International Children's Advisory Network

Abbreviation/term	Explanation
ICH	International Conference on Harmonisation
Infants	Paediatric population from 1 month to less than 12 months of age
INC	International Neonatal Consortium
JAS	Juvenile Animal Study
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MRP	Mutual Recognition Procedure (a non-centralised procedure for authorisation of medicinal products)
MSWG	Modelling and Simulation Working Group (an EMA informal scientific group)
NCA	National Competent Authority
NcWG	Non-clinical Working Group (an informal subgroup that assists the PDCO on issues regarding non-clinical development of products for children)
Newborns	Paediatric population from birth to less than 28 days of age
NPO	National Patent Office (awarding patents, SPCs and SPC extensions)
OPT	Office of Pediatric Therapeutics at FDA
PA	Protocol Assistance
Paediatric population	Population from birth to less than 18 years of age
PedRA	Paediatric Records Application at EMA
PD	Pharmacodynamics
PDCO	Paediatric Committee at EMA
PEG	Paediatric Expert Group (predecessor of PDCO)
PIL	Patient Information Leaflet
PIP	Paediatric Investigation Plan
PK	Pharmacodynamics
PMDA	Pharmaceuticals and Medical Devices Agency, Japan
PRAC	Pharmacovigilance Risk Assessment Committee
PREA	Pediatric Research Equity Act (U.S. legislation)
PSP	Pediatric Study Plan under PREA at FDA (similar to a PIP)
PUMA	PUMA: Paediatric Use Marketing Authorisation (Legal basis: Article 30 of Regulation (EC) 1901/2006 in conjunction with Article 8(3) of Directive 2001/83/EC, as amended)
RAPS	Regulatory Affairs Professionals Society
RMP	Risk Management Plan
RMS	Reference Member State in a non-centralised procedure
SA	Scientific Advice
SAWP	Scientific Advice Working Party at EMA
SIAMED	Product information and application tracking system at EMA
SME	Small and Medium-sized Enterprise
SmPC	Summary of Product Characteristics; Paediatric information is reflected in the following sections: Section 4.1 Indication(s) Section 4.2 Posology and method of administration Section 4.4 Special warnings and precaution for use Section 4.5 Interactions Section 4.8 Undesirable effects Section 5.1 Pharmacodynamics properties

Abbreviation/term	Explanation
	Section 5.2 Pharmacokinetic properties
SPC	Supplementary Protection Certificate (an extension of the 'basic' patent)
Toddlers	Paediatric population from 1 year to less than 2 years of age
TOPRA	The Organisation for Professionals in Regulatory Affairs
Type II variation	Variation of EU marketing authorisation that may have a significant impact on the quality, safety or efficacy information of a medicinal product (for example, to include a new therapeutic indication)
Waiver	Exemption from the obligations of art. 7 and 8 of the Paediatric Regulation
WHO	World Health Organization
WR	Written Request of FDA, under BPCA (similar to a PIP)



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Annex

10-year Report to the European Commission

Note: The report covers in principle the period from January 2007 to December 2015. This version of the report is an update to the one provided to the European Commission in 2016. The scope of the update was to include data from 2016 into key analyses such as the number of paediatric medicine authorisations and paediatric clinical trials; the reporting periods are indicated in the respective analyses.



Table of content

Table of content	2
1. New medicines for children	3
1.1. New medicines, new indications and new pharmaceutical forms	3
1.1.1. Centrally authorised medicines	3
1.1.2. Nationally authorised medicines (including DCP and MRP)	19
1.2. Effect of the Paediatric Regulation on the authorisation of medicines for children.....	46
1.3. Paediatric Use Marketing Authorisation (PUMA)	47
1.4. Statements of compliance in marketing authorisations	54
1.4.1. Statements of compliance (CAPs)	55
1.4.2. Statements of compliance (NAPs, DCP/MRP)	56
1.4.3. PDCO opinions on PIP compliance	58
1.4.4. Supplementary protection certificate extension (6 months) granted by national patent offices	66
2. Paediatric research and development	77
2.1. Paediatric investigation plans	77
2.1.1. Addressing unmet paediatric needs	77
2.2. Paediatric research incentives	79
2.2.1. Projects on off-patent medicines funded by the European Commission through the EU Framework programme	79
2.2.2. National funding	81
2.3. Paediatric clinical trials	85
2.3.1. Selection of fields and trials	85
2.3.2. Number of paediatric clinical trials	86
2.3.3. Clinical trials by phase and design	87
2.3.4. Number of children in clinical trials	87
2.4. European Network for Paediatric research at the EMA (Enpr-EMA)	90
2.4.1. Enpr-EMA milestones	90
2.4.2. Enpr-EMA networks	92
2.5. External experts, workshops and scientific guidelines.....	98
2.5.1. Expert meetings and workshops	98
2.5.2. Guidelines	100
3. Other initiatives	102
3.1. Publications relating to the Paediatric Regulation	102
3.1.1. Publications by EMA/PDCO on the Paediatric Regulation	102
3.1.2. Publications by external authors on the Paediatric Regulation.....	108

1. New medicines for children

1.1. New medicines, new indications and new pharmaceutical forms

1.1.1. Centrally authorised medicines

New medicines

- One hundred and one new medicinal products were centrally authorised from 2007 to 2016 with a paediatric indication at the time of the initial marketing authorisation. Sixty of these were linked to the Paediatric Regulation.
- Out of these medicines, eleven were authorised for use in the paediatric population only.

Table 1. New medicines (CAPs, initial marketing authorisations) including a paediatric indication by year of authorisation (2007-2016)

Year	Active substance(s)	Trade name	Indication paediatric-only or mixed ¹
2007	Retapamulin	Altargo	Mixed
2007	Nelarabine	Atriance	Mixed
2007	Human papillomavirus vaccine [types 16, 18]	Cervarix	Mixed
2007	Hydroxocobalamin	Cyanokit	Mixed
2007	Idursulfase	Elaprase	Mixed
2007	Gadoversetamide	Optimark	Mixed
2007	Betaine anhydrous	Cystadane	Mixed
2007	Stiripentol	Diacomit	Paediatric-only
2007	Mecasermin	Increlex	Paediatric-only
2007	Rufinamide	Inovelon	Mixed
2007	Hydroxycarbamide	Siklos	Mixed
2007	Human normal immunoglobulin (ivig)	Flebogamma DIF	Mixed
2008	Fluticasone furoate	Avamys	Mixed
2008	Human normal immunoglobulin	Privigen	Mixed
2008	Lacosamide	Vimpat	Mixed
2008	Micafungin	Mycamine	Mixed
2008	Sapropterin	Kuvan	Mixed
2008	Sugammadex	Bridion	Mixed
2009	Tocofersonal d-alpha tocopheryl polyethylene glycol succinate	Vedrop	Paediatric-only
2009	Mifamurtide	Mepact	Mixed
2009	Riloncept	Riloncept Regeneron	Mixed
2009	Tacrolimus	Modigraf	Mixed
2009	Pneumococcal polysaccharide conjugate vaccine (absorbed)	Synflorix	Paediatric-only

¹ Adult and paediatric

Year	Active substance(s)	Trade name	Indication paediatric-only or mixed ¹
2009	Canakinumab	Ilaris (PIP not yet completed)	Mixed
2009	Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)	Prevenar 13 (PIP not yet completed)	Paediatric-only
2010	Meningococcal group a, c, w135 and y conjugate vaccine	Menveo (PIP completed)	Mixed
2010	Velaglucerase alfa	Vpriv (PIP not yet completed)	Mixed
2011	Influenza vaccine (live attenuated, nasal)	Fluenz (waiver)	Paediatric-only
2011	C1 inhibitor, human	Cinryze (PIP not yet completed)	Mixed
2011	Dihydroartemisinin / piperaquine phosphate	Eurartesim (PIP not yet completed)	Mixed
2011	Midazolam	Buccolam (PIP completed)	Paediatric-only (PUMA)
2011	Everolimus	Votubia (PIP not yet completed)	Mixed
2011	Tobramycin	Tobi Podhaler (PIP not yet completed)	Mixed
2011	Nomegestrol / estradiol	loa, Zoely (PIP completed)	Mixed
2012	Repandemic influenza vaccine (h5n1) (whole virion, inactivated, prepared in cell culture)	Vepacel	Mixed
2012	Mercaptopurine	Xaluprine	Mixed
2012	Colistimethate sodium	Colobreathe	Mixed
2012	Perampanel	Fycompa	Mixed
2012	Ivacaftor	Kalydeco	Mixed
2012	Meningococcal group a, c, w135 and y conjugate vaccine	Nimenrix	Mixed
2012	Catridecacog	Novothirteen	Mixed
2013	Meningococcal group b vaccine (rdna, component, adsorbed)	Bexsero	Mixed
2013	Diphtheria (d), tetanus (t), pertussis (acellular, component) (pa), hepatitis b (rdna) (hbv), poliomyelitis (inactivated) (ipv) and haemophilus influenzae type b (hib) conjugate vaccine (adsorbed)	Hexacima	Paediatric-only

Year	Active substance(s)	Trade name	Indication paediatric-only or mixed ¹
2013	Diphtheria (d), tetanus (t), pertussis (acellular, component) (pa), hepatitis b (rdna) (hbv), poliomyelitis (inactivated) (ipv) and haemophilus influenzae type b (hib) conjugate vaccine (adsorbed)	Hexyon	Paediatric-only
2013	Somatropin	Somatropin Biopartners	Mixed
2013	Human coagulation factor viii / human von willebrand factor	Voncento	Mixed
2013	Defibrotide	Defitelio	Mixed
2013	Fluticasone furoate / vilanterol	Relvar Ellipta	Mixed
2013	Influenza vaccine (live attenuated, nasal)	Fluenz Tetra	Mixed
2013	Filgrastim	Grastofil	Mixed
2013	Turoctocog alfa	NovoEight	Mixed
2013	Mercaptamine	Procysbi	Mixed
2013	Bosentan	Stayveer	Mixed
2014	Simoctocog alfa	Nuwiq	Mixed
2014	Dolutegravir	Tivicay	Mixed
2014	Ataluren	Translarna	Mixed
2014	Dolutegravir / abacavir / lamivudine	Triumeq	Mixed
2014	Elosulfase alfa	Vimizim	Mixed
2014	Propranolol	HEMANGIOL	Paediatric only (PUMA)
2014	Cholic acid	Kolbam	Mixed
2015	Lamivudine / raltegravir potassium	DUTREBIS	Mixed
2015	Human papillomavirus vaccine [types 6, 11, 16, 18, 31, 33, 45, 52, 58] (recombinant, adsorbed)	Gardasil 9	Mixed
2015	Sebelipase alfa	Kanuma	Mixed
2015	Idebenone	Raxone	Mixed
2015	Evolocumab	Repatha	Mixed
2015	Efmoroctocog alfa	ELOCTA	Mixed
2015	Elvitegravir / cobicistat / emtricitabine / tenofovir alafenamide	Genvoya	Mixed
2015	Lumacaftor / ivacaftor	Orkambi	Mixed
2016	Eftrenonacog alfa	Alprolix	Mixed
2016	Brivaracetam	Briviact	Mixed
2016	Human coagulation factor x	Coagadex	Mixed
2016	Emtricitabine / tenofovir alafenamide	Descovy	Mixed
2016	Pancreas powder	Enzepi	Mixed
2016	Migalastat	Galafold	Mixed
2016	Octocog alfa	Iblias/Kovaltry	Mixed
2016	Albutrepenonacog alfa	IDELVION	Mixed
2016	Emtricitabine / rilpivirine / tenofovir alafenamide	Odefsey	Mixed
2016	Pegaspargase	Oncaspar	Mixed

Year	Active substance(s)	Trade name	Indication paediatric-only or mixed ¹
2016	Pandemic influenza vaccine (h5n1) (live attenuated, nasal)	Pandemic influenza vaccine H5N1 MedImmune	Mixed
2016	Asparaginase	Spectrila	Mixed
2016	Autologous cd34+ enriched cell fraction that contains cd34+ cells transduced with retroviral vector that encodes for the human ada cDNA sequence	Strimvelis	Mixed
2016	Diphtheria, tetanus, pertussis (acellular, component), hepatitis b (rdna), poliomyelitis (inact.) and haemophilus type b conjugate vaccine (adsorbed)	Vaxelis	Paediatric only

Note: This list excludes medicines that are not subjected to the obligations of the Paediatric Regulation (e.g. generics, hybrid medicines, biosimilars etc.).

Source: EMA database (SIAMED)

New paediatric indications

- ninety nine new paediatric indications for already authorised products were approved from 2007 to 2016. Seventy eight of these were linked to the Paediatric Regulation.

Table 2. New paediatric indications by year of authorisation (CAPs, variations of existing marketing authorisations) (2007-2016)

Year	Active substance (INN)	Trade name	Subject of extension	MAH
2007	Levetiracetam	Keppra	Extension of the indication to include adjunctive therapy in the treatment of primary generalised tonic-clonic (PGTC) seizures in adults and adolescents from 12 years of age with idiopathic generalized epilepsy	UCB Pharma SA
2007	Pneumococcal saccharide conjugated vaccine, adsorbed	Prevenar	Extension of the indication to include new information on efficacy against disease caused by Streptococcus pneumoniae serotypes 4, 6B, 9V, 14, 18C, 19F and 23F in otitis media.	Wyeth Lederle Vaccines S.A.
2007	Pneumococcal saccharide conjugated vaccine, adsorbed	Prevenar	Extension of indication from active immunisation against bacteraemic pneumonia to active immunisation against pneumonia.	Wyeth Lederle Vaccines S.A.
2007	Infliximab	Remicade	Extension of indication to include treatment of severe active Crohn's disease in children aged 6 to 17 years.	Janssen Biologics B.V.

Year	Active substance (INN)	Trade name	Subject of extension	MAH
2007	Darbepoetin alfa	Aranesp	Extension of indication for CRF patients, which currently restricts the use of Nespo to paediatric subjects \geq 11 years of age	Amgen Europe B.V.
2007	Fosamprenavir	Telzir	Extension of indication of Telzir in combination with ritonavir for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults in combination with other antiretroviral medicinal products to include paediatric populations.	ViiV Healthcare UK Limited
2007	Lamivudine / zidovudine	Combivir	Extension of indication to include paediatric patients and replacement of film coated tablets by scored film coated tablets.	ViiV Healthcare UK Limited
2008	Desloratadine	Aerius	Extension of indication from 'chronic idiopathic urticaria' to 'urticaria'.	Merck Sharp & Dohme Ltd.
2008	Insulin glulisine	Apidra	Extension of indication to include 6 years old and older children based on the results of 2 paediatric studies.	Sanofi-aventis Deutschland GmbH
2008	Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)	Gardasil	Extension of indication to include the prevention of high-grade vaginal dysplastic lesions (VaIN 2/3).	Sanofi Pasteur MSD, SNC
2008	Adalimumab	Humira	Extension of indication to include treatment of active polyarticular juvenile idiopathic arthritis in adolescents from 13 to 17 years of age.	Abbott Laboratories Ltd.
2008	Caspofungin	Cancidas	Extension of the indication to include the paediatric population.	Merck Sharp & Dohme Ltd.
2008	Etanercept	Enbrel	Extension of indication to include the treatment of chronic severe plaque psoriasis in children and adolescents from the age of 8 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.	Pfizer Ltd.
2009	Miglustat	Zavesca	Extension of indication to include the treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease.	Actelion Registration Ltd.

Year	Active substance (INN)	Trade name	Subject of extension	MAH
2009	Tacrolimus	Protopic	Extension of indication to 'maintenance treatment' further to completion of one study in adult patients and one in paediatric patients.	Astellas Pharma Europe B.V.
2009	Tipranavir	Aptivus	Extension of indication to include the treatment of HIV-1 infection in highly pre-treated adolescents 12 years of age or older with virus resistant to multiple protease inhibitors.	Boehringer Ingelheim International GmbH
2009	Omalizumab	Xolair	Extension of indication to children from 6 to <12 years of age as add-on therapy to improve allergic asthma control.	Novartis Europharm Ltd.
2009	Aripiprazole	Abilify	Extension of indication to include treatment of schizophrenia in adolescents 15 years and older.	Otsuka Pharmaceutical Europe Ltd.
2009	Levetiracetam	Keppra	Extension of indication to include the adjunctive treatment of partial seizures with or without secondary generalisation in children from 1 month to <4 years old.	UCB Pharma SA
2009	Peginterferon alfa-2b	PegIntron	Extension of indication of the combination therapy peginterferon alfa-2b and ribavirin to include treatment of the paediatric population.	Schering-Piough Europe
2009	Ribavirin	Rebetol	Extension of indication of the combination therapy peginterferon alfa-2b and ribavirin to include treatment of the paediatric population.	Schering-Piough Europe
2010	Abatacept	Orencia	Extension of indication to include the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis in paediatric patients 6 years of age and older who have had an insufficient response to other DMARDs including at least one TNF inhibitor.	Bristol-Myers Squibb Pharma EEIG
2010	Atazanavir sulphate	Reyataz	Extension of indication for Reyataz capsules to include the treatment of HIV-infected children and adolescents above the age of 6 in combination with other antiretroviral medicinal products.	Bristol-Myers Squibb Pharma EEIG
2010	Measles, mumps and rubella vaccine (live)	M-M-RVAXPRO	Extension of indication to include administration to healthy children from 9 months of age.	Sanofi Pasteur MSD, SNC

Year	Active substance (INN)	Trade name	Subject of extension	MAH
2011	Nitric oxide	Inomax	Extension of indication to include the treatment of pulmonary hypertension peri- and post heart surgery in children.	INO Therapeutics AB
2011	Adalimumab	Humira	Extension of indication to include treatment of active polyarticular juvenile idiopathic arthritis in the paediatric population aged from 4 to 12 years.	Abbott Laboratories Ltd.
2011	Tenofovir disoproxil fumarate	Viread	Amendment of indication based on the 48-week results of a safety and efficacy study GS-US-104-0321 in treatment-experienced adolescents aged 12 to 18 years old.	Gilead Sciences International Ltd.
2011	Paliperidone	Invega	Extension of indication to include treatment of psychotic or manic symptoms of schizoaffective disorder.	Janssen-Cilag International N.V.
2011	Sildenafil	Revatio	Extension of indication in paediatric patients aged 1 year to 17 years old with pulmonary arterial hypertension.	Pfizer Ltd.
2011	Human normal immunoglobulin	Kiovig	Extension of indication to include treatment of multifocal motor neuropathy (MMN). Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation (HSCT) in adults and children.	Baxter AG
2011	Tocilizumab	Roactemra	Extension of indication to include treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids.	Roche Registration Ltd.
2011	Pneumococcal polysaccharide conjugate vaccine (adsorbed)	Synflorix	Extension of indication to increase the upper age limit of infants and children from 2 years to 5 years.	GlaxoSmithKline Biologicals S.A.
2011	Etanercept	Enbrel	Extension of indication to include lower age range for polyarticular juvenile idiopathic arthritis (JIA) "from the age of 4 years" to "from the age of 2 years".	Pfizer Ltd.

Year	Active substance (INN)	Trade name	Subject of extension	MAH
2011	Etanercept	Enbrel	Extension of indication to include lower age range for paediatric plaque psoriasis from "from the age of 8 years" to "from the age of 6 years".	Pfizer Ltd.
2011	Insulin detemir	Levemir	Extension of indication as add-on therapy to liraglutide treatment.	Novo Nordisk A/S
2011	Insulin detemir	Levemir	Extension of indication to children aged 2-5 years	Novo Nordisk A/S
2011	Eculizumab	Soliris	Extension of indication to include atypical haemolytic uremic syndrome (aHUS). Additional vaccination and antibiotic prophylaxis recommendation have also been added in section 4.2 for treatment of aHUS in adults and children.	Alexion Europe SAS
2011	Human papillomavirus vaccine (types 16, 18) (recombinant, adjuvanted, adsorbed)	Cervarix	Extension of indication to children from 9 years.	GlaxoSmithKline Biologicals S.A.
2012	Aztreonam	Cayston	Extension of indication to children from 6 years	Gilead Sciences International Limited
2012	Etanercept	Enbrel	Extension of 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	Pfizer Limited
2012	Deferasirox	Exjade	Extension of indication for the treatment of chronic iron overload requiring chelation therapy in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older	Novartis Europharm Limited
2012	Adalimumab	Humira	Extension of indication to children from 6 years with Crohn's disease	AbbVie Ltd
2012	Insulin glargine	Lantus	Extension of indication for paediatric population age 1 to less than 6 years old	sanofi-aventis Deutschland GmbH

Year	Active substance (INN)	Trade name	Subject of extension	MAH
2012	Insulin glargine	Optisulin	Extension of indication for paediatric population age 1 to less than 6 years old	
2012	Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)	Prevenar 13	Extension of indication to include children and adolescents 6 to 17 years of age.	Pfizer Limited
2012	Measles, mumps, rubella and varicella vaccine (live)	Proquad	Extension of indication from 9 months under special circumstances	Sanofi Pasteur MSD, SNC
2012	Infliximab	Remicade	Extension of indication to children 6-17 years with ulcerative colitis	Janssen Biologics B.V.
2012	Tenofovir disoproxil	Viread	Extension of indication to include treatment-experienced adolescents 12 to < 18 years of age.	Gilead Sciences International Limited
2013	Aripiprazole	Abilify	Extension of indication to include the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.	Otsuka Pharmaceutical Europe Ltd
2013	Human papillomavirus vaccine (types 16, 18) (recombinant, adjuvanted, adsorbed)	Cervarix	Addition of prevention of premalignant vulvar and vaginal lesions	GlaxoSmithKline Biologicals S.A.
2013	Imatinib	Glivec	Extension of the indication for the treatment of paediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ALL) integrated with chemotherapy.	Novartis Europharm Ltd
2013	Canakinumab	ILARIS	Extension of indication of canakinumab for the treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids.	Novartis Europharm Ltd

Year	Active substance (INN)	Trade name	Subject of extension	MAH
2013	Japanese encephalitis vaccine (inactivated, adsorbed)	Ixiaro	Extension of indication to the paediatric segment (2 months of age and older)	Valneva Austria GmbH
2013	Eculizumab	Soliris	Extension of indication of Soliris in the Paroxysmal Nocturnal Hemoglobinuria (PNH) in children.	Alexion Europe SAS
2013	Human normal immunoglobulin	Privigen	Extension of indication to immunomodulation in adults, and children and adolescents (0-18 years) in Chronic inflammatory demyelinating polyneuropathy	CSL Behring GmbH
2013	Darunavir	Prezista	Extension of the indication in the HIV infected treatment naive patients aged 12 to 18 years.	Janssen-Cilag International NV
2013	Tocilizumab	RoActemra	Extension of indication of tocilizumab for the treatment in combination with methotrexate (MTX) of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX	Roche Registration Limited
2013	Zonisamide	Zonegran	Extension of the indication "adjunctive treatment of partial seizures with or without secondary generalisation" to include adolescents and children aged 6 years and above.	Eisai Ltd
2013	Etravirine	INTELENCE	Extension of indication to children from 6 years	Janssen-Cilag International NV
2013	Raltegravir	Isentress	Extension of indication to children from 2 years	Merck Sharp & Dohme Ltd
2013	Peginterferon alfa-2a	Pegasys	Extension of indication to children from 5 years	Roche Registration Limited
2013	Pneumococcal polysaccharide conjugate vaccine (adsorbed)	Synflorix	Extension of the indication for the prevention of pneumonia caused by Streptococcus pneumoniae in infants and children from 6 weeks up to 5 years of age	GlaxoSmithKline Biologicals S.A.

Year	Active substance (INN)	Trade name	Subject of extension	MAH
2013	Prepandemic influenza vaccine (h5n1) (whole virion, inactivated, prepared in cell culture)	Vepacel	Extension of the indication for the treatment of children and adolescent from the age of 6 months onwards	Nanotherapeutics Bohumil, s.r.o.
2013	Everolimus	Votubia	Extension of indication to include treatment of patients < 3 years of age with TSC who have SEGA.	Novartis Europharm Ltd
2014	Entecavir	Baraclude	Extension of indication to include treatment of chronic HBV infection in paediatric patients from 2 to <18 years of age with compensated liver disease and evidence of active viral replication and persistently elevated serum ALT levels.	Bristol-Myers Squibb Pharma EEIG
2014	Adalimumab	Humira	Extension of indication to include the treatment of paediatric subjects with active polyarticular juvenile idiopathic arthritis (JIA) from 4 to 17 years of age to 2 to 17 years of age.	AbbVie Ltd
2014	Paliperidone	Invega	Extension of indication to add the treatment of schizophrenia in adolescents 15 years and older.	Janssen-Cilag International NV
2014	Raltegravir	Isentress	Extension of indication to toddlers and infants from 4 weeks to less than 2 years of age	Merck Sharp & Dohme Ltd
2014	Ivacaftor	Kalydeco	Extension of Indication to include additional gating (class III) mutations in the CFTR gene: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N and S549R.	Vertex Pharmaceuticals (Europe) Ltd
2014	Catridecacog	NovoThirteen	Extension of indication to include the treatment of bleeding in children with congenital factor XIII A-subunit deficiency below 6 years of age.	Novo Nordisk A/S
2014	Darunavir	Prezista	Extension of indication to use darunavir once daily in children aged 3 to 12 years \geq 15 kg who are treatment-naive or treatment-experienced with no darunavir resistance-associated mutations (DRV RAMs)	Janssen-Cilag International NV

Year	Active substance (INN)	Trade name	Subject of extension	MAH
2014	Travoprost	Travatan	Extension of indication in children aged 2 months to <18 years with ocular hypertension or paediatric glaucoma	Alcon Laboratories (UK) Ltd
2014	Voriconazole	Vfend	New indication in prophylaxis of invasive fungal infections in high risk hematopoietic stem cell transplant recipients	Pfizer Limited
2014	Denosumab	XGEVA	Extension of indication to add treatment of giant cell tumour of bone in adults or skeletally mature adolescents.	Amgen Europe B.V.
2015	Palonosetron	Aloxi	Extension of indication to include paediatric patients 1 month of age and older	Helsinn Birex Pharmaceuticals Ltd.
2015	Lamivudine / abacavir	Kivexa	Lower the threshold for use in paediatric patients from >40kg to >25 kg	ViiV Healthcare UK Limited
2015	Sapropterin	Kuvan	Extension of indication for the 'treatment of hyperphenylalaninaemia (HPA) in adults and paediatric patients of 4 years of age and over with phenylketonuria (PKU) who have shown to be responsive to such treatment' to include the paediatric population of all ages.	Merck Serono Europe Limited
2015	Ustekinumab	Stelara	Extension of Indication to add treatment of moderate to severe plaque psoriasis in paediatric patients from the age of 12 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies	Janssen-Cilag International NV
2015	Bosentan	Tracleer	Extension of Indication to include treatment of symptomatic pulmonary arterial hypertension in paediatric patients aged from 3 months to 18 years.	Actelion Registration Ltd
2015	Tigecycline	Tygacil	Extension of Indication to include the restricted use of Tygacil in paediatric patients ≥ 8 years to <18 years of age for Tygacil	Pfizer Ltd.

Year	Active substance (INN)	Trade name	Subject of extension	MAH
2015	Human coagulation factor viii / human von willebrand factor	Voncento	Extension of indication to include prophylactic treatment of patients with VWD	CSL Behring GmbH
2015	Daptomycin	Cubicin	Extension of indication to extend the age range for the indication "complicated skin and soft-tissue infections" (cSSTI), to include paediatric patients from 1 to 17 years of age	Novartis Europharm Limited
2015	Rilpivirine	Edurant	Extension of Indication to include treatment of ARV treatment-naïve paediatric patients aged 12 to <18 years of age	Janssen-Cilag International N.V.
2016	Vandetanib	Caprelsa	Extension of Indication to include paediatric patients aged 5 to 18 with unresectable locally advanced or metastatic medullary thyroid carcinoma	Genzyme Europe BV
2016	Human papillomavirus vaccine	Cervarix	Extension of Indication to include prevention against premalignant anal lesions and anal cancer as of 9 years of age	GSK Biologicals SA
2016	Deferiprone	Ferriprox	Extension of Indication to include a new indication for Ferriprox in combination with another chelator.	Apotex Europe BV
2016	Adalimumab	Humira	Extension of Indication to include the treatment of patients with moderately paediatric active Crohn's disease.	AbbVie Ltd.
2016	Human normal immunoglobulin	HyQvia	Extension of indication to include paediatric population for all authorised indications	Baxalta Innovations GmbH
2016	Canakinumab	ILARIS	Extension of Indication to include treatment of active Still's disease including Adult-Onset Still's Disease (AOSD) in patients aged 2 years and older.	Novartis Europharm Ltd
2016	Meningococcal group a, c, w135 and y conjugate vaccine	Nimenrix	Extension of Indication to include a wider paediatric population starting from 6 weeks of age	Pfizer Limited

Year	Active substance (INN)	Trade name	Subject of extension	MAH
2016	Insulin aspart	NovoRapid	Extension of Indication to include the use of NovoRapid in children from 1 to 2 years of age for the treatment of diabetes mellitus	Novo Nordisk A/S
2016	Teduglutide	Revestive	Extension of Indication to include paediatric population	Shire Pharmaceuticals Ireland Ltd
2016	Conestat alfa	Ruconest	Extension of Indication to include adolescents in the treatment of acute angioedema attacks in patients with hereditary angioedema due to C1 esterase inhibitor deficiency	Pharming Group N.V
2016	Eltrombopag / eltrombopag olamine	Revolade	Extension of indication for paediatric (age 1 year and above) chronic immune (idiopathic) thrombocytopenic purpura	Novartis Europharm Ltd
2016	Atazanavir / atazanavir sulfate	Reyataz	An extension application covering a new pharmaceutical form (oral powder), a new strength for the oral powder presentation (50mg), and a new paediatric indication (patients from 3 months of age and weighing at least 5kg)	Bristol-Myers Squibb Pharma EEIG
2016	Insulin degludec / insulin aspart	Ryzodeg	Extension of Indication to include treatment of diabetes mellitus in paediatric population from 2 years of age	Novo Nordisk A/S
2016	Lacosamide	Vimpat	Extension of Indication to add a new indication as monotherapy in the treatment of partial-onset seizures	UCB Pharma S.A.
2016	Eslicarbazepine acetate	Zebinix	Extension of indication to add treatment of adolescents and children aged above 6 years (adjunctive therapy in patients with partial-onset seizures with or without secondary generalisation)	Bial - Portela & C ^a , S.A.
2016	Ceftaroline fosamil	Zinforo	Extension of indication to include a new population, children from the age of 2 months	AstraZeneca AB

Note: This list excludes medicines that are not subjected to the obligations of the Paediatric Regulation (e.g. generics, hybrid medicines, biosimilars etc.).

Source: EMA database (SIAMED)

New pharmaceutical forms or routes of administration

Twenty-seven centrally authorised products had either a new pharmaceutical form and/or a new route of administration or a new strength authorised that was of paediatric interest. It should be noted that even though a new strength could be of interest to the paediatric population, the addition of a new strength does not fall under Article 8 of the Paediatric Regulation.

Table 3. New pharmaceutical forms or routes of administration of paediatric relevance by year of authorisation (CAPs, line extensions of existing marketing authorisations) (2007-2016)

Year	Active substance (INN)	Trade name	Subject of extension	MAH
2007	Desloratadine	Aerius	Addition of new pharmaceutical form: orodispersible tablets, 2.5 mg and 5 mg	Merck Sharp & Dohme Ltd.
2007	Nonacog alfa	BeneFIX	Addition of new pharmaceutical form: powder and solvent for solution for injection, 250 IU, 500 IU, 1000 IU	Pfizer Ltd.
2007	Deferiprone	Ferriprox	Addition of new pharmaceutical form: oral solution 100 mg/ml.	Apotex Europe B.V.
2008	Rotavirus vaccine, live	Rotarix	Addition of new pharmaceutical form: oral suspension ("liquid formulation").	GlaxoSmithKline Biologicals S.A.
2009	Temozolomide	Temodal	Addition of new pharmaceutical form: powder for solution for infusion	Schering-Piough Europe
2009	Tipranavir	Aptivus	Addition of new pharmaceutical form: oral solution	Boehringer Ingelheim International GmbH
2010	Insulin glulisine	Apidra	Addition of new route of administration: intravenous use.	Sanofi-aventis Deutschland GmbH
2010	Ritonavir	Norvir	New strength: 100 mg film coated tablet	Abbott Laboratories Ltd.
2011	Nitric oxide	INOmax	Addition of new strength: 800 ppm	Linde Healthcare AB
2011	Moroctocog alfa	ReFacto AF	To apply for a Addition of new pharmaceutical form 3000 IU.	Pfizer Ltd
2011	Moroctocog alfa	ReFacto AF	Addition of new pharmaceutical form: 500, 1000 and 2000 IU powder and solvent for solution for injection in pre-filled syringe.	Pfizer Ltd
2011	Mycophenolate mofetil	Myclausen	Addition of a new pharmaceutical form and strength 250 mg hard capsules (two presentations)	Herbert J. Passauer GmbH & Co. KG
2011	Nevirapine	Viramune	Addition of new strengths: 50 mg, 100 mg and 400 mg + a new pharmaceutical form: Prolonged-release tablet	Boehringer Ingelheim International GmbH
2011	Rufinamide	Inovelon	New pharmaceutical form: 40 mg/ml, oral suspension.	Eisai Ltd

Year	Active substance (INN)	Trade name	Subject of extension	MAH
2011	Oseltamivir	Tamiflu	Addition of the new strength: 6 mg/ml, powder for oral suspension	Roche Registration Ltd.
2012	Darunavir	Prezista	Addition of 100mg/ml oral suspension	Janssen-Cilag International NV
2012	Tenofovir disoproxil	Viread	Addition of reduced-strength tablets (150-, 200-, and 250-mg strengths) and a TDF granules formulation	Gilead Sciences International Limited
2013	Etravirine	INTELENCE	Addition of 25 mg strength	Janssen-Cilag International NV
2013	Raltegravir	Isentress	Addition of chewable tablets	Merck Sharp & Dohme Ltd
2013	Peginterferon alfa-2a	Pegasys	Addition of 90 microgram strength	Roche Registration Limited
2013	Anakinra	Kineret	Addition of 100mg/0.67 ml strength	Biovitrum AB
2014	Raltegravir	Isentress	Addition of granules for oral suspension	Merck Sharp & Dohme Ltd
2014	Palivizumab	Synagis	Addition of oral liquid 100mg/ml	AbbVie Ltd
2015	Ritonavir	Norvir	Line extension of a new oral powder formulation of Norvir	AbbVie Ltd
2015	Ivacaftor	Kalydeco	Line extension to the Marketing Authorisation to include a new pharmaceutical form (granules) in two new strengths (50 mg and 75 mg unit doses) to enable administration of Kalydeco to patients aged 2 to less than 6 years of age.	Vertex Pharmaceuticals (Europe) Ltd
2016	Eltrombopag / eltrombopag olamine	Revolade	Line extension for new indication (age 1 year and above) and new tablet strength (12.5mg) and new powder for oral suspension formulation (25mg)	
2016	Atazanavir / atazanavir sulfate	Reyataz	An extension application covering a new pharmaceutical form (oral powder), a new strength for the oral powder presentation (50mg), and a new paediatric indication (patients from 3 months of age and weighing at least 5kg)	Bristol-Myers Squibb Pharma EEIG

Source: EMA database (SIAMED)

1.1.2. Nationally authorised medicines (including DCP and MRP)

New medicines

Table 4. New medicines (initial marketing authorisations) including a paediatric indication (2007-2016)

Year of MA	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric-only or mixed ² use
2008	Acetylsalicylic acid and pseudoephedrine hydrochloride	Asprin Complex	Bayer d.o.o.	Slovenia	Mixed
2010	Acyclovir and hydrocortisone	Zovirax Plus	GlaxoSmithKline Pharmaceuticals S.A., Medivir AB, Sweden (SME)	Poland, Sweden	Mixed
2011	Alendronic acid	Neraxer	ABIOGEN PHARMA S.p.A.	Italy	Not reported
2011	Alfacalcidol	Alpha D3 Alpha D3 Osteo	Teva Magyarország Zrt.	Hungary	Mixed
2011	Amikacin	Amikacin B. Braun	B.Braun Melsungen AG	Hungary	Mixed
2007, 2010, 2011	Alanine, arginine, aspartic acid, calcium, cysteine, glucose, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, magnesium, methionine, olive oil, ornithine, phenylalanine, potassium, proline, serine, sodium, soybean oil, taurine, threonine, tryptophan, tyrosine, valine	Numeta and associated names	Baxter Czech spol.s.r.o., Medias International d.o.o., Baxter Hungary Kft, Genzyme Europe B.V., Baxter Oy, Baxter World Trade SA/NV	Czech Republic, Slovenia, Hungary, Finland, Spain	Mixed
2011	Amisulpride	Amisulpride Mylan	Generics UK Ltd.	Hungary	Mixed

² Adult and paediatric

Year of MA	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric-only or mixed ² use
2011	Amlodipine	Norvadip	Actavis Group PTC ehf, Bluefish, Vitablans	Hungary	Mixed
2009 2014 2014	Atomoxetine	Strattera	Eli Lilly farmaceutsk a družba	Slovenia Sweden UK	Paediatric-only
2010, 2011	Atorvastatin	Lipitor (and associated names)	Pfizer Europe MA EEIG	Romania, Hungary, Finland	Mixed
2011, 2007	Attenuated poliomyelitis virus type 1	Bivalent opv, mono opv1	Novartis Vaccines and diagnostics	Italy	Not reported
2007	Attenuated poliomyelitis virus type 3	Mono opv3	Novartis Vaccines and diagnostics	Italy	Not reported
2011	Azathioprine	Azathioprin Ebewe filmtabletta	Ebewe Pharma Ges.m.b.H. Nfg.KG	Hungary	Mixed
2011	Azithromycin	Azithromycin-Q Pharma	Q Pharma Kft.	Hungary	Mixed
2011	Bacillus clausii spora	Normaflore belsőleges szuszpenzió, Normaflore kemény kapszula	Sanofi-aventis zrt.	Hungary	Mixed
2010, 2011	Benzalkonium chloride	Dettolmed Tantum Verde, Tantum Verde Forte	Reckitt Benckiser (UK) Ltd CSC Pharmaceuticals Handels GmbH	Slovenia, Hungary	Mixed
2011	Bilastine	Bilador Lendin	Menarini International O.L.S.A., Menarini Intern. Operations Luxembourg S.A.	Slovenia, Hungary	Mixed
2011	Bisacodyl	Bisacodyl gyomornedv	Pro-Pharma '93 Kft	Hungary	Mixed

Year of MA	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric-only or mixed ² use
2011	Budesonide/ formoterol fumarate dihydrate	Budfor	AstraZeneca AB	Slovenia	Mixed
2009	C1-esterase inhibitor, human	Berinerit	CSL Behring GmbH	Slovenia	Mixed
2011	Calcium carbonate	Rennie Jégmenta rgtbl.	Bayer Hungária Kft.	Hungary	Mixed
2010	Calcium polystyrene sulfonate	Sorbisterit	Fresenius Medical Care	Italy	Mixed
2011	Cefixime	Cefixim Pfizer	Pfizer Kft.	Hungary	Mixed
2011	Cefuroxime	Cefuroxim-Kabi por injekcióhoz	Freseneus Kabi Hungary Kft.	Hungary	Mixed
2011	Cetirizine	Cetimax 10 mg ftbl.	Vitablans Oy	Hungary	Mixed
2009	Chlorhexidine	Drill	Pierre Fabre Pharma s.r.l.	Italy	Not reported
2010, 2009, 2008	Ciprofloxacin	Cexidal, ibixacin, ciprofloxacin baxter	Italchimici spa, IBI Giovanni Lorenzini SpA, BAXTER	Italy	Not reported
2011	Cisatracurium	Cisatracurium-Teva Cisatracurium-Teva	Teva Gyógyszergyár Zrt.	Hungary	Mixed
2011	Cisplatin	Cisplatin Accord	Accord Healthcare Limited	Hungary	Mixed
2011, 2007	Clarithromycin	Clarithromycin Pfizer ftbl., Claritromycin Mylan Soriclar, Winclar	Pfizer Kft., Generics UK Ltd., ABIOGEN PHARMA S.p.A., Istituto Biotecnico Nazionale Savio	Hungary, Italy	Mixed
2011	C-vitamin	C-vitamin Patikus Céh filmtabletta	Patikus Céh Kft	Hungary	Mixed
2011	Desloratadine	Esradin 5 mg filmtabletta	Pharma-Regist Kft.	Hungary	Mixed
2008	Desmopressin	MINIRIN 0,1 mg; 0,2 mg tablets	PharmaSwiss d.o.o.	Slovenia	Mixed

Year of MA	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric-only or mixed ² use
2011	Dextromethorphan	Meddex Wick 20mg/15 ml méz ízű szirup, Meddex Wick 7,33 mg méz ízű szop.tbl.	Wick Pharma, Procter & Gamble GmbH	Hungary	Mixed
2008	Diphtheria, Tetanus, Pertussis (acellular component) Vaccine	BOOSTRIX suspension for injection	GSK d.o.o.	Slovenia	Mixed
2008	Diphtheria, Tetanus, Pertussis (acellular component) Vaccine	BOOSTRIX POLIO Suspension for injection in prefilled syringe, BOOSTRIX POLIO suspension for injection	GSK d.o.o.	Slovenia	Mixed
2010	Diphtheria, Tetanus, Pertussis (acellular component) Vaccine	Adacel suspension for injection	Sanofi Pasteur SA	Slovenia	Mixed
2011	Diphtheria, Tetanus, Pertussis (acellular component) Vaccine	PEDIACEL suspension for injection in pre-filled syringe	Sanofi Pasteur SA	Slovenia	Paediatric
2011	Diphtheria, Tetanus, Pertussis (acellular component) Vaccine	Pediacel, Suspension for injection in pre-filled syringe (DCP)	Sanofi Pasteur MSD	Sweden	Paediatric
2011	Diphtheria, Tetanus, Pertussis (acellular component) Vaccine	Pediacel szuszp. Inj. Előretölt. Fecsk.-ben	Sanofi Pasteur SA	Hungary	Mixed
2009	Diphtheria, Tetanus, Pertussis (acellular component) Vaccine	PEDIACEL, SUSPENSION INYECTABLE EN JERINGA PRECARGADA	Sanofi Pasteur MSD, S.A.	Spain	Not reported
2011	Dorzolamide	Dorzolep 20 mg/ml oldatos szemcsepp	Extractum Pharma Zrt.	Hungary	Mixed
2011	Ebastine	Ebastine teva	Teva	Hungary	Mixed

Year of MA	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric-only or mixed ² use
2009, 2011	Esomeprazole	Nexium 10 mg gastro-resistant granules for oral suspension, sachet, Esorin gyomornedv-ellenálló tabletta, Themospes gyomornedv-ellenálló tabletta, Esomeprazole Polpharma por oldatos inf vagy inj, Esomeprazol Mylan, Omyprex, NEXIUM,	AstraZeneca AB, Specifar S.A., Pharmaceutical Works POLPHARMA SA, Mylan, Teva, AstraZeneca	Poland, Hungary, Italy	Mixed
2011	Etoricoxib	Auxib 30/60/90/120 mg filmtabletta	MSD Magyarország Kft.	Hungary	Mixed
2010, 2011	Ezetimibe	ABSORCOL, PICOLAX powder for oral solution	MSD ITALIA S.R.L., FERRING S.P.A.	Italy	Not reported
2011	Fentanyl	Fentanyl Pharmabide 100mikrogr/óra transzd tap, Fentanyl Pharmabide 25mikrogr/óra transzd.tap, Fentanyl Pharmabide 50mikrogr/óra transzd.tap, Fentanyl Pharmabide 75mikrogr/óra transzd.tap	Pharmabide Ltd.	Hungary	Mixed
2010	Ferric carboxymaltose	Iroprem 50 mg iron/ml solution for injection/infusion	Vifor France SA	Slovenia	Mixed
2011	Fexofenadine	Allegra junior	sanofi	Hungary	Paediatric

Year of MA	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric-only or mixed ² use
2011	Fluconazole	Femgin 150 mg kemény kapszula, Fluconazole Aurobindo kemény kapszula, Fluconazole - B. Braun 2mg/ml oldatos infúzió	Actavis Group PTC ehf, Bluefish, Vitablans, Aurobindo Pharma (Malta) Limited, B. Braun Melsungen AG	Hungary	Mixed
2011	Fluoxetine hydrochloride	Fluoxetine vitabalans	Vitabalans Oy	Hungary	Mixed
2011	Folic acid	Folic acid	ESP Pharma Limited	Italy	Not available
2012 2013 2013	Formoterol/fluticasone	Flutiform/Iffera	Mundipharma	Sweden Finland Italy	Mixed
2010	Glucose	Glucorange	Polymed Srl	Italy	Not reported
2006, 2009, 2010	Grass pollen allergen extract	ORALAIR 100 IR and 300 IR sublingual tablets, ORALAIR 300 IR sublingual tablets, GRAZAX 75.000 SQ-T peroralni liofilizat, Soluprick SQ Timothy grass (Phleum pratense) 10 HEP Solution for skin-prick test, Grazura 75, 000 SQ-T, Oral lyophilisate	STALLERGEN ES S.A. ALK-Abello A/S	Slovenia, Sweden	Mixed
2011	Herbal substances	Sinupret forte filmtabletta	Bionorica AG	Hungary	Mixed
2009	Human antihepatitis B immunoglobulin	Keyven b, mencevax acwy	Kedrion Spa, GlaxoSmithKline Biologicals SA	Italy	Not reported
2008	Human coagulation factor VIII	Immunine 600 IU	Baxter Poland Sp. z o.o.	Poland	Mixed
2008	Human coagulation factor VIII	Immunine 1200 IU	Baxter Poland Sp. z o.o.	Poland	Mixed

Year of MA	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric-only or mixed ² use
2010	Human coagulation factor VIII	Willate 450 i.e./400 i.e. , 900 i.e./800 i.e. powder and solvent for solution for infusion	Willfact 100 NE/ml por és oldószer oldatos injekcióhoz	Slovenia	Mixed
2008	Human coagulation factor VIII	IMMUNINE 200 i.e., 600 i.e., 1200 i.e. powder and solvent for solution for injection or infusion	BAXTER d.o.o	Slovenia	Mixed
2009	Human coagulation factor VIII	Haemoctin 250 i.e., 500 i.e., 1000 i.e. powder and solvent for solution for injection	Biotest Pharma GmbH	Slovenia	Mixed
2011	Human coagulation factor VIII	Willfact 100 NE/ml por és oldószer oldatos injekcióhoz	LFB Biomedicaments	Hungary	Mixed
2011	Human fibrinogen	Riastap 1 g powder for solution for injection / infusion	CSL Behring GmbH	Slovenia	Mixed
2009	Human hemin	Normosang 25 mg/ml concentrate for solution for infusion	Orphan Europe Immeuble "Le Guillaumet"	Slovenia	Mixed
2010	Human hepatitis B immunoglobulin	Hepatect CP 50 i.e./ml solution for infusion	Biotest Pharma GmbH	Slovenia	Mixed
2009	Human leukocyte interferon-alpha	Multiferon 3 mio i.e./0,5 ml solution for injection in prefilled syringe	Swedish Orphan Biovitrum International AB	Slovenia	Mixed
2007, 2010, 2011	Human normal immunoglobulin (IVIg)	Octagam 100 mg/ml solution for infusion, GAMMANORM 165 mg/ml solution for injection, Intratect 50 g/l, solution for infusion, Venital	Octapharma (IP) Ltd. Biotest Pharma GmbH Kedrion spa	Slovenia, Italy	Mixed

Year of MA	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric-only or mixed ² use
2015	Human normal immunoglobulin	IOYMUNE	Laboratoire Français du Fractionnement et des Biotechnologies	Czech Republic, Hungary	Mixed
2009	Human plasma derived coagulation factor IX	Haemonine 50 I.E./ml / 100 I.E./ml Pulver und Lösungsmittel zur Herstellung einer Injektionslösung	Biotest Pharma GmbH	Austria	Mixed
2007	Human protein	Subcuvia	Baxter AG	Italy	Not reported
2010, 2011	Ibuprofen	BRUFEN 200 mg, 400 mg, 600 mg film coated tablets, Nurofen for children with the flavor of orange and strawberry 40 mg/ml oral suspension, Algoflex Baby 20mg/ml belsőleges szuszpenzió, Algoflex Norma 400 mg filmtabletta, Ibustar 20mg/ml belsőleges szuszpenzió gyermekek , IBUPAS	Abbott Laboratories d.o.o.	Slovenia, Hungary, Italy	Mixed, Paediatric
2011	Imipenem	Imipenem/Cilastatin Hospira 500 mg/500 mg por old. Inf.-hoz, Imipenem/Cilastatin Teva por old inf, Impecin 250 mg/250 mg por old. Inf.-hoz	Hospira UK Limited, Teva Magyarország Zrt. Actavis Group PTC ehf	Hungary	Mixed

Year of MA	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric-only or mixed ² use
2009	Influenza virus surface antigens (haemagglutinin and neuraminidase)* of strain A/California/7/2009 (H1N1)v like strain used (X-179A) 3.75 micrograms** per 0.25 ml dose	Celtura	Novartis Vaccines and Diagnostics GmbH	Germany	Mixed
2011	Iobenguane	Mibeg	Mallinckrodt Medical B.V.	Italy	Not reported
2010	Iobenguane (123I)	Adreview	GE HEALTHCAR E s.r.l.	Italy	Not reported
2011	Isoconazole diflucortolone	Travocort 10 mg/g + 1 mg/g krém	UniCorp Biotech Kft.	Hungary	Mixed
2011	Lamotrigine	Lamotrigine Pfizer, Lamotrigine Pfizer diszpergálódó tabletta	Pfizer	Hungary	Mixed
2010, 2011	Latanoprost	Xalatan eye drops solution 0,0005%, Laprosep 0,05 mg/ml old. Szemcsepp, Latanoprost Pfizer 0,05 mg/ml oldatos szemcsepp	Pfizer Hellas AE, Extractum Pharma Zrt., Pfizer Kft.	Cyprus, Hungary	Mixed
2011	Levetiracetam	Levil filmtabletta, Levetiracetam-Lupin, Levedia, Repident, Levetiracetam pharماسwiss, Levetiracetam Stada	Meditop Gyógyszeripari Kft, Lupin Ltd, Magyar és Társa Bt., POLPHARMA SA, PharmaSwiss, STADA Arzneimittel AG	Hungary	Mixed
2009, 2011	Levothyroxine sodium	Syntroxine	Regiomedica GmbH, IBSA Farmaceutici Spa	Hungary, Italy	Mixed

Year of MA	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric-only or mixed ² use
2007	Lidocaine and Tetracaine	Rapydan70 mg /70 mg, Medicated plaster (N)	Eurocept International B.V., The Netherlands When approved: EUSA Pharma (Europe) Ltd, United Kingdom	Sweden	Mixed
2013 2013 2013	Lisdexamfetamine	Elvanse	Shire	Denmark Finland Sweden	
2009, 2011	Losartan	COZAAR 2,5 mg/ml, Valezaar filmtabletta	Merck Sharp & Dohme Romania S.R.L., Valeant Pharma Magyarország Kft	Romania, Hungary	Mixed
2008, 2011	Macrogol '3350'/Potassium chloride/Sodium bicarbonate/Sodium chloride	MOVICOL Lax 6,9 g powder for oral solution, Regolint, Movicol pediatric	Norgine BV, Laboratori Baldacci SpA, NORGINE ITALIA S.R.L.	Slovenia, Italy	Mixed
2007	Meningococcus vaccine	Zetia	MSD-SP Limited	Italy	Not reported
2011	Meropenem	Meropenem Kabi 1000mg por old inj.v.inf., Meropenem Kabi 500mg por old inj.v.inf., Meropenem Hospira por,	Fresenius Kabi Hungary Kft., Hospira UK Limited	Hungary	Mixed
2011	Mesalamine	Mezevant	Shire Pharmaceutical Contracts Ltd	Hungary	Mixed
2011	Metamizole	Amizolmet 500 mg/ml oldatos infúzió	Sanitas A. B.	Hungary	Mixed

Year of MA	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric-only or mixed ² use
2009, 2010	Metformin hydrochloride	Glucophage 1000mg Film-coated tablets, Glucophage 500 mg; Glucophage 850 mg; Film-coated tablets, GLUCOPHAGE 1000 mg film-coated tablets	Merck Santé, s.a.s., Merck d.o.o.	Poland, Slovenia	Mixed
2011	Methotrexate	Ebetrexat 2,5 mg, methotrexate Smg, 10 mg tableta	Ebewe Pharma Ges.m.b.H. Nfg.KG	Hungary	Mixed
2007, 2008	Methylphenidate hydrochloride	Concerta, ritalin	Janssen-Cilag International N.V., Ritalin	Poland, Italy	Paediatric
2009, 2010, 2011	Montelukast	SINGULAIR, Montelukast MSD, Montelukast Sandoz 4 mg granulátum, Montelukast Orion 4 mg, rágótableta, Montelukast Orion 5 mg rágótableta, Montelukast Orion 10 mg filmtableta, Montelukast Teva 4 mg granulátum, Monalux rágótabl., Mondeo 10 mg ftbl., Montelukast Accord 4mg-5 mg rágótableta	MSD Polska Sp. z o.o., SANDOZ Hungária Kereskedelmi Kft, Orion Corporation, Teva Magyarország Zrt., Krka, d.d, Actavis Group PTC ehf, Accord Healthcare Limited	Poland, Hungary	Mixed
2009	Moxifloxacin	Vigamox, Vigamox 5 mg/ml eye drops, solution	Alcon Polska Sp. z o.o., S.A. Alcon-Couvreur N.V.,	Poland, Slovenia	Mixed

Year of MA	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric-only or mixed ² use
2011	Mycophenolate mofetil	Mycophenolate mofetil Stada 250 mg kemény kapszula, Mycophenolate mofetil Stada 500 mg filmtabletta, Mycophenolate mofetil Pharm V Solutions 500 mg filmtabl, Mycophenolate mofetil Actavis 250 mg kemény kapsz, Mycophenolat Mofetil-ratiopharm 250 mg k. Kapsz, Mycophenolat Mofetil-Ratiopharm 500 mg ftbl.	Stada Arzneimittel AG, Pharm V Solutions Ltd., Actavis Group PTC ehf., Ratiopharm GmbH	Hungary	Mixed
2008	Neisseria meningitidis group A Neisseria meningitidis group C Neisseria meningitidis group Y Neisseria meningitidis group W135	Mencevax ACWY powder and solvent for solution for injection in prefilled syringe, Meningitec Meningococca	GSK d.o.o.	Slovenia	Mixed
2008	Neisseria meningitidis group A Neisseria meningitidis group C Neisseria meningitidis group Y Neisseria meningitidis group W135	Meningitec Meningococca	John Wyeth and Brother Limited	Italy	Not reported

Year of MA	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric-only or mixed ² use
2011	Nitrous oxide	Dinitrogén Oxid Siad cseppfolyósított gáz, Livopan túlnyomásos orvosi gáz, Dinitrogén-Oxid Rad-Med Pharma cseppfoly orvosi gáz, Kalinoxal 50%/50% túlnyomásos orvosi gáz, INALOSSIN	SIAD Hungary Gázokat Forgalmazó és Termelő Kft., AGA AB, RAD-MED-PHARMA Gyógyászati, Kereskedelmi és Szolgáltató Kft., AIR LIQUIDE SANTE INTERNATIONALE, Società Italiana Acetilene e Derivati	Hungary, Italy	Mixed
2007, 2011	Nutrition	Nutriflex Lipid peri emulziós infúzió, Smoflipid	B. Braun Melsungen AG, FRESENIUS KABI ITALIA S.R.L.	Hungary, Italy	Mixed, Not available
2011	Octocog alfa	Recombinate 250 iu, recombine 500 iu, recombine 1000 iu	Baxter Polska Sp. z o.o.	Poland	Mixed
2011	Omeprazole	Omeprazole pfizer	Pfizer Kft.	Hungary	Mixed
2011	Oxycodone	Codoxy retard tabletta	G.L. Pharma GmbH	Hungary	Mixed

Year of MA	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric-only or mixed ² use
2009, 2010, 2011	Oxygen	Oxigén Vifamed mélyhűtött orvosi gáz, Oxigén Vifamed túlnyomásos orvosi gáz, ARIA AIR LIQUIDE SANITA', ARIA CRIOSALENTO, ARIA MEDICAIR, ARIA OSSIGAS, ARIA RIVOIRA, ARIA SIAD, ARIA SICO, ARIA LINDE MEDICALE, OSSIGENO C.I.O., OSSIGENO CRIOSALENTO, OSSIGENO EUROXAN, OSSIGENO IBO, OSSIGENO MEDICAIR, Ossigeno Ossigas, OSSIGENO SON-OX	Vifamed Bt., AIR LIQUIDE SANTE, CRIOSALENTO s.r.l., MEDICAIR ITALIA s.r.l., OSSIGAS s.r.l., RIVOIRA S.p.A., S.I.A.D. S.p.A, SICO S.p.A., LINDE MEDICALE s.r.l., CONSORZIO ITALIANO OSSIGENO, CRIOSALENTO S.R.L., EUROXAN srl, INDUSTRIA BRESCIANA OSSIGENO S.R.L., MEDICAIR ITALIA S.R.L., OSSIGAS S.r.l., OSSIGENO SOCIETA' OSSIGENO NAPOLI	Hungary, Italy	Mixed
2008, 2011	Oxymetazoline-hydrochloride	Sinex Wick Eukaliptusz 0,5 mg/ml oldatos orrspray, Ossimetazolina Carlo Erba	Wick Pharma Zweigniederlassung der Procter & Gamble GmbH, Carlo Erba OTC	Hungary, Italy	Mixed

Year of MA	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric-only or mixed ² use
2011	Pantoprazole	Pantoprazol Krka gyomoredv-ellenálló tabletta, Adozol 20 mg gyomoredv-ellenálló tabletta, Adozol 20 mg gyomoredv-ellenálló tabletta, Pantoprazol Goodwill 40 mg por oldatos injekcióhoz, Acidostop ratiopharm 20 mg gyomoredv-ellenálló tabl	Krka, d.d, Plus-Pharma Arzneimittel GmbH, Goodwill Pharma Kft., Ratiopharm GmbH	Hungary	Mixed
2008, 2011	Paracetamol	Paracetamol Actavis 24 mg/ml belsőleges oldat, Doloramol 1000 mg, 250 mg, 500 mg filmtabletta, Paracetamol Actavis 10 mg/ml old. Inf., Paracetamol Panpharma 10 mg/ml old. Inf., Panadol Rapid 500 mg filmtabletta, Paracetamol Kabi 10 mg/ml oldatos infúzió, symptomed Wick Citrom ízű por belsőleges oldathoz, symptomed Wick Feketeribizli ízű por belsőleges oldathoz, GALAFIN	Actavis Group PTC ehf, Sigillata Ltd., Panmedica, GSK Consumer Healthcare, Fresenius Kabi Hungary Kft., Wick Pharma Zweigniederlassung der Procter & Gamble GmbH, Marvecspharma Services S.r.l.	Hungary, Italy	Mixed
2008, 2011	Paracetamol, ascorbic acid, fenilefrin	Coldrex Maxgrip mentol és erdei gyümölcs ízű por, Flumin Béres ftbl., LISOFLU	GSK, Béres Házipatika Kft., Sanofi Aventis Spa	Hungary, Italy	Mixed

Year of MA	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric-only or mixed ² use
2011	Parenteral nutrition	Periolimel N4E, Olimel N5E, Olimel N7, Olimel N7E, Olimel N9, Olimel N9E emulsion for infusion	Baxter d.o.o.	Slovenia	Mixed
2007, 2010, 2011	Pelargonium sidoides extract	Kaloba, keyven, umkan	Dr Willmar Schwabe Gmbh, Kedrion SpA, Dr Willmar Schwabe Gmbh & Co Kg	Italy	
2007	Phenelzine	Margyl	Dimensione Ricerca Srl	Italy	
2011	Piperacillin	Piperan por old. Inj. - hoz, Zytobact por old inj vagy inf	Ranbaxy UK Limited, Teva Magyarország Zrt.	Hungary	Mixed
2007	Potassium chloride, Magnesium chloride hexahydrate, Calcium chloride dihydrate, Sodium acetate trihydrate L-Malic acid	Sterofundin	B. BRAUN MELSUNGEN AG	Italy	
2011	Propofol	Propofol Pfizer emulziós injekció vagy infúzió, Curtega emulziós injekció vagy infúzió	Pfizer	Hungary	Mixed
2011, 2007	Racecadotril	Hidrasec 10 mg, Hidrasec 30 mg, granules for oral suspension, TIORFAN CHILDREN 30 and 10 mg	Bioprojet Europe Ltd., BIOPROJET FERRER	Poland, Italy	Paediatric

Year of MA	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric-only or mixed ² use
2011	Remifentanil	Remifentanil Hospira por oldatos injekcióhoz vagy infúzióhoz való koncentrátumhoz, Remifentanil Teva por oldatos injekcióhoz vagy infúzióhoz való koncentrátumhoz	Hospira UK Limited, Teva Gyógyszergyár Zrt.	Hungary	Mixed
2011	Rifaximin	Flonorm, ximinorm	Alfa Biotech Srl, Alfa Wassermann SpA	Italy	
2011	Rocuronium-bromide	Rocuronium-Teva oldatos injekció vagy infúzió	Teva Magyarország Zrt.	Hungary	Mixed
2011	Ropivacaine	Ropivacain B. Braun old. Inj.	B. Braun Melsungen AG	Hungary	Mixed
2009	Rosuvastatin calcium	Crestor	Astra Zeneca AB	Poland	Mixed
2008 2012 2013 2014	Rupatadine	Rupafin 10 mg tablets	J. Uriach & Cía., S.A.	Slovenia, Estonia, Romania Finland	Mixed
2010	Sodium alginate / Potassium hydrogen carbonate	Gaviscon advance	Reckitt Benckiser (Poland) S.A.	Poland	Mixed
2011	Sodium picosulphate	Pico-salax	Ferring Magyarország Gyógyszerkereskedelmi	Hungary	Mixed
2011	Somatropin	Saizen 5,83 mg/ml oldatos injekció, Saizen 8 mg/ml oldatos injekció	Merck Kft	Hungary	Mixed
2011	Spirolactone	Spitonep 25 mg tabletta, spitonep 50 mg tabletta	Extractum Pharma Zrt.	Hungary	Mixed

Year of MA	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric-only or mixed ² use
2009	Split influenza virus, inactivated containing antigen equivalent to A/California/7/2009 (H1N1)-like strain (A/California/7/2009 (NYMC X-179A))	Panenza suspension inyectable en vial multidosis, panenza suspension inyectable en jeringa precargada	Sanofi Pasteur S.A.	Spain	
2011	Tacrolimus	Tacrolimus Astron kemény kapszula, Tacrolimus Lambda kemény kapszula, Tacrolimus Mylan kemény kapszula, Tacrolimus Sandoz kemény kapszula, Tacrolimus Intas,	Astron Research Limited, Lambda Therapeutics Limited, Mylan S.A.S., Sandoz Hungária Kft, Intas Pharmaceuticals Limited	Hungary	Mixed
2007	Tetrabenazine	Xenazina	Chiesi Farmaceutici SpA	Italy	
2011	Trace minerals	Béres Csepp Extra belsőlegesen oldatos cseppek	Béres Gyógyszergyár Zrt.	Hungary	Mixed
2011	Tramadol	Noax 50 mg szájban diszp. Tbl.	CSC Pharmaceuticals Handels GmbH	Hungary	Mixed
2008	Tramadol / paracetamol	Zaldiar 37,5 mg/325 mg effervescent tablets, KOLIBRI, Tramadololo e Paracetamolo	Grünenthal GmbH, Zieglerstrasse 6, Aachen, Germany, Alfa Wassermann SpA	Slovenia, Italy	Mixed
2013 2013 2014	Tretinoin/clindamycin	Acnatac/Acnex	Meda	Denmark Sweden France	Mixed
2011	Triptorelin	Diphereline SR 22,5 mg por és oldószer szuszp. Injekc.	Ipsen Pharma	Hungary	Mixed

Year of MA	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric-only or mixed ² use
2010	Valsartan	Diovan 3mg/ml, Valmed filmlibretto, Valsartan propharma, Valsartan Arrow filmlibretto	Novartis s.r.o., Helm AG, Propharma, Arrow	Czech Republic, Hungary	Paediatric, Mixed
2011	Vancomycin	Vancomycin Actavis por old. Inf.-hoz, Vancomycin Kabi por oldatos injekcióhoz, Vancomycin Pharmaswiss por old. Inf.-hoz	Actavis Group PTC ehf, Freseneus Kabi Hungary Kft., PharmaSwiss Česká republika s.r.o.	Hungary	Mixed
2008	Ziprasidone hydrochloride	Zeldox	Pfizer AB	Italy	Not reported
2011	Not reported	Rifaximina	ALFA WASSERMAN N S.P.A	Italy	Not reported
2011	Not reported	Rivonox	Rivoira SPA	Italy	Not reported
2007	Not reported	Torvast	Parke-Davis	Italy	Not reported
2016	Split influenza virus	VAXIGRIPTETRA	SANOFI PASTEUR	France	Mixed
2016	Human normal immunoglobulin	PANZYGA	OCTAPHARM A	France	Mixed

Source: NCA questionnaire

New paediatric indications

Table 5. New paediatric indications³ (variations of existing marketing authorisations) (2007-2016)

Year of variation	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric indication
2007	Atovaquone / Proguanil hydrochloride	Malarone	Glaxosmithkline	Italy	Not reported
2007	Fluoxetine hydrochloride	Prozac and associated names	Eli Lilly Italia Spa	Italy	Not reported
2007	Oxybutynin hydrochloride	Various	Various	Italy United Kingdom	Not reported

³ New indications associated with article 45 assessment have not been included.

Year of variation	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric indication
2007	Pantoprazole	Peptazol	Recordati Industria Chimica E Farmaceutica S.P.A.	Italy	Not reported
2007-2008	Somatropin	Humatrope and associated names	Eli Lilly Oy	Italy Finland	Not reported
2008	Desmopressin	Nocutil	Gebro Pharma Gmbh	Austria	Nocturnal enuresis (over 6 5 years of age) [...]vasopressin - sensitive cranial diabetes insipidus.
2008	Glatiramer acetate	Copaxone	Teva Pharmaceuticals Ltd	Finland United Kingdom	well-defined first clinical episode and are determined to be at high risk of developing clinically definite multiple sclerosis (CDMS) [...] limited published data suggest that the safety profile in adolescents from 12 to 18 years of age receiving Copaxone 20 mg subcutaneously every day is similar to that seen in adults
2008	Inactivated poliovirus 1-3	Imovax polio (n)	Sanofi Pasteur Msd, Belgium	Sweden	Active immunisation against polio virus
2008	Ropivacaine hydrochloride	Narop, 2 mg/ml Solution for injection/infusion (N)	Astrazeneca AB, Sweden	Sweden	Acute perioperative and post operative pain relief in children

Year of variation	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric indication
2009	Ciprofloxacin	Ciprofloxacin Merck NM (now Mylan), 100 mg, 250 mg, 500 mg, 750 mg, Film-coated tablets (MRP)	Mylan AB	Sweden Italy	Broncho-pulmonary infections in cystic fibrosis caused by Pseudomonas aeruginosa, Complicated urinary tract infections and pyelonephritis, Inhalation anthrax (post-exposure prophylaxis and curative treatment)
2009	DI-alfa-tocopherol, medium chain triglycerides, purified fish oil, purified olive oil, soybean oil	Smoflipid	Medias International	Slovenia	Not reported
2009	Gadobutrol	Gadovist	Bayer Schering Pharma Oy	Finland	Not reported
2009	Human normal immunoglobulin	Subcuvia	Baxter AG	Finland	Not reported
2009	Measles Mumps Rubella vaccine	Priorix	Glaxosmithkline S.P.A.	Italy	Vaccination against measles, mumps, rubella
2009	Metformin hydrochloride	Various	Various	Italy	Diabetes mellitus
2009	Piperacillin sodium / tazobactam sodium	Piperacillina e tazobactam ibigen (dcp)	Ibigen S.R.L.	Italy	Not reported
2009	Zanavimir	Relenza	Glaxosmithkline Spa	Italy	Not reported

Year of variation	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric indication
2009	Ziprasidone	Zeldox	Pfizer AB	Italy Sweden	Treatment of manic or mixed episodes of moderate severity in bipolar disorder in adults and children and adolescents aged 10-17 years
2009-2010	Losartan	Cozaar and associated names	Merck Sharp & Dohme	Romania Italy Finland	Hypertension
2009-2011	Grass pollen allergen extract	GRAZAX and associated names	Alk-Abelló A/S, Denmark	Sweden Italy	Treatment of grass pollen induced rhinitis and conjunctivitis in adults and children (5 years or older), with clinically relevant symptoms and diagnosed with a positive skin prick test and/or specific IgE test to grass pollen.
2010	Atorvastatin	Lipitor and associated names	Pfizer Hellas Ae	Cyprus Estonia Romania Finland	Hypercholesterolemia children & adolescents over 10 years of age
2010	Montelukast	Singulair	Merck Sharp & Dohme Romania S.R.L.	Romania	Asthma
2010	Rosuvastatin calcium	Crestor 5 mg, 10 mg, 20 mg, 40 mg tabletti, kalvo-päällysteinen	Astra Zeneca Oy	Finland	Not reported
2010	Soiae oleum raffinatum triglyceride saturate media piscis oleum omega-3-acidis abundans*	Smoflipid 200 mg/ml infuusioneste, emulsio	Fresenius Kabi Ab	Finland	Not reported

Year of variation	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric indication
2010	Sumatriptan succinate	Sumatriptan tablets 50, 100mg	Apotex Europe Bv	United Kingdom	Not reported
2010	Valsartan	Diovan fctabs 40mg	Novartis Pharmaceuticals Uk Ltd	Cyprus Estonia Romania Finland Sweden	Hypertension in children & adolescents 6 to 18 years of age
2010-2011	Latanoprost	Xalatan and associated names	Pfizer Enterprises Sar	Estonia Finland Romania Spain Sweden	Glaucoma
2011	Acyclovir	Ciclofarm and associated names	Tillomed Laboratories Limited	United Kingdom	Not reported
2011	Esomeprazole	Nexium	Astrazeneca UK Limited	Slovenia Sweden Spain	Children 1-11 years old, Children over 4 years of age, In combination with antibiotics in treatment of duodenal ulcer caused by Helicobacter pylori
2011	Ezetimibe	Ezetrol tabs	Merck Sharp & Dohme Bv, Netherlands	Cyprus	Primary non-familial hypercholesterolaemia/heterozygous familial hypercholesterolaemia, adolescents 10 to 17 years of age
2011	Metoclopramide hydrochloride	Antigen metoclopramide injection bp 10mg/2ml	Antigen International Limited	UK	Not reported

Year of variation	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric indication
2011	Ondansetron	Zofran	Glaxosmithkline AB, Sweden	Sweden	Profylax och behandling av illamående och kräkningar inducerade av kemoterapi [...] postoperativt illamående och kräkningar hos barn ? 1 månad.
2011	Rizatriptan	Maxalt	Merck Sharp & Dohme	Czech Republic	Migraine
2012	Flumazenil	Anexate 100 micrograms/ml solution for injection/infusion	Roche	Slovenia	Reversal of sedation from benzodiazepines
2012	Esomeprazole	Nexium	Astra Zeneca	Slovenia	Gastric antisecretory treatment
2012	Milirinone	Corotrope	Sanofi Aventis	Spain	short-term treatment (up to 35 hours) of severe congestive heart failure unresponsive to conventional maintenance therapy
2012	Lenograstim	GRANOCYTE	Italfarmaco	Spain	neutropenia
2012	mivacurium chloride	Mivacron	GlaxoSmithKline	Sweden	Muscle relaxant associated with endotracheal intubation (translated from Swedish)
2013	candesartan	Atacand	AstraZeneca	Cyprus	Treatment of hypertension
2013	Azithromycin eye drops	Azyter	Thea pharmaceuticals	Finland	Treatment of eye infections
2013	Alfentanil	Rapifen	Janssen-Cliag	Finland	Analgesia associated with mechanical ventilation

Year of variation	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric indication
2013	Baclofen	Baclofen	Sintetica Italia	Spain	
2013	Nitric oxide	Noxap		Spain	Persistent pulmonary hypertension
2014	Rupatadine	Rupatal	J Uriach & Cia	BelgiumCzech Republic Estonia Finland Lithuania Poland Spain	Allergic rhinoconjunctivitis
2014	Valganciclovir	VALCYTE	Roche	Czech Republic Estonia Finland Poland Portugal RomaniaSlovenia	
2014	Adenosine	Adenocor	Sanofi	Hungary	
2014	Gadoteric acid	Dotarem	Guerbet Roissy	Hungary Slovenia	
2014	Rosuvastatin	Crestor	AstraZeneca	Italy, PortugalRomania	Primary hypercholesterolemia
2014	Tiotropine	Spiriva Respimat	Boehringer Ingelheim International GmbH	Poland	
2014	Atomoxetine	Strattera	Eli Lilly	UK	
2015	Gadobutrol	Gadovist	BAYER	Austria Cyprus Germany Sweden	diagnostic
2015	Metronidazole	Supplin	Sandoz GmbH	Lithuania	
2015	atomoxetine	Strattera	Eli Lilly	Czech Republic	
2016	solifenacin succinate	Vesicare	Astellas Pharma BV	Belgium	Not reported

Source: NCA questionnaire

New pharmaceutical forms or routes of administration

Table 6. New pharmaceutical forms or routes of administration of paediatric relevance (line extensions of existing marketing authorisations) (2007-2016)

Year	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric formulation / route of administration
2010	Atorvastatin	Sortis and associated names	Pfizer Corporation Austria GmbH	Austria Cyprus Czech Republic Estonia Lithuania Slovenia Spain United Kingdom	Chewable tablets
2011	DTP/Hib/Polio vaccine	Pediacel	Sanofi Pasteur SA	Poland United Kingdom	New route of administration, Prefilled syringe
2007	Esomeprazole	Nexium and associated names	AstraZeneca AB	Sweden	Paediatric formulation: Granules for oral suspension in sachet
2011	Ibuprofen	Brufen	Abbott Laboratories	Slovenia	New paediatric formulation: oral suspension
2009	Losartan	Cozaar and associated names	Merck Sharp & Dohme	Cyprus Estonia Italy Spain United Kingdom	Paediatric formulation: Powder for oral solution, oral suspension
2009	Metformin hydrochloride	Glucophage	Merck Santé, s.a.s.	Poland Sweden	New paediatric formulation: Powder for oral solution in sachets
2008	MMRV vaccine	Priorix-Tetra	GlaxoSmithKline GmbH & Co. KG	Italy	
2009	Montelukast	Singulair	Merck Sharp & Dohme GmbH	Austria Czech Republic Lithuania	Granules, Chewable tablet
2011	Rizatriptan	Maxalt	Merck Sharp & Dohme	Lithuania	Tablet, oral lyophilisate, oral use

Year	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric formulation / route of administration
2009	Somatropin	Zomacton	Ferring	Italy	
2010	Valsartan	Diovan and associated names	Novartis Pharma GmbH	Austria Cyprus Czech Republic Estonia Finland Italy Romania Slovenia Spain Sweden United Kingdom	Paediatric formulation: oral solution, divisibility of the tablet
2012	Rupatadine	Rupafin	J. Uriach & Cia.	Slovenia Estonia Italy	Oral solution
2014	Atomoxetine	Strattera	Eli Lilly	Denmark Estonia United Kingdom Czech Republic	Oral solution
2015	Meningococcal group C oligosaccharide conjugated to Corynebacterium diptheriae CRM197 protein (MenC-CRM)	MENJUGATE	NOVARTIS VACCINES AND DIAGNOSTICS	France	
2016	Split influenza virus	VAXIGRIPTETRA	SANOVI PASTEUR	France	
2016	Human normal immunoglobulin	PANZYGA	OCTAPHARMA	France	

Source: NCA questionnaire

1.2. Effect of the Paediatric Regulation on the authorisation of medicines for children

Table 7. Overview of paediatric medicine changes in SmPC in 2004-2006 and 2012-2014

Initial marketing authorisations		Already authorised products (type II variations or line extensions)					Other paediatric changes to SmPC (sections)								
Year	Initial MA with a clear paediatric indication (section 4.1)	New paediatric indication (section 4.1)	Update to 4.1 (not new indication)	New paediatric posology (section 4.2)	Update to 4.2 (not new posology)	New pharmaceutical form or strength for children (line extension)	4.3	4.4	4.5	4.7	4.8	4.9	5.1	5.2	5.3
2004	4	3	0	7	0	2	0	11	0	0	5	1	4	2	1
2005	2	4	0	10	4	1	2	7	2	0	5	1	7	7	1
2006	14	3	0	4	5	5	0	7	0	0	13	1	9	9	0
Sum 2004 - 2006	20	10	0	21	9	8	2	25	2	0	23	3	20	18	2
2012	7	11	3	12	27	1	0	19	2	0	25	1	20	18	1
2013	12	16	0	11	16	1	1	12	7	1	26	3	27	18	0
2014	7	10	3	12	20	1	1	17	8	0	18	2	16	13	1
Sum 2012 - 2014	26	37	6	35	63	3	2	48	17	1	69	6	63	49	2

Source: EMA database (SIAMED)

Table 8. Initial Marketing Authorisations (INITIAL_MA) and Type II Variations (TYPE_II) with new paediatric indications in 2004-2006

Year	Active substance (INN)	Trade name	Application type	Linked to a PIP
2004	Octocog alfa	Advate	INITIAL_MA	N/A
2004	Cholera vaccine	Dukoral	INITIAL_MA	N/A
2004	Abacavir / lamivudine	Kivexa	INITIAL_MA	N/A
2004	Insulin detemir	Levemir	INITIAL_MA	N/A
2004	Octocog alfa	Advate	TYPE_II	N/A
2004	Desloratadine	Aerius	TYPE_II	N/A
2004	Hepatitis-A (inactivated) and hepatitis-B (rDNA) (HAB) vaccine (adsorbed)	Ambirix	TYPE_II	N/A
2005	Hepatitis B (rDNA) vaccine (adjuvanted, adsorbed)	Fendrix	INITIAL_MA	N/A
2005	Omalizumab	Xolair	INITIAL_MA	N/A
2005	Interferon alfa-2b	IntronA	TYPE_II	N/A
2005	Ertapenem	Invanz	TYPE_II	N/A

Year	Active substance (INN)	Trade name	Application type	Linked to a PIP
2005	Levetiracetam	Keppra	TYPE_II	N/A
2005	Ribavirin	Rebetol	TYPE_II	N/A
2006	Clofarabine	Evoltra	INITIAL_MA	N/A
2006	Deferasirox	Exjade	INITIAL_MA	N/A
2006	Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)	Gardasil	INITIAL_MA	N/A
2006	Human normal immunoglobulin	Kiovig	INITIAL_MA	N/A
2006	Measles, mumps and rubella vaccine (live)	M-M-RVAXPRO	INITIAL_MA	N/A
2006	Alglucosidase alfa	Myozyme	INITIAL_MA	N/A
2006	Galsulfase	Naglazyme	INITIAL_MA	N/A
2006	Somatropin	Omnitrope	INITIAL_MA	N/A
2006	Measles, mumps, rubella and varicella vaccine (live)	Proquad	INITIAL_MA	N/A
2006	Rotavirus vaccine, live, attenuated	Rotarix	INITIAL_MA	N/A
2006	Rotavirus vaccine, live	RotaTeq	INITIAL_MA	N/A
2006	Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)	Silgard	INITIAL_MA	N/A
2006	Buprenorphine / naloxone	Suboxone	INITIAL_MA	N/A
2006	Somatropin	Valtropin	INITIAL_MA	N/A
2006	Imatinib	Glivec	TYPE_II	N/A
2006	Levetiracetam	Keppra	TYPE_II	N/A
2006	Oseltamivir	Tamiflu	TYPE_II	N/A

Source: EMA database (SIAMED)

1.3. Paediatric Use Marketing Authorisation (PUMA)

Table 9. Agreed PIPs for potential PUMAs (2007-2015)

PIP number	Active substance (INN)	Condition (therapeutic area)	Age groups in studies	Type of studies
EMA-000717-PIP02-13	Vigabatrin	Treatment of epilepsy (Neurology)	From 1 month to less than 7 years	Development of an age-appropriate pharmaceutical form. Observational acceptability study to evaluate acceptability/palatability, safety and tolerability of the new pharmaceutical form.

PIP number	Active substance (INN)	Condition (therapeutic area)	Age groups in studies	Type of studies
EMA-000184-PIP02-14	Tobramycin	Treatment of pseudomonas aeruginosa infection/colonisation in cystic fibrosis patients (Infectious diseases)	From 3 months to less than 7 years	Randomised, double-blind, placebo-controlled, multi-centre study to assess efficacy and safety.
EMA-001241-PIP02-13	Enalapril (maleate)	Treatment of heart failure (Cardiovascular diseases)	From birth to less than 18 years	<p>Development of an age-appropriate formulation.</p> <p>Adult trained taste panel to assess the palatability new formulation prior to its use in children</p> <p>Assessment of in vitro stability of enalapril in the new formulation.</p> <p>Bioequivalence study comparing the new formulation of enalapril with the licensed enalapril tablet.</p> <p>Population pharmacokinetic study of oral enalapril administered to children.</p> <p>Safety study in children.</p> <p>Systematic literature review.</p> <p>Population pharmacokinetic study of oral enalapril administered to term neonates.</p> <p>Safety study in term neonates.</p>

PIP number	Active substance (INN)	Condition (therapeutic area)	Age groups in studies	Type of studies
EMA-001324-PIP01-12	Glibenclamide	Treatment of neonatal diabetes mellitus (Endocrinology/metabolic diseases/neonatology)	From birth to less than 18 years	Development of an oral suspension. Study of dosing accuracy with proposed syringe. Safety and activity study to elucidate the genetic mechanism of a new form of diabetes mellitus. Study to investigate the activity and safety of oral sulfonylurea medication in children (and adults) with neonatal diabetes carrying a mutation in the KCNJ11 gene. Bioequivalence study of two glibenclamide suspensions versus crushed tablets of the reference product. Study to investigate the activity and safety of oral sulfonylurea medication in children (and adults) with permanent neonatal diabetes due to mutations in the genes coding for the Kir6.2 and SUR1 subunits of the Pancreatic Beta-cell ATP-sensitive K ⁺ Channel. Study to evaluate tolerance and acceptability of Glibenclamide and gather pharmacokinetic data in paediatric patients.
EMA-000294-PIP02-12	Idursulfase	Treatment of mucopolysaccharidosis type II (Hunter syndrome) (Endocrinology/metabolic diseases)	From birth to less than 18 years	Study to evaluate, pharmacokinetics/pharmacodynamic, safety, immunogenicity and efficacy of intrathecal (IT) administration of idursulfase. Extension study to evaluate, safety, pharmacokinetics, activity, immunogenicity of intrathecal administration of idursulfase.

PIP number	Active substance (INN)	Condition (therapeutic area)	Age groups in studies	Type of studies
EMA-001366-PIP01-12	Glycopyrronium (bromide)	Treatment of sialorrhoea (Neurology)	From 2 to less than 18 years	Development of an age-appropriate oral liquid formulation. Crossover study to compare the bioavailability of 2 mg glycopyrronium bromide from a new oral solution (2 mg/5 ml) (test product) with that of 2 mg glycopyrronium bromide from Cuvposa 1 mg/5 ml solution (reference product). Systematic literature review of glycopyrronium bromide use in children for the treatment of sialorrhoea to support its safe and effective use.
EMA-001303-PIP01-12	Bumetanide	Treatment of autistic spectrum disorder (Neurology)	From 2 to less than 18 years	Development of prolonged-release minitables. Development of age-appropriate oral liquid formulation. In-vitro genotoxicity study. Dose finding study to evaluate the pharmacokinetic and efficacy of Bumetanide in children. Study to evaluate safety and efficacy, of Bumetanide in children. Study to evaluate the efficacy of Bumetanide minitables in children.
EMA-001311-PIP01-12	Vancomycin	Treatment of bacterial sepsis (Neonatology/PI CU)	From birth to less than 90 days	Development of a 125mg powder for concentrate for solution for infusion. Determination of pharmacokinetic-pharmacodynamic (PK-PD) relationships from the hollow fibre infection model (HFIM) and a rabbit model. Study to compare the efficacy, safety and pharmacokinetics (PK) of an optimised dosing regimen compared to a standard dosing regimen of vancomycin. Population PK meta-analysis.

PIP number	Active substance (INN)	Condition (therapeutic area)	Age groups in studies	Type of studies
EMA-001310-PIP01-12	Gabapentin	Treatment of chronic pain (Pain)	From 3 months to less than 18 years	Development of an age-appropriate 75 mg /ml oral solution. Juvenile repeated rat toxicity study. Study to evaluate the pharmacokinetic, efficacy and safety of gabapentin liquid formulation in children. Study to evaluate safety, pharmacokinetics and efficacy of gabapentin as add-on to morphine in children. Model-based bridging of clinical data for children from 3 months to less than 3 years.
EMA-001316-PIP01-12	Clonidine (hydrochloride)	Sedation (Anaesthesiology)	From birth to less than 18 years	Development of three different strengths (ready-to-use) vials. Study to evaluate pharmacokinetics, safety and efficacy of Clonidine for sedation in children.
EMA-001262-PIP01-12	Dobutamine (hydrochloride)	Treatment of neonatal circulatory failure (Neonatology/PICU)	From birth to less than 1 month	Development of an age-appropriate pharmaceutical form (solution for injection). Observational study of dobutamine in neonates. Dose-finding study for dobutamine in premature neonates. Study to evaluate the safety and efficacy of dobutamine as a treatment for haemodynamic insufficiency in preterm neonates. Systematic review on the use of dobutamine in patients from 33 weeks gestational age to less than 28 days postnatal age.
EMA-000530-PIP02-11	Cyclophosphamide	Treatment of malignant diseases (Oncology)	From birth to less than 18 years	Development of a soluble tablet. Study to evaluate pharmacokinetics, toxicity and safety of cyclophosphamide soluble tablet compared with authorised cyclophosphamide products in children. Physiology-based pharmacokinetic model.

PIP number	Active substance (INN)	Condition (therapeutic area)	Age groups in studies	Type of studies
EMA-000711-PIP01-09	Morphine (hydrochloride)	Treatment of pain (Pain/neonatology)	From birth to less than 6 months	Development of an intravenous formulation for neonatal use. Stability testing. Non linear mixed model trial to determine PK/PD parameters of morphine and to derive an algorithm for morphine administration in preterm and term neonates. Observational and descriptive study to refine the PK/PD model and to collect safety data. Interpolation and modeling study.
EMA-001120-PIP01-10	Budesonide	Prevention of bronchopulmonary dysplasia (Neonatology)	From 23 to less than 28 weeks of gestational age	Study to evaluate safety and efficacy of budesonide for the prevention of bronchopulmonary dysplasia in preterm infants. Substudy to study 1 to evaluate pharmacokinetics / pharmacodynamics . Substudy to study 1 to evaluate genetic susceptibility to bronchopulmonary dysplasia. Substudy to study 1 to evaluate pituitary / adrenal gland function.
EMA-001034-PIP01-10	Risperidone	Treatment of conduct disorder (Psychiatry)	From 5 to less than 18 years	Study to evaluate safety and efficacy of risperidone in paediatric patients. Discontinuation (relapse prevention) trial to evaluate safety and efficacy of risperidone in paediatric patients. Study to evaluate safety of risperidone in paediatric patients.

PIP number	Active substance (INN)	Condition (therapeutic area)	Age groups in studies	Type of studies
EMA-000712-PIP01-09	Fentanyl (citrate)	Prevention and treatment of acute pain (Neonatology)	From birth to less than 2 years	Development of an intravenous formulation for neonatal use. Stability testing. PK/PD study to establish the (log) concentration versus effect curve of intravenous fentanyl in newborn children. Observational and descriptive study to evaluate the use of an optimal fentanyl dose derived from the PK/PD study and to collect safety data in newborn children. Interpolation and modeling study to extend dosing recommendations of intravenous fentanyl for the treatment of acute pain.
EMA-000606-PIP01-09	Levonorgestrel	Contraception (Gynaecology)	Girls from age of menarche to less than 18 years	Study to assess the safety, bleeding pattern, discontinuation rates (compliance), pharmacokinetics, and efficacy of the ultra low dose LNG intrauterine contraceptive system (LCS) in adolescents.
EMA-000511-PIP01-08	Propranolol (hydrochloride)	Haemangioma (Dermatology)	From 35 days to less than 11 months	Study to evaluate the compatibility and stability of the formulation in the presence of milk. Study to evaluate the palatability of a new formulation (solution). Bioequivalence study of a new formulation (solution) compared to the reference formulation (tablet). Study to assess safety and efficacy of 4 regimens of propranolol compared to placebo. Study to evaluate the pharmacokinetics of propranolol in paediatric subjects.
EMA-000415-PIP01-08	Human normal immunoglobulin	Dermatopolymyositis (Dermatology)	From 2 to less than 18 years	Study to evaluate efficacy and safety of human normal immunoglobulin product for intravenous administration (IVIg) in children.
EMA-000395-PIP01-08	Midazolam (hydrochloride)	Epileptic seizures (Neurology)	From 3 months to less than 18 years	Development of age-specified pre-filled syringes. Pharmacokinetic study of oromucosal midazolam administered to children.

PIP number	Active substance (INN)	Condition (therapeutic area)	Age groups in studies	Type of studies
EMA-000221-PIP01-08	Glucose (monohydrate)	Treatment of mild to moderate procedural pain (Pain/neonatology)	From birth to less than 12 months	Dose finding study, following heel lancing. Study to assess the efficacy and safety of identified concentration for the prevention of pain during heel lancing puncture. Study to assess the efficacy and safety of identified concentration for the prevention of pain during vaccination. Study to assess the efficacy and safety of identified concentration for the prevention of pain during venipuncture. Study to assess the efficacy and safety of identified concentration for the prevention of pain during venipuncture.
EMA-000149-PIP01-07	Influenza virus surface antigens	Influenza (Vaccines)	From 2 months to less than 18 years	Development of a suspension for injection. Safety and immunogenicity study of revaccination. Safety, immunogenicity and efficacy study of two doses of Flud vaccine in children. Safety and immunogenicity study of two doses of Flud vaccine in children. Safety and immunogenicity study of a single dose of Flud vaccine in children. Safety and immunogenicity study of one or two doses of Flud vaccine in children.

Source: EMA database (PedRA)

1.4. Statements of compliance in marketing authorisations

The statement of compliance as mentioned in Article 28 (3) of the Paediatric Regulation allows to identify that:

- a marketing authorisation or a variation application complied with all the measures contained in the agreed completed paediatric investigation plan and
- the SmPC reflects the results of studies conducted in compliance with that agreed paediatric investigation plan.

1.4.1. Statements of compliance (CAPs)

Table 10. Statements of compliance for CAPs (2007-2015)

Year	Active substance (INN)	Trade name	MAH	Application type
2008	Caspofungin	Cancidas	Merck Sharp and Dohme	Variation
2009 2009	Peginterferon alfa-2b	PegIntron, ViraferonPeg	Schering-Plough Europe	Variation
2009	Ribavirin	Rebetol	Schering-Plough Europe	Variation
2010	Abatacept	Orencia	Bristol-Myers Squibb Pharma EEIG	Variation
2010	Zoledronic acid	Zometa	Novartis Europharm Ltd	Variation
2011	Clopidogrel	Plavix and associated names	Sanofi BMS	Variation
2011	Colesevelam	Cholestagel	Genzyme	Variation
2011	Midazolam	Buccolam	Viropharma SPRL	Initial MA
2011	Nevirapine	Viramune	Boehringer	Variation
2011	HPV vaccine	Gardasil	Sanofi Pasteur	Variation
2011	Nomegestrol / estradiol	loa,* Zoely*	N.V. Organon, Merck Serono Europe	Initial MA
2012	Etanercept	Enbrel	Pfizer Limited	Variation
2013	Imatinib	Glivec	Novartis Europharm Ltd	Variation
2013	pandemic influenza vaccine (H5N1) (whole virion, inactivated, prepared in cell culture)	Pandemic Influenza Vaccine H5N1 Baxter	Baxter AG	Variation
2013	Darunavir	Prezista	Janssen-Cilag International N.V.	Variation
2014	Baraclude	Entecavir	Bristol-Myers Squibb Pharma EEIG	Variation
2014	Travatan	Travoprost	Alcon Laboratories (UK) Ltd	Variation
2014	Hemangirol	Propranolol	Pierre Fabre Dermatologie	Initial MA
2014	Invega	Paliperidone	Janssen-Cilag International NV	Variation
2014	Prezista	Darunavir	Janssen-Cilag International NV	Variation
2014	Synagis	Palivizumab	AbbVie Ltd	Line extension
2014	Xagrid	Anagrelide	Shire Pharmaceutical Contracts Limited	Variation
2015	DUTREBIS	Lamivudine / raltegravir potassium	Merck Sharp & Dohme Limited	Initial MA

Year	Active substance (INN)	Trade name	MAH	Application type
2015	Gardasil 9	Human papillomavirus vaccine (types 6, 11, 16, 18, 31, 33, 45, 52, 58) (recombinant, adsorbed)	Sanofi Pasteur MSD	Initial MA
2015	Flebogamma DIF	Human normal immunoglobulin	Instituto Grifols S.A.	Variation
2015	Resolor	Prucalopride	Shire Pharmaceuticals Ireland Ltd	Variation
2015	Soliris	Eculizumab	Alexion Europe SAS	Variation
2015	Stayveer	Bosentan	Marklas Nederlands BV	Variation
2015	Tygaclil	Tigecycline	Pfizer Ltd	Variation

Source: EMA databases (SIAMED, PedRA)

1.4.2. Statements of compliance (NAPs, DCP/MRP)

Table 11. Statement of compliance for NAPs, DCP/MRP (2007-2015)

Year	Active substance (INN)	Trade name	MAH
2009-2010	Anastrozole	Arimidex	AstraZeneca AB
2010	Atorvastatin	Sortis and associated names	Pfizer
2011	Alanine, arginine, aspartic acid, calcium, cysteine, glucose, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, magnesium, methionine, olive oil, ornithine, phenylalanine, potassium, proline, serine, sodium, soybean oil, taurine, threonine, tryptophan, tyrosine, valine	Numeta and associated names	Baxter
2011	DTP Polio HiB vaccine	Pediacel	Sanofi Pasteur
2011	Esomeprazole sodium / esomeprazole magnesium	Nexium and associated names	Astra Zeneca AB
2010-2011	Latanoprost	Xalatan and associated names	Pfizer
2008-2009	Losartan	Cosaar and associated names	Merck Sharp and Dohme
2010-2011	Montelukast	Singulair	MSD
2011	Rizatriptan	Maxalt and associated names	Merck Sharpe and Dohme
2009-2010	Valsartan	Diovan and associated names	Novartis
2012	acetylsalicylic acid, bisoprolol	Bisoprolol Aspirin	ASA Pharma
2012	tapentadol	Palexia, Palexias, Yantil	Grünenthal GmbH

Year	Active substance (INN)	Trade name	MAH
2012	beclometasone dipropionate, formoterol fumarate dihydrate	Foster Nexthaler	Chiesi Pharmaceuticals GmbH
2012	fluticasone propionate/ formoterol fumarate	Flutiform, Iffeza	Mundipharma GmbH, Germany
2012	formoterol fumarate dihydrate, fluticasone propionate	Flutiform, Iffeza	Mundipharma AB
2013	Ezetimibe	Ezetrol	Merck Sharp & Dohme BV
2013	Tiotropium bromide monohydrate	Spiriva	Boehringer Ingelheim International GmbH
2013	Azelastin/fluticasone	Synaze, Azeflu, Dymista, Xatalin, Bileni, Sycara	MEDA Pharma
2013	Misoprostol	Misodel	Ferring
2013	Clindamycin/tretinoin	Zanea	MEDA Pharma
2014	Valganciclovir	Valcyte, RoValcyte	Roche
2014	Rupatadine	Rupatall, Rupafin, Tamalis	J Uriach & Cia
2014	Rosuvastatin	Crestor	AstraZeneca
2014	Misoprostol	Misodel, Mysodelle	Ferring
2014	Betamethasone/Calcipotriol	Xamiol	LEO Pharmaceutical products DK
2014/ 2015	Atomoxetine	Strattera	Eli Lilly
2014	Clindamycin phosphate / Tretinoin	Acnex / Zaria	MEDA Pharma GmbH & Co. KG
2014	Tiotropium	Spiriva Respimat	Boehringer Ingelheim International GmbH
2014	Ezetimibe	Ezetrol	Merck Sharp & Dohme
2015	Human normal immunoglobulin	IQYMUNE	Laboratoire Français du Fractionnement et des Biotechnologies
2015	Gadobutrol	Gadovist	Bayer GmbH
2015	allergen extract mixture 12 SQ-HDM	ACARIZAX	ALK-Abelló A/S
2015	LANREOTIDE	Somatuline Autogel	IPSEN LIMITED
2015	IVERMECTIN	Soolantra 10 mg/g cream	GALDERMA (UK) LIMITED

Year	Active substance (INN)	Trade name	MAH
2015	TAPENTADOL HYDROCHLORIDE	PALEXIA	GRUNENTHAL LIMITED

Source: NCA questionnaire

1.4.3. PDCO opinions on PIP compliance

The EMA/PDCO adopted opinions confirming the compliance of the studies and measures with the agreed PIP, after its completion, in 97 cases (excluding duplicates). In 2 cases the initial opinion was negative, but the final opinion (after a procedure of modification of an agreed PIP) was positive (total positive opinions: 99). The EMA/PDCO also checked partial (interim) compliance as part of the validation of regulatory procedures in 299 procedures, of which 12 had an initial negative outcome.

The opinions on compliance are mentioned and summarised in the PDCO monthly reports (<http://bit.ly/xGFZEw>).

No Member State reported to have issued an opinion on compliance with an agreed PIP.

Table 12. PDCO opinions on PIP compliance (2007-2015)

Active substance (INN)	Therapeutic area	Company name	Compliance opinion date
Ipilimumab	Oncology	Bristol-Myers Squibb Pharma EEIG	11/12/2015
Bevacizumab	Oncology	F.Hoffmann-La Roche Ltd	13/11/2015
Bilastine	Dermatology / pneumology- allergology / oto- rhino-laryngology	FAES FARMA, S.A.	13/11/2015
Human normal immunoglobulin	Immunology- rheumatology- transplantation	Baxalta Innovations GmbH	30/10/2015
Artemether / lumefantrine	Infectious diseases (malaria)	Novartis Europharm Limited	09/10/2015
Canakinumab	Immunology- rheumatology- transplantation	Novartis Europharm LTD	09/10/2015
Insulin aspart / insulin degludec	Endocrinology- gynaecology- fertility- metabolism	Novo Nordisk A/S	11/09/2015
Lopinavir / ritonavir	Infectious diseases	AbbVie Ltd.	17/07/2015
Canakinumab	Immunology- rheumatology- transplantation	Novartis Europharm Ltd	19/06/2015

Active substance (INN)	Therapeutic area	Company name	Compliance opinion date
Sieved freeze-dried allergen extract of Dermatophagoides pteronyssinus / sieved freeze-dried allergen extract of Dermatophagoides farinae	Pneumology - allergology	Stallergenes S.A.	19/06/2015
Everolimus	Immunology-rheumatology-transplantation	Novartis Europharm Limited	22/05/2015
Solifenacin (succinate)	Uro-nephrology	Astellas Pharma Europe B.V.	22/05/2015
Eculizumab	Immunology-rheumatology-transplantation	ALEXION EUROPE SAS	22/05/2015
Von Willebrand Factor / human coagulation Factor VIII	Haematology-hemostaseology	CSL Behring GmbH	22/05/2015
Fluticasone Propionate / formoterol fumarate dihydrate	Pneumology - allergology	Mundipharma Research Limited	13/02/2015
Atazanavir (sulphate)	Infectious diseases	Bristol-Myers Squibb Pharma EEIG	13/02/2015
Human normal immunoglobulin	Immunology-rheumatology-transplantation	Baxter Innovations GmbH	16/01/2015
Anakinra	Immunology-rheumatology-transplantation	Swedish Orphan Biovitrum AB (publ)	12/12/2014
Pandemic influenza vaccine (H1N1) (split virion, inactivated, adjuvanted), containing antigen equivalent to Influenza A/California/7/2009 (Produced at Quebec manufacturing site)	Vaccines	GlaxoSmithKline Biologicals S.A.	12/12/2014
Purified antigen fractions of inactivated split virion Influenza virus type A, H1N1 A/California/7/2009	Vaccines	GlaxoSmithKline Biologicals S.A.	12/12/2014
Tigecycline	Infectious diseases	Pfizer Limited	12/12/2014
Autologous CD34+ cells transduced ex vivo with retroviral vector (GIADAI) containing human adenosine deaminase gene from cDNA	Immunology-rheumatology-transplantation	GlaxoSmithKline Trading Services Limited	14/11/2014
Eltrombopag	Infectious diseases / oncology / gastroenterology-hepatology / haematology-hemostaseology	Novartis Pharmaceuticals UKLtd	14/11/2014

Active substance (INN)	Therapeutic area	Company name	Compliance opinion date
Glycopyrronium bromide	Neurology	Proveca Limited	14/11/2014
Insulin detemir	Endocrinology- gynaecology- fertility- metabolism	Novo Nordisk A/S	14/11/2014
Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), inactivated poliovirus and Haemophilus type b (meningococcal protein conjugate) vaccine (adsorbed)	Vaccines	Sanofi Pasteur MSD	10/10/2014
Ivabradine hydrochloride	Cardiovascular diseases	LES LABORATOIRES SERVIER	10/10/2014
Pneumococcal Polysaccharide Serotype 5 - Diphtheria-CRM197 conjugate / Pneumococcal Polysaccharide Serotype 7F - Diphtheria-CRM197 conjugate / Pneumococcal Polysaccharide Serotype 23F - Diphtheria-CRM197 conjugate / Pneumococcal Polysaccharide Serotype 1 - Diphtheria-CRM197 conjugate / Pneumococcal Polysaccharide Serotype 3 - Diphtheria-CRM197 conjugate / Pneumococcal Polysaccharide Serotype 6B - Diphtheria-CRM197 conjugate / Pneumococcal Polysaccharide Serotype 18C - Diphtheria-CRM197 conjugate / Pneumococcal Polysaccharide Serotype 9V - Diphtheria-CRM197 conjugate / Pneumococcal Polysaccharide Serotype 14 - Diphtheria-CRM197 conjugate / Pneumococcal Polysaccharide Serotype 19A - Diphtheria-CRM197 conjugate / Pneumococcal Polysaccharide Serotype 6A - Diphtheria-CRM197 conjugate / Pneumococcal Polysaccharide Serotype 4 - Diphtheria-CRM197 conjugate / Pneumococcal Polysaccharide Serotype 19F - Diphtheria-CRM197 conjugate	Vaccines	Pfizer Limited	10/10/2014
Sapropterin dihydrochloride	Endocrinology- gynaecology- fertility- metabolism	Merck Serono Europe Ltd	10/10/2014
Aprepitant	Oncology	Merck Sharp & Dohme (Europe) Inc.	10/10/2014
Fosaprepitant dimeglumine	Oncology	Merck Sharp & Dohme (Europe) Inc.	10/10/2014

Active substance (INN)	Therapeutic area	Company name	Compliance opinion date
Golimumab	Immunology-rheumatology-transplantation	Janssen Biologics BV	10/10/2014
Benzylpenicilloyl octa-L-lysine / Sodium benzylpenilloate	Diagnostic	DIATER, Laboratorio de Diagnóstico y Aplicaciones Terapéuticas, S.A	12/09/2014
Tobramycin	Infectious diseases	Novartis Europharm Ltd.	12/09/2014
Adalimumab	Immunology-rheumatology-transplantation / dermatology	AbbVie Limited	20/06/2014
Vandetanib	Oncology	AstraZeneca AB	20/06/2014
Entecavir	Infectious diseases	Bristol-Myers Squibb Pharma EEIG	20/06/2014
Gadobutrol	Diagnostic	Bayer Pharma AG	20/06/2014
Human normal immunoglobulin	Immunology-rheumatology-transplantation	LFB Biotechnologies	23/05/2014
Insulin degludec	Endocrinology-gynaecology-fertility-metabolism	Novo Nordisk A/S	23/05/2014
Travoprost	Ophthalmology	Alcon Laboratories (UK) Ltd	23/05/2014
Rupadatine fumarate	Dermatology / pneumology - allergology / oto-rhino-laryngology	J. Uriach y Compañía, S.A.	21/03/2014
Bosentan (monohydrate)	Cardiovascular diseases	Actelion Registration Ltd	21/03/2014
Lamivudine / raltegravir	Infectious diseases	Merck Sharp & Dohme (Europe), Inc.	21/03/2014
Anagrelide hydrochloride	Haematology-hemostaseology	Shire Pharmaceutical Contracts Limited	14/02/2014
Human Papillomavirus 9-valent Vaccine recombinant (Types 6, 11, 16, 18, 31, 33, 45, 52, 58)	Vaccines	Sanofi Pasteur MSD S.N.C.	17/01/2014
Nitisinone	Endocrinology-gynaecology-fertility-metabolism	Swedish Orphan Biovitrum International AB	17/01/2014
Atomoxetine hydrochloride	Psychiatry	Eli Lilly & Company	06/12/2013
Guanfacine hydrochloride	Psychiatry	Shire Pharmaceutical Contracts Ltd	06/12/2013

Active substance (INN)	Therapeutic area	Company name	Compliance opinion date
Prucalopride succinate	Gastroenterology -hepatology	Shire Pharmaceuticals Ireland Limited	06/12/2013
Ulipristal acetate	Endocrinology- gynaecology- fertility- metabolism	Laboratoire HRA Pharma	08/11/2013
Human normal immunoglobulin	Immunology- rheumatology- transplantation / haematology- hemostaseology	Octapharma Pharmazeutika Produktionsges.m.b.H	11/10/2013
Rosuvastatin (calcium)	Cardiovascular diseases	AstraZeneca AB	11/10/2013
Rupatadine fumarate	Dermatology / pneumology - allergology / oto- rhino-laryngology	J. Uriach y Compañía, S.A.	11/10/2013
Valganciclovir hydrochloride	Infectious diseases	Roche Registration Limited	11/10/2013
Split influenza virus, inactivated containing antigen equivalent to A/California/7/2009 (H1N1)-like strain (A/California/7/2009 (NYMC X-179A)), non-adjuvanted	Vaccines	Sanofi Pasteur SA	13/09/2013
Palivizumab	Neonatology - paediatric intensive care	AbbVie Ltd	09/08/2013
Voriconazole	Infectious diseases	Pfizer Limited	09/08/2013
Influenza Virus Type A, H1N1 / Influenza virus Type B, Victoria lineage / Influenza Virus Type A, H3N2 / Influenza virus Type B, Yamagata lineage	Vaccines	MedImmune Limited	14/06/2013
Recombinant L-asparaginase	Oncology / haematology- hemostaseology	medac Gesellschaft für klinische Spezialpräparate mbH	14/06/2013
Paliperidone / paliperidone palmitate	Psychiatry	JANSSEN-CILAG INTERNATIONAL NV	08/02/2013
Propranolol hydrochloride	Dermatology	PIERRE FABRE DERMATOLOGIE	08/02/2013
A/H5N1 pre-pandemic influenza vaccine (whole Virion, vero cell derived, inactivated)	Vaccines	Baxter Innovations GmbH	11/01/2013
Ezetimibe	Cardiovascular diseases	Merck Sharp & Dohme Limited	11/01/2013

Active substance (INN)	Therapeutic area	Company name	Compliance opinion date
Human normal immunoglobulin	Immunology- rheumatology- transplantation	LFB Biotechnologies	05/10/2012
Misoprostol	Other / endocrinology- gynaecology- fertility- metabolism	Ferring Pharmaceuticals A/S	05/10/2012
Tiotropium bromide (monohydrate)	Pneumology - allergology	Boehringer Ingelheim International GmbH	17/08/2012
Imatinib (mesylate)	Oncology	Novartis Europharm Limited	09/03/2012
Darunavir (as ethanolate)	Infectious diseases	Tibotec BVBA on behalf of Janssen-Cilag International NV	09/12/2011
Etanercept	Immunology- rheumatology- transplantation / dermatology	Pfizer Limited	09/12/2011
Insulin glargine	Endocrinology- gynaecology- fertility- metabolism	Sanofi-Aventis Deutschland GmbH	11/11/2011
Rizatriptan (benzoate)	Pain	Merck Sharp & Dohme (Europe) Inc.	09/09/2011
Infliximab	Immunology- rheumatology- transplantation / dermatology / gastroenterology- hepatology	Janssen Biologics B.V.	09/09/2011
Rotavirus type G2 / rotavirus type G4 / rotavirus type G1 / rotavirus type G3 / rotavirus type P1A[8]	Vaccines	Sanofi Pasteur MSD SNC	15/07/2011
Fluticasone propionate / azelastine hydrochloride	Pneumology - allergology	MEDA Pharma GmbH & Co. KG	17/06/2011

Active substance (INN)	Therapeutic area	Company name	Compliance opinion date
Meningococcal group W-135 oligosaccharide Conjugated to Corynebacterium diphtheriae CRM197 protein (MenW-CRM) / Meningococcal group Y oligosaccharide Conjugated to Corynebacterium diphtheriae CRM197 protein (MenY-CRM) / Meningococcal group A oligosaccharide Conjugated to Corynebacterium diphtheriae CRM197 protein (MenA-CRM) / Meningococcal group C oligosaccharide Conjugated to Corynebacterium diphtheriae CRM197 protein (MenC-CRM)	Vaccines	Novartis Vaccines and Diagnostics S.r.L	20/05/2011
Clindamycin phosphate / Tretinoin	Dermatology	MEDA Pharma GmbH & Co. KG	10/12/2010
Clopidogrel	Cardiovascular diseases	Sanofi Pharma Bristol-Myers Squibb SNC	10/12/2010
Nevirapine	Infectious diseases	Boehringer Ingelheim International GmbH	06/08/2010
Midazolam (as hydrochloride)	Neurology	ViroPharma SPRL	06/08/2010
Esomeprazole magnesium trihydrate / esomeprazole sodium	Gastroenterology -hepatology	AstraZeneca AB, European regulatory affairs	16/07/2010
Nomegestrol / 17betaestradiol	Endocrinology-gynaecology-fertility-metabolism	N.V. Organon	21/05/2010
Human Papillomavirus type 6 L1 protein / Human Papillomavirus type 11 L1 protein / Human Papillomavirus type 16 L1 protein / Human Papillomavirus type 18 L1 protein	Vaccines	Sanofi Pasteur MSD	16/04/2010
Latanoprost	Ophthalmology	Dr Jiri Kos	19/03/2010
Montelukast	Pneumology - allergology	Merck Sharp & Dohme Ltd.	15/01/2010
Atorvastatin calcium (trihydrate)	Endocrinology-gynaecology-fertility-metabolism	Pfizer Limited	13/11/2009

Active substance (INN)	Therapeutic area	Company name	Compliance opinion date
Alanine isoleucine serine potassium acetate arginine leucine taurine magnesium acetate, tetrahydrate aspartic acid lysine monohydrate threonine calcium chloride, dihydrate Cysteine / cystine methionine tryptophan sodium glycerophosphate, hydrated glutamic acid ornithine hydrochloride tyrosine glucose, monohydrate glycine phenylalanine valine olive oil, refined histidine proline sodium chloride soya-bean oil, refined	Nutrition	BAXTER World Trade SA/NV	16/10/2009
Purified diphtheria toxoid, Purified tetanus toxoid, Five component acellular pertussis [Purified Pertussis Toxoid (PT), Purified Filamentous Haemagglutinin (FHA), Purified Fimbriae Types 2 and 3 (FIM) and Purified Pertactin (PRN)], Inactivated poliomyelitis vaccine (Vero) – Type 1 (Mahoney), Type 2 (MEF-1) and Type 3 (Saukett), Purified polyribosylribitol phosphate capsular polysaccharide of Haemophilus influenzae type b covalently bound to Tetanus protein (PRP-T)	Vaccines	Sanofi Pasteur MSD	18/09/2009
Valsartan	Cardiovascular diseases	Novartis Europharm Limited	21/08/2009
Alanine, Arginine, Aspartic acid, Cysteine/Cystine, Glutamic acid, Glycine, Histidine, Isoleucine, Leucine, Lysine monohydrate, Methionine, Ornithine hydrochloride, Phenylalanine, Proline, Serine, Taurine, Threonine, Tryptophan, Tyrosine, Valine, Sodium chloride, Potassium acetate, Magnesium acetate, tetrahydrate, Calcium chloride, Sodium glycerophosphate, Glucose, Olive oil, refined, Soya-bean oil, refined	Nutrition	BAXTER World Trade SA/NV	24/07/2009
Colesevelam hydrochloride	Endocrinology-gynaecology-fertility-metabolism	Genzyme Europe B.V	24/07/2009

Active substance (INN)	Therapeutic area	Company name	Compliance opinion date
Abatacept	Endocrinology- gynaecology- fertility- metabolism	Bristol-Myers Squibb Pharma EEIG	29/05/2009
Anastrozole	Endocrinology- gynaecology- fertility- metabolism	AstraZeneca AB	03/04/2009
Losartan potassium	Cardiovascular diseases	Merck, Sharp & Dohme (Europe) Inc	06/02/2009
Zoledronic acid	Endocrinology- gynaecology- fertility- metabolism	Novartis Europharm Limited	12/12/2008
Peginterferon alfa-2b	Infectious diseases / gastroenterology- hepatology	Schering-Plough Europe	17/10/2008
Ribavirin	Infectious diseases / gastroenterology- hepatology	Schering-Plough Europe	17/10/2008
Caspofungin acetate	Infectious diseases	Merck Sharp & Dohme (Europe) Inc.	04/06/2008

Source: EMA database (PedRA)

1.4.4. Supplementary protection certificate extension (6 months) granted by national patent offices

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

By December 2015, 322 national SPCs were reported as having been granted or pending an extension (not all member states respond to the annual survey – more information can be found in the annual reports).

Table 13. Medicines and companies that have received the 6-month extension of the supplementary protection certificate (SPC) (2007-2015)

Active substance (INN) (Invented name)	MAH	SPC extension granted in MS (year)	SPC extension pending in MS (year)
Abatacept (Orencia)	Bristol-Myers Squibb Pharma EEIG	Austria (2011) Denmark (2010) Estonia (2011) Finland (2011) France (2010) Germany (2010) Ireland (2010) Luxembourg (2010) The Netherlands (2010) Portugal 2010) Slovenia (2011) Sweden (2011) United Kingdom (2011) Bulgaria (2012) Italy (2012) Romania (2012)	Greece (2010) Lithuania (2011) Luxembourg (2011) Spain (2010) Czech Republic (2014) Hungary (2014)
Adalimumab (Humira)	AbbVie Ltd	Austria (2015) Denmark (2015) France (2015) Germany (2015) Hungary (2015) Ireland (2015) Italy (2015) Luxembourg (2015) Netherlands (2015) Poland (2015) Slovenia (2015) Sweden (2015) UK (2015)	Bulgaria (2015) Greece (2015) Romania (2015) Slovakia (2015) Spain (2015)
Anastrozole (Arimidex and associated names)	AstraZeneca AB	Austria (2010) Belgium (2010) Denmark (2010) Finland (2 March 2010) France (11 June 2010) Germany (19 July 2010) Ireland (29 June 2010) Italy (16 March 2010) Luxembourg (27 July 2010) The Netherlands (1 April 2010) Sweden (27 April 2010) United Kingdom (10 June 2010)	Romania (2010, 2011; <i>SPC granted after appeal</i>)

Active substance (INN) (Invented name)	MAH	SPC extension granted in MS (year)	SPC extension pending in MS (year)
Aripiprazole (Abilify)	Otsuka Pharmaceutical Europe Ltd	Italy (2014)	Denmark(2012) Germany (2012) Romania(2012) Sweden(2012) The Netherlands(2012) United Kingdom(2012) France (2013) Spain (2015)
Atorvastatin (Sortis and associated names)	Pfizer	Austria (year not reported, possibly 2011) Denmark (2011) Germany (2011) Ireland (2011) Italy (2011) Luxembourg 2011) Sweden (2011) The Netherlands (2011) United Kingdom (2011)	France (2010)
Paclitaxel (Abraxane)	Celgene Europe Limited		Germany (2015)
Entecavir (Baraclude)	Bristol-Myers Squibb Pharma EEIG	Denmark (2014) Finland (2014) Ireland (2014) Italy (2014) Austria (2015) Greece (2015) Hungary (2015) Luxembourg (2015) Poland (2015) Romania (2015) Spain (2015)	Belgium (2014) France (2014) Germany (2014) Netherlands (2014) Sweden (2014) UK (2014)
Bevacizumab (Avastin)	Roche Registration Ltd		Czech Republic (2015) Hungary (2015) Slovakia (2015)
Bosentan (Tracleer)	Actelion Registration Ltd	Denmark (2015) Finland (2015) France (2015) Germany (2015) Hungary (2015) Ireland (2015) Italy (2015) Netherlands (2015) Romania (2015) Spain (2015) Sweden (2015)	Belgium (2014) Slovakia (2014) UK (2014) Austria (2015) Greece (2015) Luxembourg (2015) Slovakia (2015)

Active substance (INN) (Invented name)	MAH	SPC extension granted in MS (year)	SPC extension pending in MS (year)
Caspofungin (Cancidas)	Merck Sharp and Dohme	Austria (2010) Belgium 2010) Finland (2011) Greece (2010) Italy (2010) Portugal 2010) Slovenia (2010) Denmark (2009) France (2009) Germany (2009) Ireland (2009) The Netherlands (2009) Sweden (2009) United Kingdom (2009) Romania (2012) Bulgaria (2013) Czech Republic (2013) Slovakia (2013) Luxembourg (2015)	Czech Republic (2010, 2011) Hungary (2010, 2011) Poland (2011) Spain (2010)
Clopidogrel (Plavix and associated names)	Sanofi BMS	Denmark (2012) Finland (2011) Germany (2011) Portugal (2011) Sweden (2011) Belgium (2012) Denmark (2012) Ireland (2012) Italy (2012) Spain (2012)	Austria (2012) Ireland (2011) Italy (2011) The Netherlands (2011) United Kingdom (2011)
Colesevelam (Cholestagel)	Genzyme Europe BV		United Kingdom(2012) The Netherlands (2014)
Colistimethate(Colobreath e)	Forest Laboratories UK		Germany (2013)
Darunavir (Prezista)	Janssen-Cilag International NV	Denmark (2015) Finland (2015) France (2015) Greece (2015) Ireland (2015) Italy (2015) Luxembourg (2015) Spain(2015) Sweden (2015)	UK (2014) Austria (2014) Germany (2015)

Active substance (INN) (Invented name)	MAH	SPC extension granted in MS (year)	SPC extension pending in MS (year)
Etanercept (Enbrel)	Pfizer Limited	France(2012) Ireland (2012) Italy (2012) Sweden (2012) The Netherlands (2012) Finland (2013) France (2013) Germany (2013) Greece (2013) United Kingdom (2013) Belgium (2014) Bulgaria (2015)	Austria (2012) Bulgaria (2012) Denmark (2012) Luxembourg (2012) Spain (2012)
Ezetimibe (Ezetrol and associated names)	Merck Sharp & Dohme	Denmark (2015) Italy (2015) Netherlands (2015) Sweden (2015)	Austria (2015) Czech Republic (2015) Finland (2015) France (2015) Germany (2015) Greece (2015) Ireland (2015) Slovakia (2015) Spain (2015) UK (2015)
Human papillomavirus vaccine (Gardasil)	Sanofi Pasteur MSD	France (2014) Italy (2014) UK (2014) Austria (2015) Denmark (2015) Greece (2015) Ireland (2015) Luxembourg (2015) Spain (2015) Sweden (2015)	Belgium (2014) Germany (2014) Ireland (2014) Netherlands (2014)
Imatinib (Glivec)	Novartis Europharm Limited	Sweden (2013) Denmark (2014) Finland (2014) France (2014) Germany (2014) Italy (2014) Netherlands (2014) UK (2014) Austria (2015) Czech Republic (2015) Hungary (2015) Luxembourg (2015) Spain (2015)	Finland (2013) Greece (2013) Italy (2013) Ireland (2013)

Active substance (INN) (Invented name)	MAH	SPC extension granted in MS (year)	SPC extension pending in MS (year)
Infliximab (Remicade)	Janssen Biologics B.V.	Austria (2013) Germany (2013) Greece (2013) United Kingdom (2013) Belgium (2014)	
Insulin detemir (Levemir)	Novo Nordisk	Denmark (2015) Italy (2015) Slovenia (2015)	Austria (2015) Bulgaria (2015) Czech Republic (2015) Finland (2015) France (2015) Germany (2015) Greece (2015) Hungary (2015) Ireland (2015) Lithuania (2015) Luxembourg (2015) Romania (2015) Slovakia (2015) Sweden (2015) UK (2015)
Insulin – glargine (Lantus Optisulin)	Sanofi-Aventis Deutschland GmbH	Denmark (2012) Ireland (2012) Italy (2012) Sweden (2012) Finland (2013) France (2013) Germany (2013) Greece (2013) United Kingdom (2013) Belgium (2014)	Belgium (2012) Luxembourg (2012) Spain (2012)
Ivabradine (Corlentor/ Procoralan)	Les Laboratoires Servier	Denmark (2015) France (2015) Italy (2015) Sweden (2015) UK (2015)	Austria (2015) Germany (2015) Greece (2015) Ireland (2015) Luxembourg (2015) Spain (2015)

Active substance (INN) (Invented name)	MAH	SPC extension granted in MS (year)	SPC extension pending in MS (year)
Latanoprost (Xalatan and associated names)	Pfizer	Austria (year not reported, possibly 2011) Denmark (2011) Finland (2011) Germany (2011) Ireland (2011) Italy (2011) Luxembourg (2011) Portugal (2011) Sweden (2011) The Netherlands (2011) United Kingdom (2011)	Spain (2010)
Losartan (Cozaar and associated names)	Merck Sharp & Dohme BV	Austria (2010) The Netherlands (2009) Germany(2009) Denmark (2009) Finland (2009) France (2009) Ireland (2009) Italy (2009) Sweden (2009) United Kingdom (2009) Luxembourg (2009)	Cyprus (2010)
Montelukast (Singulair)	Merck Sharp & Dohme	Denmark (2012) Ireland (2011) Slovenia (2011) Sweden (2011) The Netherlands (2011) United Kingdom (2012) Germany (2012) Italy (2012) Luxembourg (2012) Spain (2012)	The Netherlands (2011)
Nevirapine (Viramune)	Boehringer	Denmark (2012) Portugal (2011) Sweden (2011) Belgium(2012) Germany (2012) Italy (2012) Luxembourg (2012) Spain (2012) The Netherlands (2012) United Kingdom (2012)	

Active substance (INN) (Invented name)	MAH	SPC extension granted in MS (year)	SPC extension pending in MS (year)
Rizatriptan (benzoate) (Maxalt and associated names)	Merck Sharp & Dohme	Belgium (2012) Denmark (2012) France(2012) Germany (2012) Ireland (2012) Italy (2012) Luxembourg (2012) Spain (2012) Sweden (2012) The Netherlands(2012) United Kingdom (2012) Austria (2013) Czech Republic (2015)	Portugal (2012) Czech Republic (2013)
Rosuvastatin (Crestor and associated names)	AstraZeneca AB	Denmark (2015) France (2015) Germany (2015) Italy (2015) Luxembourg (2015) Netherlands (2015) Sweden (2015)	Austria (2015) Greece (2015) Hungary (2015) Spain (2015) UK (2015)
Rupatadine (Rupafin)	J. Uriach y Compañía, S.A.	Italy (2014) Netherlands (2014) Austria (2015) Spain (2015)	Belgium (2014) Czech Republic (2014) France (2014) Ireland (2014) Slovakia (2014) UK (2014) Germany (2015) Greece (2015) Luxembourg (2015)
Sitagliptin (Januvia)	Merck Sharp and Dohme (Europe), Inc.		Czech Republic (2014) Hungary (2014)
Sugammadex (Bridion)	Merck Sharp & Dohme		Czech Republic (2014)

Active substance (INN) (Invented name)	MAH	SPC extension granted in MS (year)	SPC extension pending in MS (year)
Tiotropium bromide (Spiriva)	Boehringer Ingelheim	Austria (2013) Bulgaria (2013) Czech Republic (2013) Denmark (2013) Ireland (2013) Germany (2013) Greece (2013) France (2013) Slovakia (2013) Spain (2013) Sweden (2013) The Netherlands (2013) United Kingdom(2013) Poland (2014) Czech Republic (2015) Romania (2015)	Finland (2013) Italy (2013) Czech Republic (2014) Romania (2014)
Tolvaptan (Samsca)	Otsuka Pharmaceutical Europe Ltd.		Denmark (2013) France (2013) Germany (2013) Spain (2013) Sweden (2013) The Netherlands (2013) United Kingdom (2013) Romania (2013)
Travoprost (Travatan)	Alcon Laboratories (UK) Ltd	Italy (2015) Netherlands (2015) Slovenia (2015)	Belgium (2014) Denmark (2014) Ireland (2014) Italy (2014) Lithuania (2014) Slovenia (2014) Sweden (2014) UK (2014) Austria (2014) Germany (2015) Greece (2015) Luxembourg (2015) Spain (2015)
Tigecycline (Tygacil)	Pfizer Limited	Denmark (2015) Finland (2015) France (2015) Hungary (2015) Ireland (2015) Italy (2015) Netherlands (2015) Sweden (2015) UK (2015)	Austria (2015) Czech Republic (2015) Germany (2015) Greece (2015) Luxembourg (2015) Spain (2015)

Active substance (INN) (Invented name)	MAH	SPC extension granted in MS (year)	SPC extension pending in MS (year)
Valganciclovir (Valcyte)	Roche Registration Limited	Italy (2014) Austria (2014) Finland (2015) Greece (2015) Ireland (2015)	Belgium (2014) Czech Republic (2014) Denmark (2014) France (2014) Hungary (2014) Netherlands (2014) Poland (2014) Spain (2014) Sweden (2014) UK (2014) Germany (2015)
Valsartan (Diovan and associated names)	Novartis Pharma AG	Austria (2010) Denmark (2010) Finland (2010) France (2010) Germany (2011) Ireland (2010) Italy (2010) Luxembourg (2010) The Netherlands 2010) Portugal (2010) Sweden (2010) United Kingdom (2011)	Spain (2010)
Voriconazole (Vfend)	Pfizer Limited	Denmark (2014) Finland (2014) France (2014) Italy (2014) Netherlands (2014) UK (2014) Austria (2015) Czech Republic (2015) Germany (2015) Greece (2015) Hungary (2015) Ireland (2015) Luxembourg (2015) Romania (2015) Slovakia (2015) Spain (2015)	Belgium (2014) Latvia (2014) Sweden (2014)

Active substance (INN) (Invented name)	MAH	SPC extension granted in MS (year)	SPC extension pending in MS (year)
Zoledronic acid (Zometa and associated names)	Novartis	Austria (year not reported possibly 2011) Denmark (2010) France (2010) Finland (2011) Germany (2010) Ireland (2010) Italy (2010) Luxembourg (2010) The Netherlands (2010) Portugal (2010) Slovenia (2010) Sweden (2010) United Kingdom (2010) Romania (2012)	Cyprus (2010) Greece (2010) Hungary (2010, 2011) Spain (2010)

Source: NPO questionnaire

2. Paediatric research and development

2.1. Paediatric investigation plans

2.1.1. Addressing unmet paediatric needs

Table 14. Paediatric medicine development in PIPs correlated with survey of all paediatric needs (2007-2015)

Paediatric therapeutic area	Paediatric need	Active substance or class	Addressed by ⁴	Comments
Infectious diseases	Treatment of bacterial infections in very young children	Macrolides Betalactamines plus beta-lactamase inhibitors Carbapenems	Solithromycin (EMA-001581-PIP01-13), Fidaxomicin (EMA-000636-PIP01-09) Avibactam / ceftazidime (EMA-001313-PIP01-12), Sulbactam / ceftriaxone (EMA-001568-PIP03-14), Tazobactam / ceftolozane (EMA-001142-PIP01-11), Vaborbactam in combination with meropenem (EMA-001740-PIP01-14) Doripenem (EMA-000015-PIP01-07), Meropenem (EMA-000898-PIP01-10), Meropenem in combination with vaborbactam (EMA-001731-PIP01-14)	PIPs agreed for quinolones and other antibiotics
Cardiovascular diseases	Treatment of hypertension (primary and secondary)	Renin-angiotensin inhibitors Beta-blocker	Aliskiren (EMA-000362-PIP01-08), Alizisartan (EMA-000237-PIP01-08), Candesartan (EMA-000023-PIP01-07), Valsartan (EMA-000005-PIP01-07), Losartan (EMA-000008-PIP01-07), Enalapril (EMA-001516-PIP01-13)	
Cardiovascular diseases	Treatment of arrhythmia	Antiarrhythmics	Landiolol (EMA-001150-PIP02-13)	

⁴ Procedure for example FP6, FP7, PIP etc.

Paediatric therapeutic area	Paediatric need	Active substance or class	Addressed by⁴	Comments
Gastroenterology	Treatment of reflux disease	Proton pump inhibitors H2-receptor antagonists	Rabeprazole (EMA-000055-PIP01-07), esomeprazole (EMA-000331-PIP01-08)	
Pulmonology / respiratory medicine	Treatment of asthma	Antiasthmatics (including montelukast, salbutamol)	Montelukast (EMA-000012-PIP01-07) Tulobuterol (EMA-000763-PIP01-09)	PIPs agreed for long acting beta agonists
Psychiatry	Treatment of depressive disorder	Selective serotonin reuptake inhibitors Serotonin-norepinephrine reuptake inhibitors Tricyclic antidepressants	No PIP	PIPs agreed for Vortioxetine (EMA-000455-PIPO2-10), Agomelatine (EMA-001181-PIP01-11)
Dermatology	Treatment of atopic eczema	Glucocorticosteroids, topical use	Prednicarbate / octenidine dihydrochloride (EMA-000993-PIP01-10)	PIPs agreed for monoclonal antibodies
Endocrinology	Prevention of pregnancy	Oral contraceptives	Ulipristal (EMA-000305-PIP01-08), Levonorgestrel (EMA-000606-PIP01-09), Nomegestrol / estradiol (EMA-000250-PIP01-08), Estetrol / drospirenone (EMA-001332-PIP01-12), Drospirenone (EMA-001495-PIP01-13), Estetrol / levonorgestrel (EMA-001513-PIP01-13)	
Endocrinology	Various uses	Dexamethasone, systemic use	No PIP	
Endocrinology	Not specified	Multivitamin preparations	No PIP	

Source: Survey of all paediatric needs, EMA database (PedRA), European Commission

2.2. Paediatric research incentives

2.2.1. Projects on off-patent medicines funded by the European Commission through the EU Framework programme

1. HEALTH: Area 4.2 Off-patent medicines calls 2, 3, 4 and 5
2. HEALTH-2007-4.2-1 Adapting off-patent medicines to the specific needs of paediatric populations
3. HEALTH-2009-4.2-1 Adapting off-patent medicines to the specific needs of paediatric populations
4. HEALTH.2010.4.2-1 Off-Patent Medicines for Children. FP7-HEALTH-2010-single-stage
5. HEALTH-2011.4.2-1 Investigator-driven clinical trials on off-patent medicines for children

Further information on these projects is available on: <http://bit.ly/wUPuOb>.

Opinions and decisions on PIPs for active substances addressed in projects are available on: <http://bit.ly/xTshyn>.

Table 15. Funded off-patent medicines projects (starting by 31 December 2015) and agreed PIPs, if existing (2007-2015)

Acronym	Year	Objectives (active substance in bold)	PIP
NeoVanc	2014	To develop a new age-appropriate formulation of vancomycin for neonates; define the circulating concentration of vancomycin that is needed to kill CoNS in in vitro biofilm and animal model, and use that data to derive the concentration and best PD target that will be maximally effective in neonates; define the neonatal dosage that is needed to attain the concentration that can kill CoNS and enterococci by conducting a systematic meta-analysis of all available PK data and develop an optimal dosing and therapeutic drug monitoring regimen. NeoVanc will then conduct a Phase 2 b randomised clinical trial to compare the proportion of neonates reaching the PD target derived from the pre-clinical studies when treated with the current standard vs new "optimised" treatment regimens and to obtain data on dosing, efficacy and short and long-term safety leading to a PUMA	EMA-001311-PIP01-12-M01
LENA	2013	To provide a basis for a future PUMA of enalapril by developing an age-appropriate solid oral formulation suitable for all paediatric subsets; generating PK and PD data; collecting data on the safety of enalapril in young paediatric patients; and providing dose recommendations based on PK/PD modelling and bridging from adult data.	EMA-001241-PIP02-13-M01
METFIZZ	2013	METFIZZ will conduct the required product development and clinical studies to establish efficacy and safety of administering age-appropriate innovative effervescent soluble formulations of metformin for treatment of polycystic ovary disease.	EMA-001352-PIP01-12-M01
GAPP	2013	The GAPP Project is focused on the development of gabapentin for the treatment of paediatric chronic pain	EMA-001310-PIP01-12-M01

Acronym	Year	Objectives (active substance in bold)	PIP
CloSed	2013	The objectives of this project are a) to develop an age appropriate formulation of clonidine suitable for sedation of children in PICU b) to conduct a randomised, phase III, double-blind, active-controlled parallel group clinical trial of clonidine vs midazolam in patients from birth to 18 years to establish the efficacy and safety, including long-term outcomes and dose-dependent effects of clonidine and c) to establish an European consensus guideline for sedation of critically ill children. The ultimate goal is to use these data and to apply for a PUMA. On this basis a Paediatric Investigation Plan (PIP) has been approved by the EMA in February 2013 and is reflected in the work plan of CloSed.	EMA-001316-PIP01-12-M01
DEVELOPA KURE	2012	To fund the clinical development of nitisinone for the treatment of Alkaptonuria	PIP agreed for the treatment of tyrosinemia type 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
NEO-CIRC	2011	To provide safety and efficacy data for dobutamine , to perform pre-clinical studies, to develop biomarker of hypotension and to adapt a formulation for newborns	NA
TAIN	2011	To develop a neonatal formulation of hydrocortisone for the treatment of congenital and acquired adrenal insufficiency and for use in oncology (brain tumours and leukaemia)	NA
DEEP	2010	To evaluate PK & PD of deferiprone in 2-10 years old children in order to produce an approved Paediatric Investigational Plan to be used for regulatory purposes	EMA-001126-PIP01-10
HIP Trial	2010	Evaluates the efficacy safety, PK, PD of adrenaline and dopamine in the management of neonatal hypotension in premature babies and to develop and adapt a formulation of both suitable for newborns in order to apply for a Paediatric Use Marketing Authorisation (PUMA)	EMA-001105-PIP01-10
TINN2	2010	To evaluate PK & PD of azithromycin against urea plasma and in BPD in neonates.	NA
NEMO	2009	Evaluates the efficacy safety, PK, PD, mechanisms of action of bumetanide in neonatal seizures, including the effect on neurodevelopment and to develop and adapt a bumetanide formulation suitable for newborns in order to apply for a Paediatric Use Marketing Authorisation (PUMA).	NA
NeoMero	2009	European multicentre network to evaluate pharmacokinetics, safety and efficacy of meropenem in neonatal sepsis and meningitis	EMA-000898-PIP01-10

Acronym	Year	Objectives (active substance in bold)	PIP
PERS	2009	Focuses on two indications, the use of risperidone in children and adolescents with conduct disorder who are not mentally retarded, and the use of risperidone in adolescents with schizophrenia	EMA-001034-PIP01-10
EPOC	2008	To evaluate pharmacokinetics and pharmacodynamics of doxorubicin	NA
LOULLA & PHILLA	2008	Development of oral liquid formulations of methotrexate and 6-mercaptopurine for paediatric acute lymphoblastic leukaemia (ALL).	NA
NeoOpioid	2008	Compares morphine and fentanyl in pain relief in pre-term infants	EMA-000712-PIP01-09
NEuroSIS	2008	Efficacy of budesonide (BS) in reducing bronchopulmonary dysplasia (BPD)	EMA-001120-PIP01-10
O3K	2008	Oral liquid formulations of cyclophosphamide and temozolomide	EMA-000530-PIP02-11 / NA
TINN	2008	Aims to evaluate PK & PD of ciprofloxacin and fluconazole in neonates	NA

Source: European Commission, note: NA = Not available

2.2.2. National funding

Austria

1. Since 2012, clinical trial applications concerning paediatric trials are flagged automatically in the national database of the NCA. Applications are immediately screened by an assessor, and a prioritised scientific review is performed, if necessary.
2. OKids <http://www.okids-net.at/> is a consortium to implement a platform for paediatric research for both academia and industry.

Belgium

1. Between 2007 and 2009, the Belgian agency launched the Belgian Paediatric Research Network in collaboration with the Belgian Paediatric Association. In 2010, The Belgian Paediatric Society granted funding to establish the list of paediatric clinical research centres and researchers existing in Belgium, as a basis for the Belgian paediatric research network.

Finland

1. Although not specific to paediatrics, funding can be applied from e.g. Tekes – the Finnish Funding Agency for Technology and Innovation (tekes.fi) or SITRA, the Finnish Innovation Fund (sitra.fi).

France

1. As reported in 2011, paediatrics was a priority axis in the national PHRC programme (Programme Hospitalier de Recherche Clinique or hospital clinical research plan), funding for trials in public hospitals.

2. Then, a new legislative framework with the aim to reduce and regulate drug off-label use was implemented in France (law number 2011-2012, December 29, 2011) together with a related decree for "Temporary Recommendations for Use" (RTUs; Decree number 2012-743, May 9, 2012). The legislation has provided "a regulatory process for temporarily supervising the prescribing of drugs for indications for which they are not licensed". This legislation applies for any medicinal product and may have an impact on use of medicines in children for which the off label use is frequent. At this time, no RTU has yet been granted and it is too early to assess any impact of this new legislation in paediatrics.

Germany

1. A survey on off-label use "Off-Label-Use von Arzneimitteln bei Kindern und Jugendlichen in Deutschland – Ergebnisse von KiGGS (Kinder-und Jugendgesundheitssurvey)" (Off-label use of medicinal products in children and adolescents in Germany - Results from the KiGGS (Children and Adolescents Health Survey) has been conducted, Budget Euros 28,520.00.
2. Results of the KiGGS study (2003-2012), a first health survey of the German paediatric population can be found: <http://www.kiggs-studie.de/english/home.html>.

Hungary

1. There are some measures of general scope which may promote the research and development of paediatric medicines.
2. In July 2009, an Action Plan for the Pharmaceutical Industry and Biotechnology was adopted which provides for the deduction of R&D costs from certain payment obligations on pharmaceutical companies. Initially the deduction rate was 20% of the R&D investment, but from 2011 the total amount invested had to be taken into account. Although so far this incentive has not been explicitly used for paediatric medicines R&D, it is hoped that pharmaceutical companies will extend their innovation activities in this direction as well.
3. In 2011, it was reported that medicinal products included in the National Immunisation Programme were provided free of charge by the Hungarian government.

Italy

1. Independent research is funded by AIFA. The promotion of independent research on drugs represents one of the strategic tasks assigned to AIFA by Italian Legislation. The general aim of the program is to support clinical research on drugs in areas of interest for the National Health Service (NHS) and where commercial support is normally insufficient. The target populations are patients normally excluded by clinical studies on efficacy and safety, such as children, pregnant women and the elderly. The focusing research issues are those less explored in commercial research, such as clinically relevant end points, relative efficacy of drugs (including the assessment of multimodal strategies) and long term follow up on efficacy and safety of therapies.
2. AIFA set up the program on independent research in 2005, and five calls for proposals (2005-2006-2006-2007-2008-2009) have already been launched. The call for proposals is aimed at investigators working in public (e.g. national health service [SSN], universities, etc.) or non-profit organisations (e.g. scientific foundations, patient associations, etc.). The way of funding this independent research derives from an ad hoc fund set up, requiring pharmaceutical companies to contribute 5% of their yearly expenditure devoted to promotional initiatives.

3. Framework agreements in 2008-2009: The Italian Medicines Agency, through the Framework Agreements on Research & Development, promotes at national level investment in production, research and development in the pharmaceutical sector, according to the ten-year European Union Programme of renewal and encouragement of the economic and social environment, as defined by the Lisbon European Council. Framework Agreements are intended for pharmaceutical companies operating in the Italian territory, which are selected for admission to the funding through a specific call for proposals that AIFA launched in 2008. Investment, amounting to a total of €100 million, is destined to:
 - The promotion of phase I and II clinical trials in Italy.
 - The establishment or expansion of production sites (including feasibility studies, land, buildings, machinery).
 - The opening or improvement of research laboratories.
 - The hiring of new permanent staff involved in production.
 - The hiring of new permanent staff assigned to R&D activities.
4. In 2008, 52 companies submitted proposals for 114 projects. An appointed Commission assessed the most interesting projects to be funded: 29 projects are focusing on pre-clinical research; 15 on clinical trials and 15 on production sites. Projects involving paediatrics are listed in the document "Framework Agreements by AIFA in 2008 (Projects in Paediatric Field)" (Additional information provided by Member States).
5. Reimbursement of paediatric medicines: Several medicines, not licensed in Italy for specific paediatric indications, have been included in a list according to Italian Law 648. Law 648 allows physicians to prescribe a medicine where no therapeutic alternatives are available, including for paediatric patients, in specific therapeutic indications, and after having received a positive opinion from the Italian Medicine Agency's Commissione Tecnico Scientifica. The medicine will be reimbursed by the National Health System (Servizio Sanitario Nazionale). Law 648 may apply to off-label indications for products marketed in Italy, or for products not (yet) marketed in Italy. Importantly, the inclusion in the Law 648 list does not modify the SmPC and therefore the paediatric indications remain unauthorised and not extendable to other Member States.

The Netherlands

1. There is a grant for development via ZonMw, the Netherlands organisation for health research and development. The Ministry of Health has given ZonMw the assignment to start a programme on the promotion of pharmaceuticals for children. The programme started in 2009 and lasts till 2017 with a budget of 14.3 million Euros.
2. The Medicines for Children Research Network (MCRN) is a network of Dutch paediatricians of university paediatric hospitals. The MCRN receives its money from a starting grant (2008-2011) of the Netherlands Federation of University Medical Centres (NFU), Nefarma and the Ministry of Health. The MCRN needs to generate its own income from 2012 onwards and be financially independent.

Lithuania

1. There are possibilities to get financial support available through available financial programmes coordinated by the Ministry of Economy. So far, domestic companies involved in research and development of medicinal product did not submit any applications to take part in tendering processes.

Malta

1. Research on medicinal products, including those for paediatric use, can be funded under the National Research and Innovation Programme set up by the Malta Council for Science and Technology. However there is no specific incentive in place for developing paediatric medicines.

Poland

1. In 2013, it was reported that priority review of paediatric data was decided on a case-by-case basis.

Spain

1. Special measures for pricing of paediatric medicines: Since the entry into force of Royal Decree 16/2012, pharmaceutical forms specifically intended for the treatment of the paediatric population are excluded from the system of prices of reference.
2. Paediatric and perinatal medicines are considered priorities by "Instituto de Salud Carlos III" in a decision on 11th June 2013 to fund strategic health actions as part of a state programme for investigation of social objectives.

Slovenia

1. In 2012, fee waivers for clinical trials with the paediatric population were reported:
 - EudraCT: 2010-019722-13; sponsor: University of Debrecen, Hungary; INN: daunorubicin, doxorubicin
 - EudraCT: 2012-004270-26; sponsor: Oshadi Drug Administration, Israel; INN: oral insulin

United Kingdom

1. The UK Government provides support for the NIHR Medicines for Children Research Network (MCRN) which provides infrastructure across all of England to encourage and support the development and delivery of paediatric studies although not direct funding. The work of this Network is described in a separate document (Additional information provided by Member States).
2. From its establishment in 2006 to the end of 2014, the MCRN/CRN Children has supported a total of 336 industry studies, 56 of which were taken on in 2014. 222 public (academic/health service) studies have been taken on by the network since 2006, 13 in 2014, with grants awarded under a number of European, UK and other research programmes. Further information is available on: (<http://www.crn.nihr.ac.uk/children/>).

3. Of the 27 publicly-sponsored studies taken on in 2013, funding was provided by:
 - UK government (NIHR, MRC etc; 13 studies, 48%)
 - Charities (6 studies, 22%; for 2 studies this funding was in partnership with companies or a Royal College)
 - European Commission FP7 (3, 11%)
 - Companies (2, 7%; not including study jointly funded with a charity)
 - Professional societies (2 study, 7%)
 - US government (NIH; 1 study, 4%)
 - Of the 13 publicly-sponsored studies taken on in 2014, funding was provided by:
 - UK government (NIHR, Public Health England etc.; 5 studies)
 - Charities (5 studies, 1 of which has been included in above set as well, for 2 studies this is also in collaboration with companies)
 - European Commission (2 studies)
 - National Institute of Health, United States (1 study)
 - Companies (1 study).
4. Grants for particular products intended for use in children may have been awarded under a number of other general research programmes, but this information is not readily available.
5. In addition to the research network, the UK NHS provides experts who advise the UK Licensing Authority on the quality, safety and efficacy of paediatric medicines in the context of the Paediatric Regulation, through the Paediatric Medicines Expert Advisory Group of the Commission on Human Medicines. This work is not directly remunerated and is therefore supported by the UK Government.
6. Since 2014, financial incentives to encourage use of authorised paediatric medicines including PUMA: The Pharmaceutical Price Regulation Scheme (PPRS) is the mechanism that the UK Department of Health uses to control the prices of branded prescription medicines supplied to the National Health Service (NHS) by regulating the profits that companies can make on their NHS sales. It provides support for research and development (R&D) through an allowance for R&D in its assessment of a company's profitability of its business with the NHS.

2.3. Paediatric clinical trials

2.3.1. Selection of fields and trials

Information on clinical trials was retrieved from the EudraCT database. Based on EudraCT, the EU Clinical Trials Register currently presents as start date the date on which a trial was authorised to proceed in the EU, or the date of upload into EudraCT for trials outside the EU. However, in preparatory analyses it was found that the date of upload into EudraCT does not correspond well with the planned date of initiation of the trial, in particular for third-country trials.

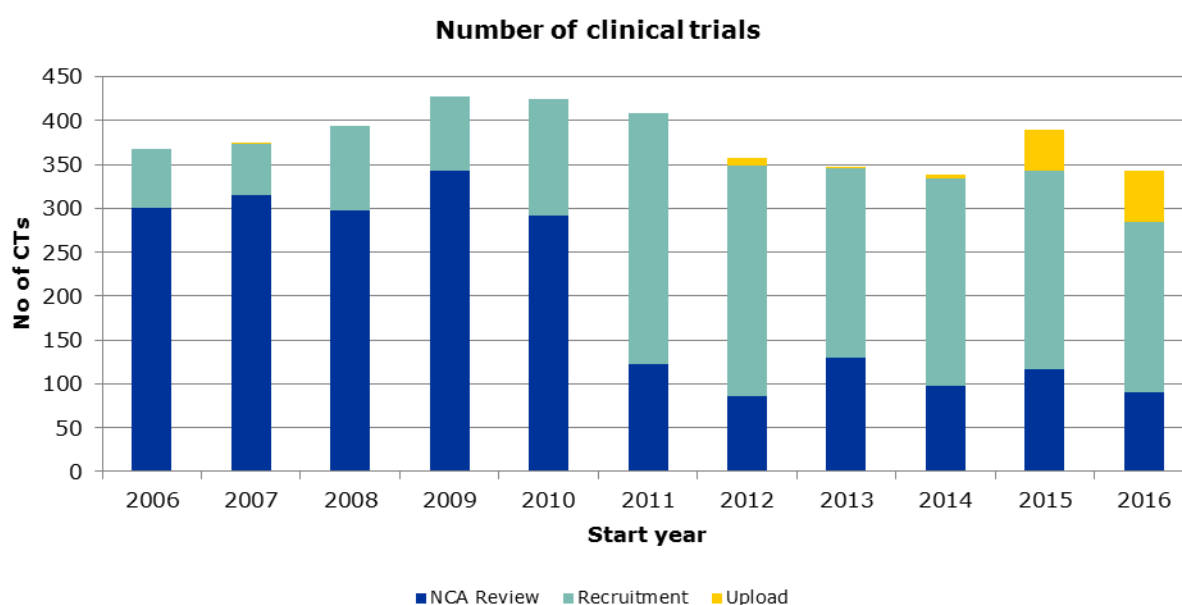
Therefore, in deviation from the EU Clinical Trials Register, information from the following fields was used for the start of the trial: in order of preference, planned date of initiation of the trial, alternatively date of authorisation, alternatively date of upload.

Paediatric trials were defined as those trials in EudraCT that are documented to be open for recruitment of any age group of the paediatric population (from birth to less than 18 years of age). This includes trials that are open for both adult and paediatric populations.

No restrictions were made as to the phases of development or other criteria in EudraCT. In particular, paediatric trials stated to pertain to a phase 4 clinical development were not removed, because some of these were stated to be included in agreed PIPs and because this phase may have been interpreted to reflect the use of the medicinal product which is authorised in adults, irrespective of any authorisation for children.

Accordingly, the number of paediatric trials newly started in a given year is shown in Figure 1.

Figure 1. Number of paediatric trials by start year, indicating the source of the information for the date of start.



Source: EudraCT database.

2.3.2. Number of paediatric clinical trials

Table 16. Paediatric clinical trials by year of authorisation (or, if not available, by year of protocol upload into EudraCT)

Trials	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Paediatric ¹ trials	340	362	339	407	391	372	400	346	436	717	503
Total number of trials	4273	4856	4635	4570	4139	3977	3870	3577	3584	3929	3515
Proportion of paediatric trials of all trials (%)	8.0	7.5	7.3	8.9	9.5	9.4	10.3	9.7	12.2	18.3	14.3
Exclusively ² paediatric trials	196	188	182	241	230	218	255	211	280	450	287

Note: ¹ A paediatric trial is a trial that includes at least one participant below 18 years of age. ² An exclusively paediatric trial is a trial that includes only participants below 18 years of age.

Source: EudraCT database.

2.3.3. Clinical trials by phase and design

Table 17. Overview of authorised clinical trials with the paediatric population by start date¹.

Type	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Paediatric ² trials	368	375	394	428	425	408	357	346	338	390	343
Paediatric trials planned as											
Phase 1	28	30	29	32	53	40	39	51	40	48	49
Phase 2-3	241	269	262	298	282	305	268	251	257	276	246
Phase 4	98	85	105	98	94	74	67	65	55	81	64
Controlled (various types of control)	263	255	270	280	263	248	210	202	204	210	194
Active controlled	45	60	61	69	75	66	45	63	63	53	54
Placebo controlled / placebo use	98	106	120	114	103	109	100	95	82	96	89
Paediatric trials planned to be conducted											
In EEA only	300	314	299	338	325	301	284	296	285	313	268
In and outside of EEA	4	11	14	28	26	40	21	19	11	15	6
only outside of EEA	64	50	81	62	74	67	52	31	42	62	69
Reference: All trials (adults, elderly and / or children)	3938	4543	4371	4327	3903	3861	3539	3335	3324	3363	2763

Note: ¹ Start date according to planned start of recruitment (if not available then according to NCA review date; if not available then according to upload date).

² A paediatric trial is a trial that includes at least one participant below 18 years of age. ³ An exclusively paediatric trial is a trial that includes only participants below 18 years of age.

Source: EudraCT database

2.3.4. Number of children in clinical trials

Table 18. Number of children planned to be enrolled in clinical trials, by year of protocol upload into EudraCT database

CTA Load Year	Preterm newborns	Newborns	Infants and toddlers	Children	Adolescents	Total
2006	0	0	540	2,669	439	3,648
2007	0	98	134	637	36,528	37,397
2008	210	125	54,714	719	1,162	56,930
2009	207	64	56	4,463	5,329	10,119

CTA Load Year	Preterm newborns	Newborns	Infants and toddlers	Children	Adolescents	Total
2010	126	252	2,381	4,376	5,925	13,060
2011	2,285	1,295	13,780	30,381	21,672	69,413
2012	1,694	2,286	61,907	24,054	22,112	112,053
2013	4,187	1,507	14,917	25,056	18,258	63,925
2014	3,351	2,147	39,733	61,900	40,459	147,590
2015	2,539	1,696	122,026	53,640	39,998	219,899
2016	3,365	10,484	32,381	37,717	23,708	107,655

Note: The date these trials were uploaded to the EudraCT database may not represent accurately the date of trial initiation, therefore the actual trial may be initiated at a different year than the one recorded by the upload date.

Source: EudraCT database.

Basic filters used for EudraCT analyses

All trials (adults and/or children):

	First Past the Post(FPP) Flag is equal to / is in Yes
and	N. Latest/Older Review is equal to / is in Yes
	or N. Latest/Older Review is null
and	N. NCA Decision is equal to / is in Authorised
	or CASE WHEN A.1 NCA = 'EMA' THEN '3rd' ELSE 'EU' END is equal to / is in 3rd

Paediatric trials:

	First Past the Post(FPP) Flag is equal to / is in Yes
and	F.1.1.2 Preterm Newborn Infants is equal to / is in Yes
	or F.1.1.3 Newborns (0-27 days) is equal to / is in Yes
	or F.1.1.4 Infants and Toddlers (28 days - 23 months) is equal to / is in Yes
	or F.1.1.5 Children (2-11 years) is equal to / is in Yes
	or F.1.1.6 Adolescents (12-17 years) is equal to / is in Yes
	or F.1.1 Age Range <18 yrs is equal to / is in Yes
and	N. Latest/Older Review is equal to / is in Yes
	or N. Latest/Older Review is null

Exclusively paediatric trials (no adults included):

	First Past the Post(FPP) Flag is equal to / is in Yes
and	F.1.1.2 Preterm Newborn Infants is equal to / is in Yes
	or F.1.1.3 Newborns (0-27 days) is equal to / is in Yes
	or F.1.1.4 Infants and Toddlers (28 days - 23 months) is equal to / is in Yes

	First Past the Post(FPP) Flag is equal to / is in Yes
	or F.1.1.5 Children (2-11 years) is equal to / is in Yes
	or F.1.1.6 Adolescents (12-17 years) is equal to / is in Yes
	or F.1.1 Age Range <18 yrs is equal to / is in Yes
and	N. Latest/Older Review is equal to / is in Yes
	or N. Latest/Older Review is null
and	F.1.2 Adults (18-64 years) is not equal to / is not in Yes
and	F.1.3 Elderly (>= 65 years) is not equal to / is not in Yes

Add-on filters used for EudraCT analyses

Trials included in an agreed PIP:

	A.7 Trial Part of a PIP is equal to / is in Yes
or	A.8 PIP Decision Number is not null

Phase 1 trials:

E.7.1 Human Pharmacology (phase I) is equal to / is in Yes
--

Phase 2-3 trials:

E.7.2 Therapeutic Exploratory (Phase II) is equal to / is in Yes
or E.7.3 Therapeutic Confirmatory (Phase III) is equal to / is in Yes

Phase 4 trials:

E.7.4 Therapeutic Use (phase IV) is equal to / is in Yes
--

Controlled trials:

E.8.1 Controlled is equal to / is in Yes
--

Trials with active control:

E.8.2.3 Comparator is Other is equal to / is in Yes

Trials with placebo control:

E.8.2.2 Comparator is Placebo is equal to / is in Yes

Trials with sites inside EU only:

	A.2 EudraCT Number is equal to any A.2 EudraCT Number in Child - All EU CTs (A.1 NCA is not equal to / is not in EMA (i.e. third country))
and	A.2 EudraCT Number is not equal to any A.2 EudraCT Number in Child - All Non EU CTs (A.1 NCA is equal to / is in EMA (i.e. third country))

Trials with sites inside and outside EU:

	A.2 EudraCT Number is equal to any A.2 EudraCT Number in Child - All EU CTs (A.1 NCA is not equal to / is not in EMA (i.e. third country))
and	A.2 EudraCT Number is equal to any A.2 EudraCT Number in Child - All Non EU CTs (A.1 NCA is equal to / is in EMA (i.e. third country))

Trials with site outside EU only:

	A.2 EudraCT Number is not equal to any A.2 EudraCT Number in Child - All EU CTs (A.1 NCA is not equal to / is not in EMA (i.e. third country))
and	A.2 EudraCT Number is equal to any A.2 EudraCT Number in Child - All Non EU CTs (A.1 NCA is equal to / is in EMA (i.e. third country))

Consideration for all EudraCT analyses per authorisation date

Year Column if 'N.NCA Decision Date' is null than 'A.CTA Created Year' else Year('N.NCA Decision Date').

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

2.4.1. Enpr-EMA milestones

Table 19. Main Enpr-EMA milestones (2007-2015)

Year	Milestones
2007	<ul style="list-style-type: none"> • Consultation of Paediatric Committee on network strategy • Public consultation on network strategy
2008	<ul style="list-style-type: none"> • Adoption of <u>Enpr-EMA Implementing Strategy</u> by EMA Management Board • Call for European Paediatric Research Networks to identify additional networks
2009	<ul style="list-style-type: none"> • First networks workshop • Proposed organisational structure of Enpr-EMA • Finalisation of proposal for recognition criteria
2010	<ul style="list-style-type: none"> • Second networks workshop • Agreement on and publication of recognition criteria • Agreement of organisational structure and composition of Enpr-EMA Coordination Group (CG)

2011	<ul style="list-style-type: none"> • Official launch of Enpr-EMA at first annual workshop open to all stakeholders, i.e. networks, industry and patients organisations • Publication of list of networks becoming member of Enpr-EMA • Workshop on emerging networks in the therapeutic areas of cardiology, endocrinology and gastroenterology to fill the identified gap of networks
2012	<ul style="list-style-type: none"> • Nomination of a representative of the EMA Patient and Consumer Working Party (PCWP) as observer member of the Enpr-EMA CG. Survey among all networks, to analyse how paediatric networks in Europe support the engagement of young people in research: results showed that only a minority (3 networks) had dedicated resources and strategies to achieve this objective. A need for training on how to establish and maintain young person's advisory groups was identified • Establishment of collaboration with micro, small and medium-sized enterprises and Enpr-EMA network members through the Agency's SME office • Publication of first annual Enpr-EMA newsletter
2013	<ul style="list-style-type: none"> • Publication of an online searchable Enpr-EMA Network Database providing easy access to data about each individual registered network and their expertise in paediatric research. • Establishment of Enpr-EMA Working Groups (WGs), including network and industry representatives, tasked with addressing the most important needs identified during the fifth annual open workshop, such as <ul style="list-style-type: none"> • Joint WG on public-private partnership • WG on ethics • WG on neonatology • Joint Enpr-EMA/ENCePP WG on paediatric pharmacovigilance • Corporate Enpr-EMA response during public consultation on the EU guideline on the format and content of PIP and waiver applications. It was proposed to add a recommendation to consult Enpr-EMA members, i.e. networks, in the development of a PIP. (This recommendation is now included in the guideline.) • Corporate Enpr-EMA response during public consultation on the revised Clinical Trial Regulation • Nomination of a representative of the EMA Health Care Professional Working Party (HCPWP) as observer member of the Enpr-EMA CG. • Establishment of task force and core groups of 3 emerging paediatric networks (cardiology: Task Force of the AEPC (Association for European Paediatric Cardiology); gastroenterology: PEDDCReN (Paediatric European Digestive Diseases Clinical Research Network); endocrinology/diabetes: EUCADET (European Children and Adolescent Diabetes and Endocrine Trial)). • Provision of practical tips and training on strategies and guidance to involve young people and families in the activities of the Enpr-EMA networks.

2014	<ul style="list-style-type: none"> Existing European young persons' advisory groups linked up with established North American ones into a Communicating International Network for worldwide involvement of young people in research (iCAN). A framework was established to allow industry representatives from EFPIA and EUCOPE as observers within the Enpr-EMA CG for ad-hoc topics in order to improve communication and collaboration with industry. A plenary discussion on future approaches to funding of paediatric clinical trials was held during the November PDCO meeting, with representatives from the European Commission and EFPIA/IMI as well as the Enpr-EMA chair/co-chair and representatives from Enpr-EMA networks.
2015	<ul style="list-style-type: none"> Participation of several neonatal Enpr-EMA networks in the "International Neonatal Consortium" (official launch May 2015) Participation of young people advisory groups (YPAGs) from several Enpr-EMA network members at the first international summit of the International Children's' Advisory Network (iCAN) Representatives from the YPAG of the Scottish clinical research network presented to the PDCO plenary as well as to EMA staff at the 20th EMA anniversary lunch event their work and proposals how YPAGs could be involved in the activities of the Agency and its committees. Publication of a table listing requirements to obtain Informed Consent for paediatric clinical trials in the various EU member states Publication of an article summarising the results of a survey among industry and networks: "Pharmaceutical industry and paediatric clinical trial networks in Europe – How do they communicate?" (Lepola et al. 2016)

Source: Enpr-EMA records

2.4.2. Enpr-EMA networks

Table 20. presents all Enpr-EMA networks and their therapeutic areas. Networks have been classified according to 4 categories:

- Category 1 networks fulfilling all minimum criteria for membership;
- Category 2 networks potentially fulfilling all minimum criteria but in need of clarifying issues before becoming a member;
- Category 3 networks currently not yet fulfilling minimum criteria;
- Category 4 networks that do not run paediatric clinical trials but have expertise in clinical trial methodology, or support infrastructure, etc.

Table 20. Enpr-EMA registered networks and their therapeutic areas

Type / therapeutic area of the network	Category 1	Category 2	Category 3	Category 4
Allergology / Immunology/ Rheumatology	PRINTO	--	JSWG of PRES	--
Cardiovascular diseases / Nephrology	--	--	--	--
Diabetes / Endocrinology / metabolic disorders / Gynaecology	--	--	AMIKI	--
European Paediatric Pharmacists	--	--	--	--
Expertise in Clinical Trial Methodology	--	--	--	TEDDY* PRIOMEDCHIL D* ECRIN* GRIP*
Gastroenterology / Hepatology	--	--	ESPGHAN PEDDCReN EPLTN	--
Infectious diseases / Vaccinology	PENTA-ID UKPVG	--	--	--
Intensive Care / Pain / Anaesthesiology / Surgery	--	Network of Excellence for research in paediatric clinical care- NL	ESPNIC Research Network	--
National and multispecialty	NIHR-MCRN FinPedMed MCRN-NL MICYRN ScotCRN CICPed RIPPS OKIDS	RED SAMID	IPCRN NCCHD BLF Futurenest CR BPDN SwissPedNet Hospital Sant Joan De Deu	--
Neonatology	GNN	--	EuroNeoNet Neo- circulation INN INFANT	--
Oncology (solid / haematologic malignancies)	Newcastle-CLLG ITCC IBFMSG	CLG of EORTC	--	--
Pharmacology	--	--	ESDPPP	--
Psychiatry / Neurology	EUNETHYDIS	--	ECAPN	--
Respiratory diseases / Cystic Fibrosis	ECFS-CTN	--	--	--

Type / therapeutic area of the network	Category 1	Category 2	Category 3	Category 4
Special Activities (pharmacovigilance, long-term follow up, community paediatricians)	FIMP-MCRN	--	--	--
Stem Cell and Organ Transplantation / Haematology (non-malignant) / Haemostaseology	EBMT	--	IPTA	--

Note: * Did not provide self-assessment (recognition criteria not applicable to these networks)

Source: Enpr_EMA database.

Enpr-EMA survey on involvement in paediatric clinical research (2015)

Table 21. Enpr-EMA survey results 2015

Network	No. of PIP trials with involvement	Advice given by network regarding PIP			Active participation in conduct of PIP trial through enrolment of patients	Involvement of children, parents in PIP trial design, development of informed consent forms
		Design ⁵	Implementation ⁶	Trial protocol design ⁷		
SwissPedNet (Swiss Research Network of Clinical Paediatric Hubs)	12 trials	No	Yes, in all 12 trials	No	No	No
EAP (European Academy of Paediatrics)	0	No	No	No	No	No
PRINTO (Paediatric Rheumatology International Trials Organisation)	12 industry sponsored trials	Provided scientific expertise for PIP development for all 12 trials	Feasibility assessment	Provided scientific expertise for trial protocol development for all 12 trials	Yes, in all 12 trials	No
Juvenile scleroderma network	Not reported	No	Yes (through Enpr-EMA)	No	No	No

⁵ e.g. definition of therapeutic needs, standard of care

⁶ e.g. feasibility of requested trials

⁷ e.g. acceptability of clinical endpoints

Advice given by network regarding PIP						
Network	No. of PIP trials with involvement	Design ⁵	Implementation ⁶	Trial protocol design ⁷	Active participation in conduct of PIP trial through enrolment of patients	Involvement of children, parents in PIP trial design, development of informed consent forms
TEDDY (Task-force in Europe for Drug Development for the Young)	8 FP7 trials	Yes, for 7 FP7 trials	Yes, for 8 FP7 trials	Yes, for 5 FP7 trials	Yes, for 4 FP7 trials	Yes in 2 FP7 trials
FP-MCRN (Family Pediatricians Medicines for Children Research Network)	0	No; but involved in 2 projects by Italian Competent Authority: 1. Active surveillance on the use of antibiotics in children, especially in the age group between 0 and 2 years 2. Respiratory Drug Survey	No	No	No	No

Advice given by network regarding PIP						
Network	No. of PIP trials with involvement	Design ⁵	Implementation ⁶	Trial protocol design ⁷	Active participation in conduct of PIP trial through enrolment of patients	Involvement of children, parents in PIP trial design, development of informed consent forms
NIHR CRN-Children (National Institute for Health Research - Medicines for Children Clinical Research Network)	335 industry sponsored paediatric studies	Yes; 14 clinical study groups support companies in the preparation of PIPs; advise them on drug development strategies	Yes; drug development strategies; identification of participating sites; supporting the delivery of studies to time and target	Yes, advice on development of study protocols, pharmacy and formulation	Yes; performance management; study set up.	Yes; involvement of children, young people and families. Each of the Clinical Study Groups has appointed a number of parent members to their groups to ensure that the views and perspectives of families are incorporated into CSG activity and the design of new research proposals. These parent members receive training to support their involvement.
NEO-CIRC (Neocirculation)	1 FP7 study	Not reported	Not reported	Not reported	Not reported	Yes; EFCNI (European Foundation for the care of newborn infants) representative on advisory board
ECFS-CTN (European Cystic Fibrosis Society - Clinical Trials Network)	18 PIP trials (all industry sponsored)	No	Yes; for 8 different trials	Yes, protocol review conducted for all 18 trials	Yes; in all 18 trials	Yes; 1 or 2 patient/family reviewers actively involved in protocol review of 10 different trials

		Advice given by network regarding PIP				
Network	No. of PIP trials with involvement	Design ⁵	Implementation ⁶	Trial protocol design ⁷	Active participation in conduct of PIP trial through enrolment of patients	Involvement of children, parents in PIP trial design, development of informed consent forms
FINPEDMED (Finnish Investigators Network for Pediatric Medicines)	21 industry sponsored trials	No	No	No	Yes; in 14 trials	Yes; for 1 trial use of FINPEDMED Picture Cards for Informed Consent
MCRN-NL (Dutch Medicines for Children Research Network)	21 trials (16 industry sponsored, 3 FP7, 2 not specified)	No	Yes; feasibility assessment for 14 trials; selection of experts for PIP advisory board for 4 trials	No	Yes, in 2 FP7 trials	Yes, in 2 FP7 trials
PENTA-ID (Paediatric European Network for Treatment of AIDS)	6 trials (5 FP7, 1 industry sponsored)	Yes; for 3 trials	Yes; study management for 2 trials	Yes; for 3 trials	Yes; for all 6 trials	Yes; for all 6 trials
RIPPS (Réseau d'Investigation Pédiatrique des Produits de Santé)	40 trials (26 industry sponsored, 14 academic sponsored)	Yes; for 1 industry sponsored trial	Yes; feasibility assessment for 3 industry sponsored trials	Yes; for 1 industry sponsored trial	Yes; for all 26 industry sponsored trials	Yes; in 2 trials (protocol design, methodology)

Source: Enpr-EMA survey on involvement in paediatric clinical research (2015)

2.5. External experts, workshops and scientific guidelines

2.5.1. Expert meetings and workshops

Table 22. Main expert meetings and workshops organised by the EMA in 2006-2015

Topic	Year
Expert meeting on fixed dose combinations for the treatment of HIV in children	2015
European network of paediatric research - EMA meeting on rare gastrointestinal and liver diseases	2015
EMA workshop on extrapolation across age groups	2015
Applying regulatory science to neonates: launch of the International Neonatal Consortium (INC)	2015
EMA - industry stakeholders platform meeting on paediatric medicines	2015
Collaboration on neonatal issues between researchers and the European Medicines Agency	2015
Expert meeting on the clinical investigation of medicines for the treatment of paediatric hepatitis C	2014
Paediatric osteoporosis expert meeting	2014
Workshop on pharmacovigilance in the paediatric population	2014
Workshop on paediatric investigation plans in type-2 diabetes mellitus	2013
Expert meeting on paediatric anticoagulation therapy	2012
Joint European Medicines Agency / Food and Drug Administration workshop for paediatric Gaucher disease type I: exploring the way forward	2012
Workshop on endpoints for cystic fibrosis clinical trials	2012
Workshop on paediatric formulations for assessors in national regulatory agencies	2011
Ethical considerations for paediatric trials - how can ethics committees in the European Member States and the Paediatric Committee at the European Medicines Agency work together?	2011
Workshop on clinical development and scientific advice in ophthalmology	2011
Expert meeting on clinical investigation of new drugs for the treatment of chronic hepatitis C in the paediatric population	2011
Paediatric Gaucher disease – exploring the way forward	2011
High-grade glioma expert group meeting	2010
Expert group meeting on paediatric heart failure	2010
Paediatric rheumatology expert group meeting	2010
Expert meeting on paediatric gastroenterology and rheumatology	2010
Expert meeting on neonatal and paediatric sepsis	2010
Expert meeting on specific immunotherapy	2010
Second EMA workshop on European network of paediatric research	2010
Workshop on paediatric formulations for assessors in national regulatory agencies	2010
Expert meeting on paediatric asthma	2010
Applications of quantitative pharmacology to paediatric decisions	2010
Paediatric rheumatology expert group meeting	2009
Paediatric epilepsy expert group meeting	2009
Meeting of the paediatric diabetes mellitus expert group	2009
Meeting of the paediatric human immunodeficiency virus (HIV) expert group	2009
Paediatric Development and Juvenile Animal Studies - assessors meeting	2009

Topic	Year
EMA workshop on neonatal immunisation	2009
First EMA workshop on European network of paediatric research	2009
Ad-hoc expert meeting on influenza serology data	2009
Severe sepsis in paediatric intensive care, clinical study designs	2009
European Medicines Agency workshop on modelling in paediatric medicines	2008
Third National and European Commission SPC expert meeting: paediatric extensions	2008
Second workshop on regulatory and scientific issues related to the paediatric investigation plan	2008
Workshop on FP7 and off-patent medicines developed for children	2007
First workshop on regulatory and scientific issues related to the paediatric investigation plan	2007
Workshop on regulatory and scientific issues related to the investigation of medicinal products intended for neonatal use	2006

Source: EMA website and internal records

Table 23. Expert meetings and workshops by therapeutic area (2006-2015)

Area	Number of expert meetings
Antinfectives	4
Cardiovascular	1
Diabetes	1
Epilepsy	1
Extrapolation	1
Haematology	1
Immunology	1
Infective diseases	1
Metabolic diseases	1
Neonatology	1
Oncology	1
Rare diseases	1
Regulatory issues	1
Respiratory diseases	1
Rheumatology	3

Source: EMA website and internal records

Table 24. Workshops per therapeutic area (2006-2015)

Area	Number of Workshops
Bioethics	1
Diabetes	1
EnprEMA	2
FP-7	1
Gastrointestinal diseases	1
Juvenile animal studies	1
Modeling and Simulation	1
Neonatology	5
Ophtalmology	1

Area	Number of Workshops
Paediatric formulations	2
Pharmacology	1
Pharmacovigilance	1
Rare diseases	1
Regulatory science	2
Respiratory diseases	1
Stakeholder meeting	1

Source: EMA website and internal records

2.5.2. Guidelines

Table 25. EMA Guidelines with PDCO input

Publication date	Title	Document reference
22/01/2009	Requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD) in adults and for use in the treatment of asthma in children and adolescents	CPMP/EWP/4151/00 Rev. 1
25/06/2009	Guideline on the Investigation of medicinal products in the term and preterm neonate	EMEA/267484/2007
01/11/2009	Guideline on the Clinical Development of Medicinal Products for the Treatment of Cystic Fibrosis	CHMP/EWP/9147/08
01/01/2010	Addendum to the note for guidance on evaluation of medicinal products indicated for treatment of bacterial infections to specifically address the clinical development of new agents to treat disease due to Mycobacterium tuberculosis	CHMP/EWP/14377/08
01/01/2010	Guideline: Reflection Paper On Ethanol Content In Herbal Medicinal Products	EMA/HMPC/85114/2008
01/01/2010	Clinical investigation of medicinal products in the treatment of epileptic disorders	CPMP/EWP/566/1998 Rev. 2 Corrigendum
01/03/2010	Guideline on Alcohol Dependence after public consultation as well as an overview of the comments on this GL	CHMP/EWP/20097/2008
01/07/2010	Clinical investigation of medicinal products for the treatment of attention-deficit/hyperactivity disorder (ADHD)	CHMP/EWP/431734/2008
01/02/2011	Guideline on medicinal products for the treatment of insomnia	EMA/CHMP/16274/2009
01/08/2011	Guideline on clinical investigation of recombinant and human plasma-derived factor IX products	CHMP/BPWP/144552/09
01/08/2011	Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products	CHMP/BPWP/144533/09

Publication date	Title	Document reference
01/08/2011	Guideline on the treatment of Premenstrual Dysphoric Disorder	EMA/CHMP/607022/2009
01/09/2011	Reflection paper on the necessity of initiatives to stimulate the conduct of clinical studies with herbal medicinal products in the paediatric population	EMA/HMPC/833398/2009
07/10/2011	Draft guideline on clinical investigation of medicinal products in the treatment of diabetes mellitus (second and final release for public consultation)	CPMP/EWP/1080/00 Rev. 1*
01/02/2012	Paediatric addendum to the CHMP guideline on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension	CHMP/EWP/213972/10
02/10/2012	Paediatric addendum to CHMP guideline on clinical investigation of medicinal products in the treatment of lipid disorders	EMA/CHMP/494506/2012
31/10/2012	Concept paper on the need for revision of the guideline on the evaluation of medicinal products in the treatment of primary osteoporosis	EMA/CHMP/520786/2012
31/07/2013	Guideline on pharmaceutical development of medicines for paediatric use	EMA/CHMP/QWP/805880/2012 Rev. 2
25/09/2014	Guideline on the evaluation of medicinal products for the treatment of irritable bowel syndrome	CPMP/EWP/785/97 Rev. 1
31/03/2015	Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis	EMA/CHMP/771815/2011 Rev. 2
01/06/2015	Guideline on clinical investigation of recombinant and human plasma-derived factor IX products	EMA/CHMP/BPWP/144552/2009 Rev.1 Corr. 1
10/06/2015	Guideline on clinical investigation of medicinal products for the treatment of acute heart failure	CPMP/EWP/2986/03 Rev.
24/07/2015	Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg)	EMA/CHMP/BPWP/410415/2011 rev 1
14/09/2015	Guideline on the evaluation of medicinal products for the treatment of chronic constipation (including opioid induced constipation) and for bowel cleansing	EMA/CHMP/336243/2013
15/12/2015	Guideline on the clinical investigation of medicinal products for the treatment of asthma	CHMP/EWP/2922/01 Rev. 1
11/02/2016	Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products	EMA/CHMP/BPWP/144533/2009 Rev.1

Source: EMA website

3. Other initiatives

3.1. Publications relating to the Paediatric Regulation

3.1.1. Publications by EMA/PDCO on the Paediatric Regulation

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3.1.2. Publications by external authors on the Paediatric Regulation

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