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Human Medicines Research and Development Support Division

10-year Report to the European Commission

General report on the experience acquired as a result of the application of the Paediatric Regulation[1]

Prepared by the European Medicines Agency and its Paediatric Committee

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

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Table of Contents

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 nine 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.

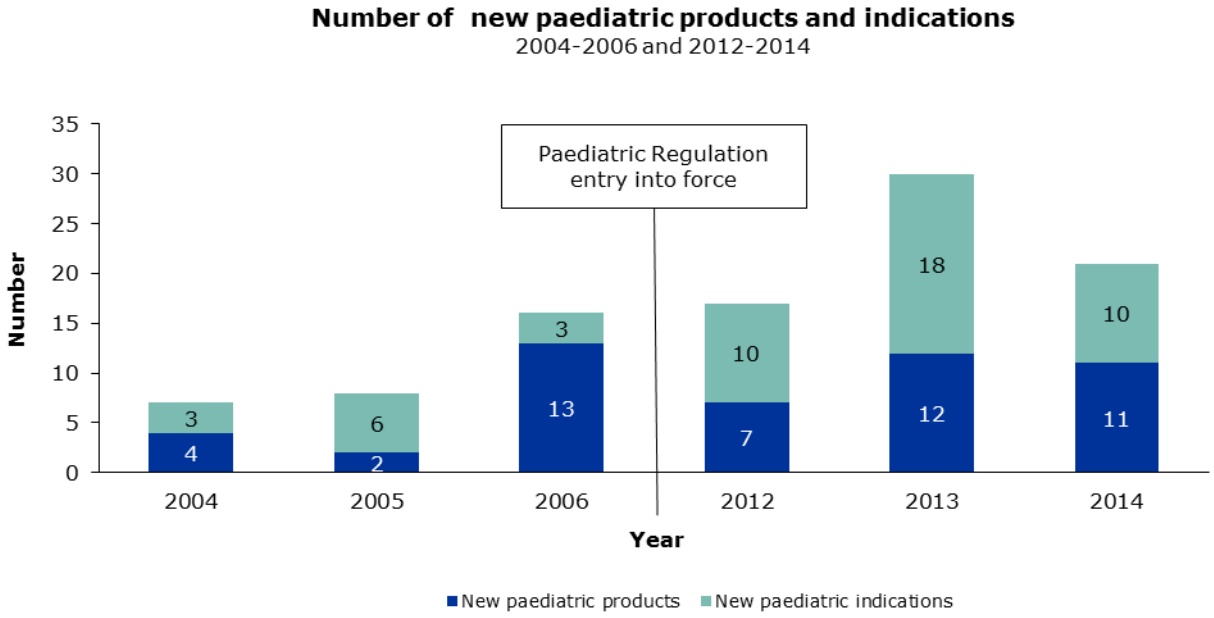
More medicines for children

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 2015, 238 new medicines for use in children and 39 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 CMDh[2]) 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 (PIP[3]) and information on paediatric clinical trials. This provides guidance for new drug developments and assists in prevention of duplications.

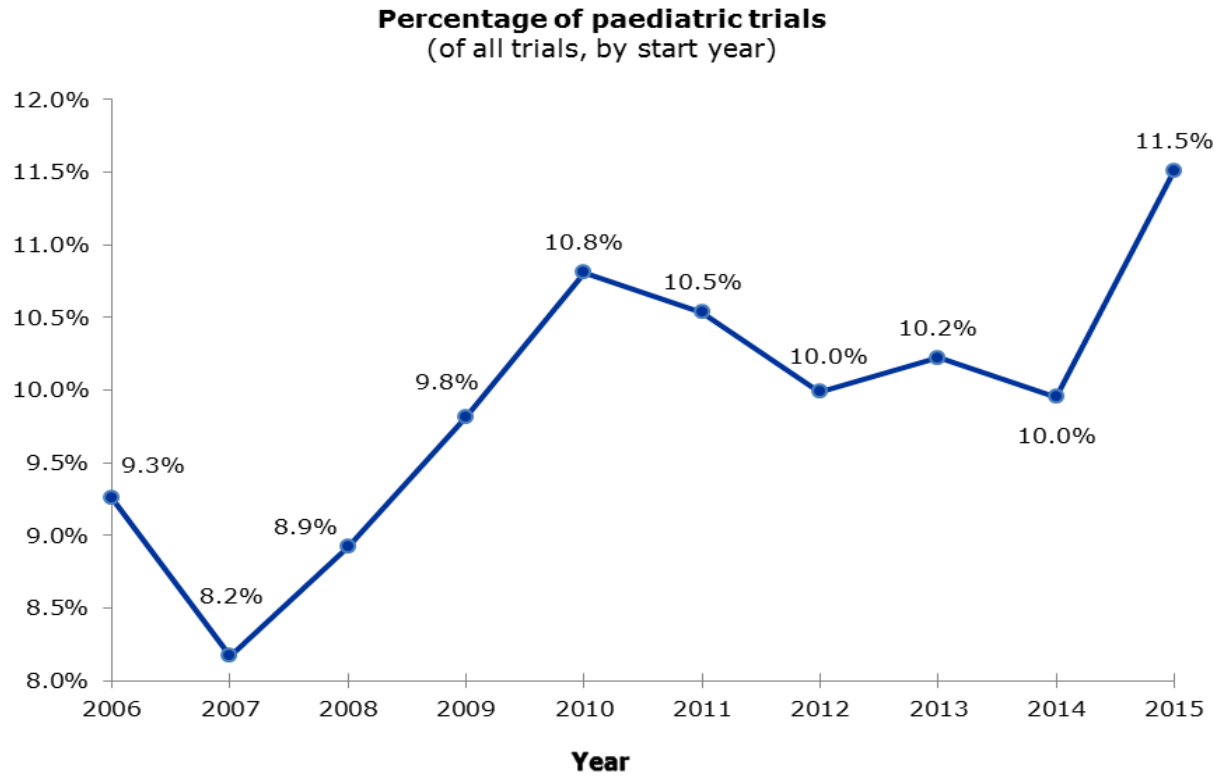
[2] The Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) is a medicines regulatory body representing the EU Member States, Iceland, Liechtenstein and Norway
[3] Paediatric Investigation Plan (PIP): a research and development programme aimed at ensuring that the necessary 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 9 years 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 30% 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. Overall, the percentage of clinical trials involving children per year compared to all clinical trials per year increased from 9.3% in 2006 to 11.5% in 2015 (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 25 times between the two periods compared: from 470 in 2007-2009 to more than 13,000 in 2013-2015.

By the end of 2015, the PDCO had adopted 860 opinions on the agreement of a PIP and in 421 (33%) cases had granted an exemption (waiver[4]) from conducting paediatric studies in one or more conditions. In addition, EMA provided scientific advice on paediatric development in 657 procedures. A further 315 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 150 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 51 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 38 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 2015, the cluster had held 119 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.

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.

[4]A 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.

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.

To date approximately 100 PIPs have been completed and more than 700 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. 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. An update of key analyses such as the number of paediatric medicine authorisations and paediatric clinical trials for 2016 will be provided in due time.

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 2015, 89 new medicines were centrally authorised for paediatric use out of 352 (26%). (Line listings are included in the Annex.) Of these 49 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 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, 85 new paediatric indications were authorised, including 64 indications related to Article 8 of the Paediatric Regulation. Of all paediatric indications approved via the variation procedure, 75% are now linked to the Paediatric Regulation.

For centrally authorised medicines, 25 new pharmaceutical forms were authorised for paediatric use, and 13 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 eight new medicines with a paediatric indication have been authorised from 2007-2015 and a total of 56 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**	**Total**
New medicines with a paediatric indication:										
Centralised procedure, linked to requirements of the Paediatric Regulation	NA	0	2	2	7	7	12	11	8	**49**
Centralised procedure, not linked to requirements of the Paediatric Regulation*	12	6	5	0	0	3	9	4	1	**40**
Total of all centralised authorisations (for reference)	*39*	*25*	*41*	*17*	*30*	*35*	*53*	*53*	*59*	***352***
National procedure (including DCP, MRP)	0	0	2	0	1	1	1	1	2	**8**
Total of new paediatric medicines	**12**	**6**	**9**	**2**	**8**	**11**	**22**	**16**	**11**	**97**

	2007	2008	2009	2010	2011	2012	2013	2014	2015	Total
New paediatric indications:										
Centralised procedure, linked to requirements of the Paediatric Regulation	NA	NA	2	1	14	10	18	10	9	**64**
Centralised procedure, not linked to requirements of the Paediatric Regulation*	7	6	6	2	0	0	0	0	0	**21**
National procedure (including DCP, MRP)	5	4	11	7	6	7	9	6	1	**56**
Total of new paediatric indications	**12**	**10**	**19**	**10**	**20**	**17**	**27**	**16**	**10**	**141**
Total of new paediatric medicines and indications	**24**	**16**	**28**	**12**	**28**	**28**	**49**	**32**	**21**	**238**
New paediatric pharmaceutical forms:										
Centralised procedure, linked to requirements of the Paediatric Regulation	NA	NA	0	0	3	2	4	2	2	**13**
Centralised procedure, not linked to requirements of the Paediatric Regulation*	3	1	2	2	4	0	0	0	0	**12**
National (DCP, MRP) procedure	1	1	4	2	3	1	0	1	1	**14**
Total of new paediatric pharmaceutical forms	**4**	**2**	**6**	**4**	**10**	**3**	**4**	**3**	**3**	**39**

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, 31 new medicines and new indications were centrally authorised for paediatric use. From 2012 to 2014, this number more than doubled to 68 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.

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

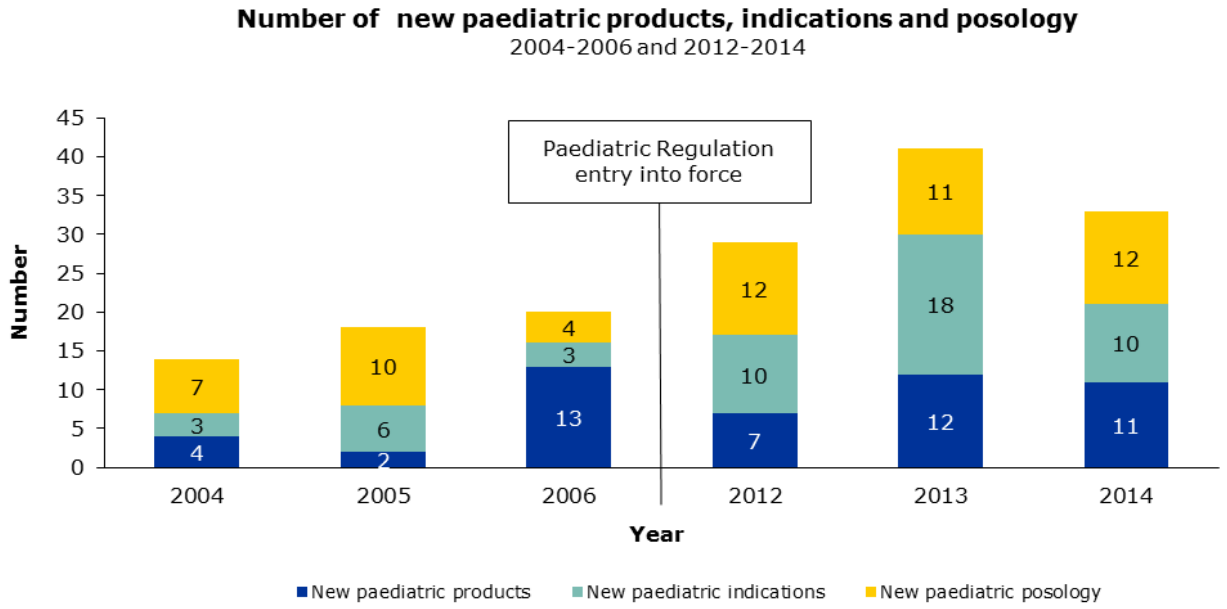
Reference period	Paediatric MAs and variations	Total of all MAs and variations	Proportion of paediatric MAs and variations of total
2004-2006	31	124	25%
2012-2014	68	192	35%

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.

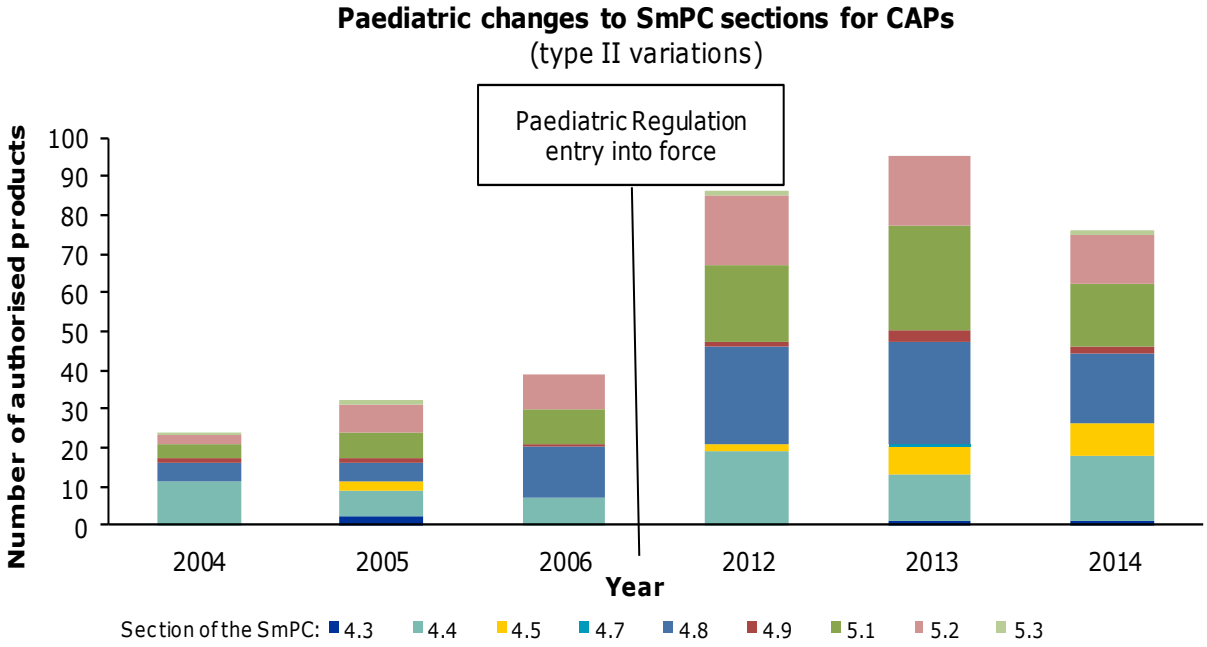
Figure 3. Number of centrally authorised products (CAPs) becoming available for children in 2004-2006 and 2012-2014 (new initial marketing authorisations, new paediatric indications (SmPC Section 4.1) or new posology information (SmPC Section 4.2) for already authorised products.



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 Hemangiol (propranolol hydrochloride, oral use) for the treatment of haemangioma.

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 2015, the PDCO had adopted opinions on final/full compliance for 99 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 a peak in 2014 (Table 3.).

Table 3. Number of final/full compliance check opinions

Outcome of compliance procedure	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**Total**
Positive	5	8	9	9	4	16	31	17	**99**
Negative		1				1			**2**

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**

	2007	2008	2009	2010	2011	2012	2013	2014	2015	Total
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	Total
Full waiver	PIP agreed*		1								**1**
	Full waiver refused		1	11	6	2	2	2	1	3	**28**
	Full waiver granted	10	35	55	44	44	47	51	46	47	**379**
PIP	PIP agreed	1	81	123	202	107	87	96	91	71	**859**
	PIP refused		1	4	1	1	1	2	1		**11**
	Full waiver on PDCO's own motion		10	13	7	1		1	5	5	**42**
Modification	Modification refused				4	2	1	3	4	3	**17**
	Modification agreed		8	50	105	152	165	184	195	200	**1059**
	Full waiver granted				1			1	2	2	**6**
Total		**11**	**137**	**256**	**370**	**309**	**303**	**340**	**345**	**331**	**2402**

Note: * 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.

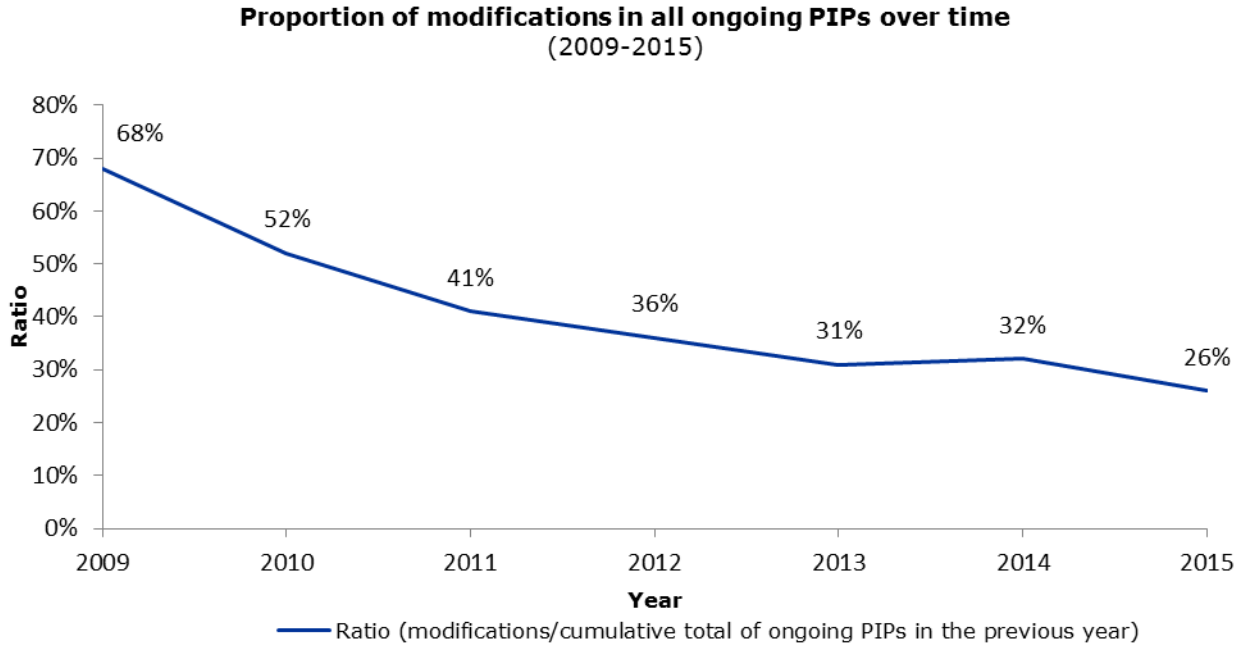
3.2. Modifications of agreed PIPs

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

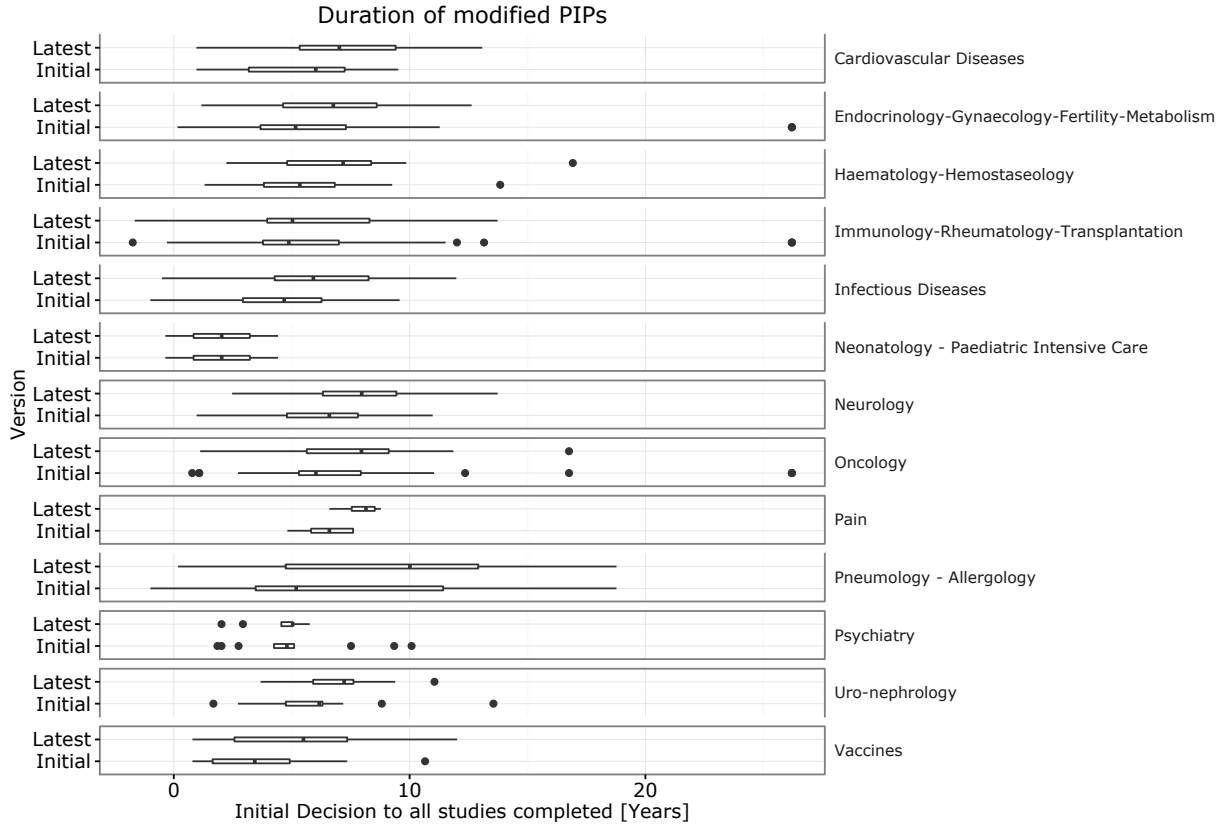
Major modification concerning	Frequency per agreed, modified PIP (%)
Timelines*	43
Sample size	14
Statistical plan	8
Deletion of study	8
Dosage or dosing rules	8
Secondary endpoint	7
Primary endpoint	7
Formulation	5
Non-clinical issues	3
Change in wording of condition	3
Removal of condition	2
Addition 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-allergology 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 is 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%*	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**		100% (8,050)	100% (645)	87	68

Note: * Allergen PIPs are not included in this analysis. ** 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.

Even though mental and behavioural disorders are often treated with non-pharmacological interventions in children and adolescents, and thus the need for medicines is not that high in this area, a discrepancy between diseases burden and number of agreed PIPs is seen in other therapeutic areas with high needs. 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 m2, 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

Active substance	Indication	Age group authorised in 2006	Age group authorised in 2015	Paediatric need in 2006	PIP condition
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
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 hyper-cholesterolaemia	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 hyper-choleste-rolaemia Treatment of homozygous familial hypercholeste-rolaemia

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

Therapeutic area	PIPs with study for age-appropriate form or formulation	All documented PIPs
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).

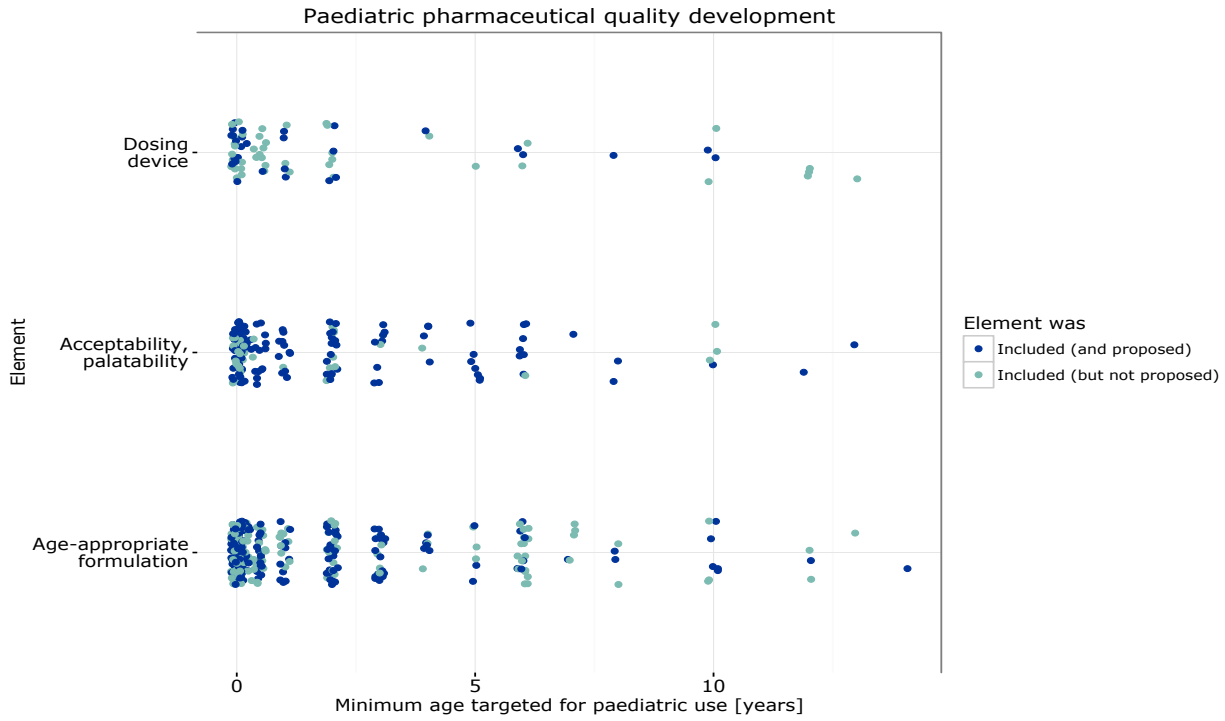
Approximately 40% of agreed PIPs include a specific measure to develop an age appropriate formulation and 10% included a request for a specific administration device. However, in many cases an age-appropriate form already existed, or the form for adults was also appropriate for the paediatric target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

Therapeutic area	**Total number of PIP conditions**	**Including neonates**	**Including preterm neonates**	**Including term neonates**	**Neonates proposed-** (requested) *	**Not including neonates**
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 TOTAL	37	6 (16.2%)	1	5	6 (0)	31
• *Gastroenterology-hepatology*	*36*	*5*	*0*	*5*	*5 (0)*	*31*
• *Neonatology gastroenterology*	*1*	*1*	*1*	*0*	*1 (0)*	
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

Therapeutic area	Total number of PIP conditions	Including neonates	Including preterm neonates	Including term neonates	Neonates proposed-(requested) *	Not including neonates
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: *Proposed 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	• Perinatal asphyxia:2-iminobiotin	Neonatal seizures: • retigabine • lacosamide • carisbamate • brivaracetam
Neonatal lung injury and circulatory failure	Bronchopulmonary dysplasia: • budenoside • azithromycin	Pulmonary arterial hypertension/pulmonary hypertension of the newborn: • treprostinil • sildenafil • tadalafil • riociguat • bosentan • macitentan
	Neonatal circulatory failure: • dobutamine	Hypotension in the extremely low gestational age newborn: • dopamine
Neonatal ophthalmology	Retinopathy of prematurity: • ranibizumab	
Perinatal/neonatal infections	Prevention • pagibaximab	Treatment: • vancomycin • meropenem • eritoran • trombomodulin alfa • ceftriaxone/sulbactam • isavocunazonium • pozaconazole • caspofungin

Source: EMA database (PedRA).

Table 16. Agreed PIPs for additional neonatal indications

Indication	Neonates only	Neonates and children
Pain	• paracetamol (moderate)	• 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: • bucelipase alfa	Supplementation of amino-acids where parenteral nutrition is required: • 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 21.3% in 2015. 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**	**Total**
Total number of advice procedures (Scientific Advice and Protocol Assistance)*	277	321	388	400	433	420	473	551	510	**3773**
Number of paediatric-only and mixed (adult and paediatric development questions) advice procedures*	21	32	74	80	57	91	96	97[+]	109[#]	**657**
Number of paediatric-only or mixed advice procedures that involved a PDCO member(s)[×]	ND	ND	68	80	55	91	93	88	97	**572**

Note: *Year of advice letter; [×]Year of start of procedure; [+]Including qualification of biomarker procedures; [#]Including 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 2015, 315 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 2015. The proportion of new paediatric trials compared to all newly initiated trials has increased slightly, from 9% in 2006 to about 12% in 2015 (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 date[1]

Trials	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Paediatric[2] trials	361	370	389	424	421	406	352	339	329	382
Total number of trials	3898	4528	4360	4321	3895	3854	3525	3317	3305	3320
Proportion of paediatric trials of all trials (%)	9.26	8.17	8.92	9.81	10.81	10.53	9.99	10.22	9.95	11.51
Paediatric trials marked as being included in agreed PIPs[3]	18	16	26	33	50	107	93	86	79	87
Exclusively[3] paediatric trials	212	195	225	256	259	257	215	200	201	229

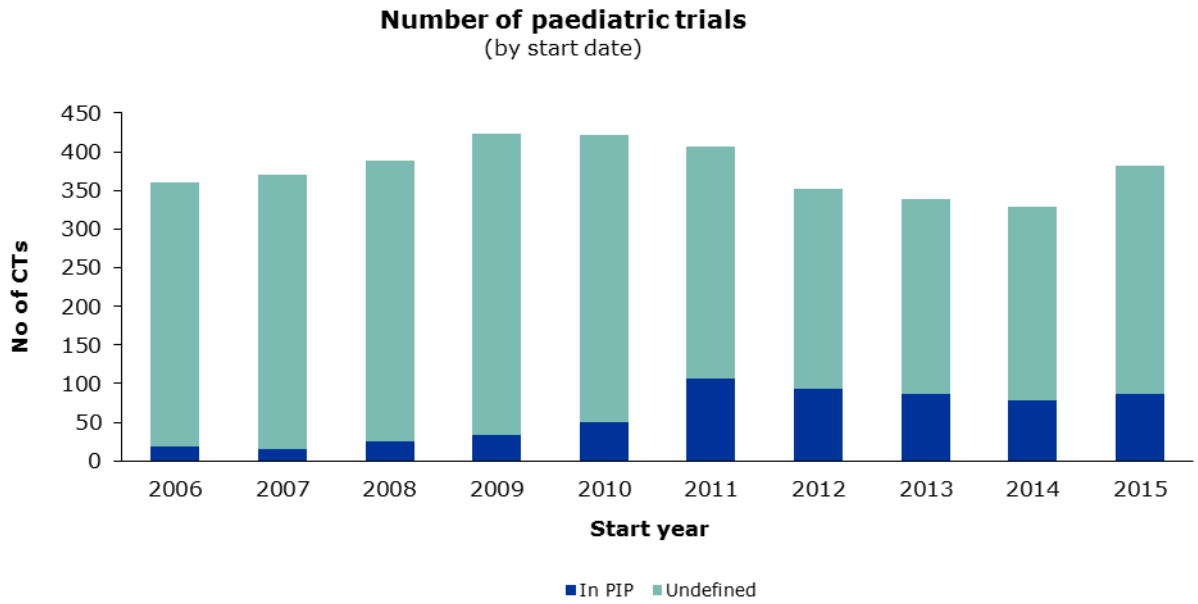
Note: [1] Start date according to planned start of recruitment (if not available then according to NCA review date; if not available then according to upload date).

[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.

[3] It is not mandatory in the EudraCT database to state whether a trial is included in an agreed PIP.

Source: EudraCT database.

Figure 8. Absolute number of authorised paediatric clinical trials[1] by start date[2]

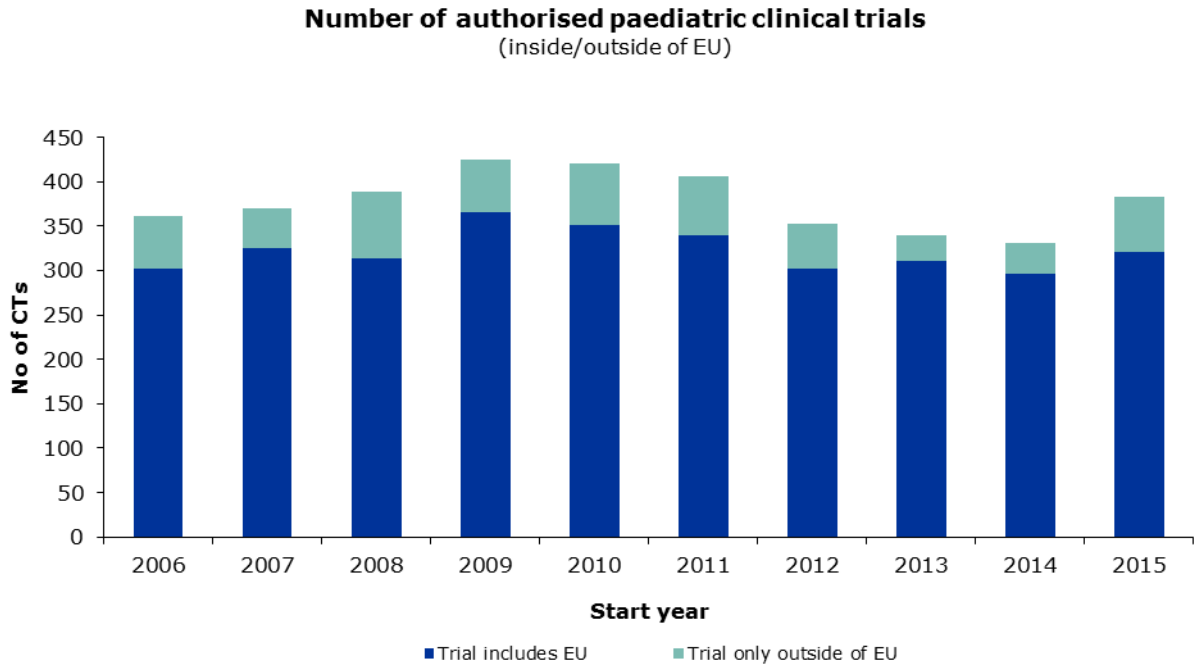


Note: 1A paediatric trial is a trial that includes at least one participant below 18 years of age. 2Start date according to planned start of recruitment (if not available then according to NCA review date; if not available then according to upload date).

Source: EudraCT database.

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 trials[1] inside/outside of the EU, by start date[2]



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.

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 date[1]

Year	Preterm newborns	Newborns	Infants and toddlers	Children	Adolescents	Total
2006	1	1	19909	6461	3785	30157
2007	0	2	32292	5202	40950	78446
2008	226	181	23202	7846	3750	35205
2009	0	61	78456	14189	7683	100389
2010	39	97	22844	13304	7285	43569
2011	2659	1848	31081	59238	38522	133348
2012	1329	3069	22709	23284	21568	71959
2013	3190	740	14518	31365	21047	70860
2014	4402	1205	15018	25015	20452	66092
2015	2006	1775	19755	17908	18080	59524
2016	595	372	3058	13507	9379	26911
Later than 2016	0	1	14	139	148	302

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).
Source: EudraCT database (23/08/2016).

Similar to the annual number of newly started paediatric trials, the number of paediatric study participants in clinical trials has not changed significantly from 214,040 in 2007-2009 to 196,476 in 2013-2015.

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 25 times between the two periods compared: from 470 in 2007-2009 to 13,318 in 2013-2015.

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).

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 1,000 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

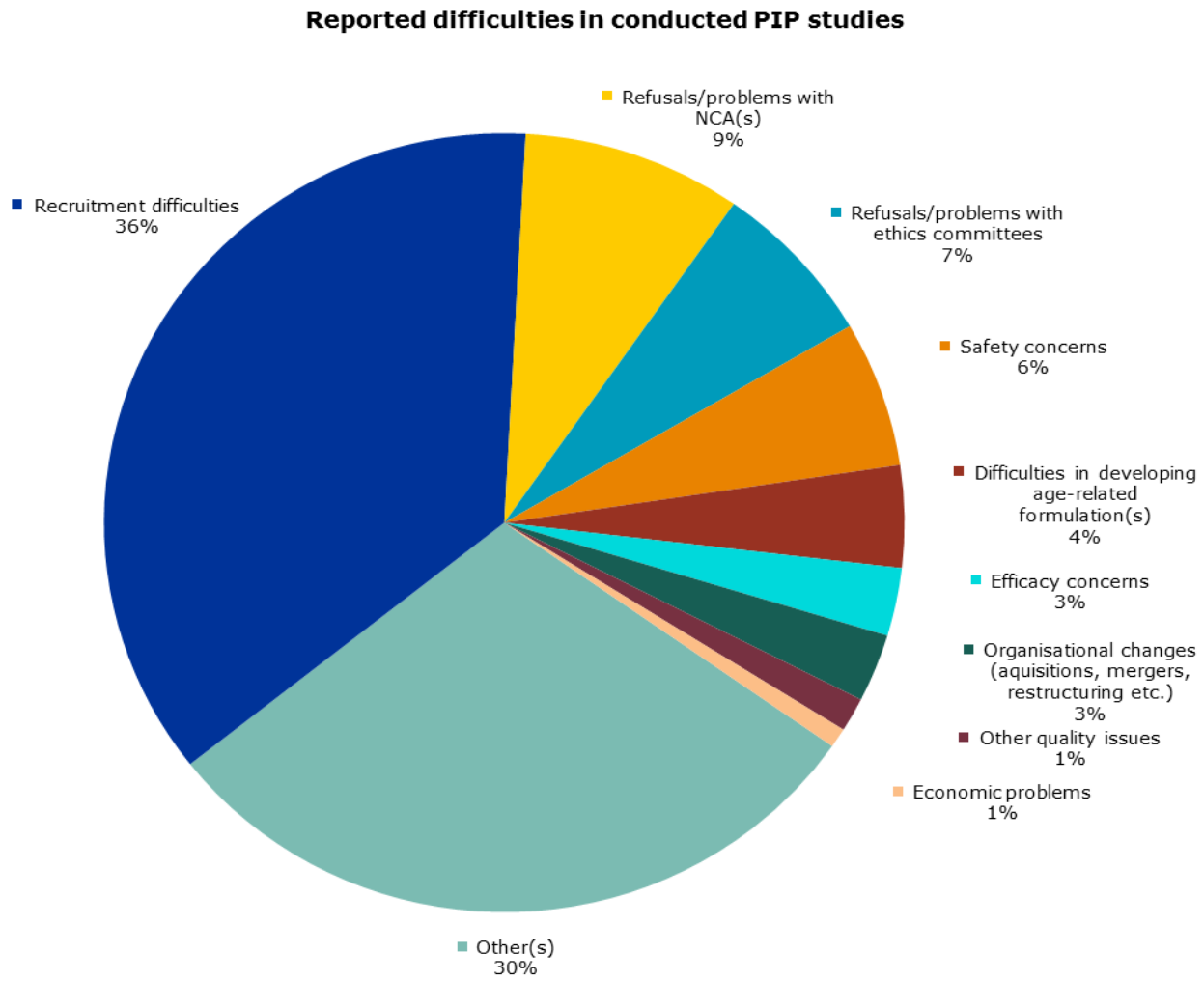
Once a medicinal product with a PIP obtains marketing authorisation in adults, the EMA receives annual reports on the paediatric measures/studies that have been deferred, i.e. that are allowed to be completed after marketing authorisation is obtained.

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 10.

It can clearly be seen that the most frequent difficulties pertain to recruitment (39% 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 10. Reported difficulties in conducting PIP studies (2007-2015)

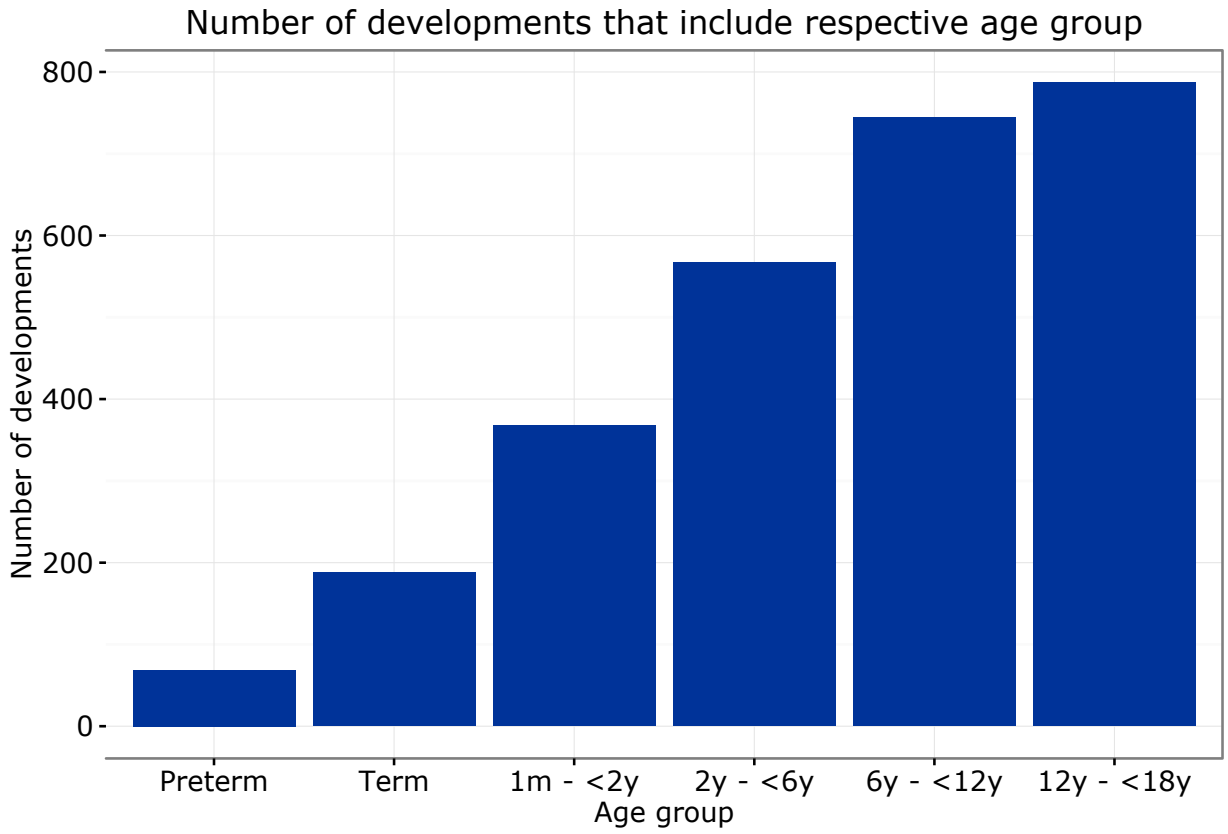


Source: EMA database (PedRA).

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 11.). 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.

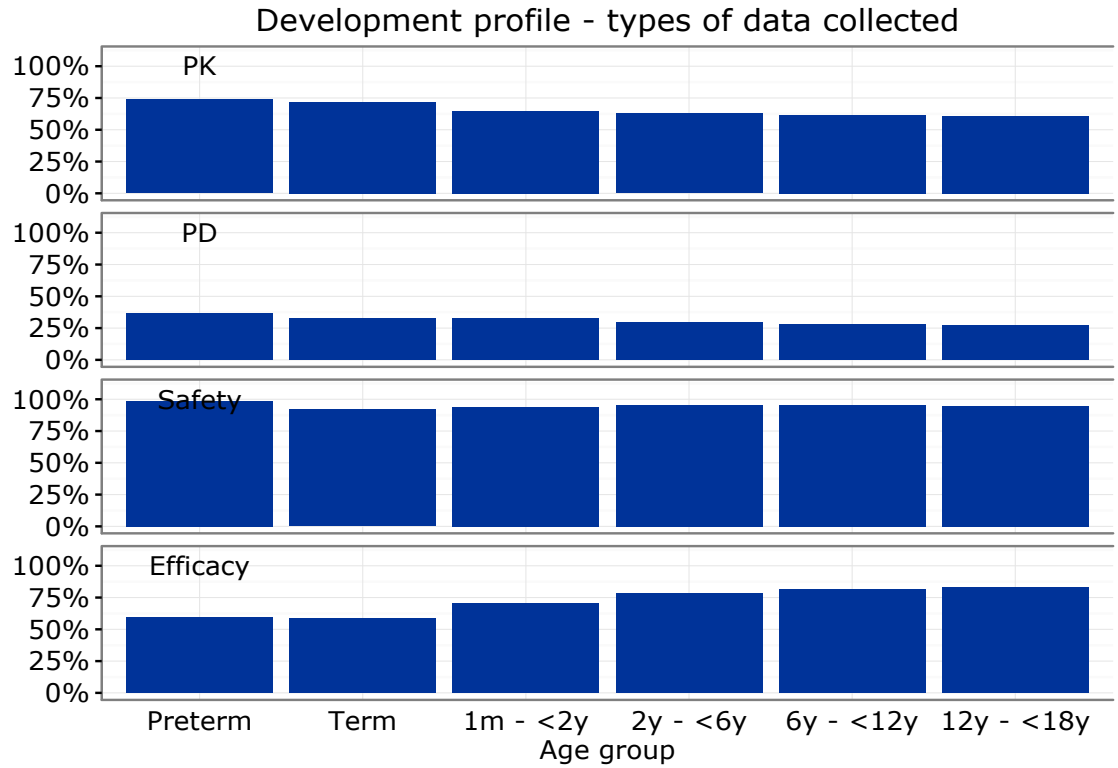
Figure 11. Number of developments including respective age groups.



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 12.).

Figure 12. 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 20.). 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 20.). 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 20. and Table 21.). 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 20. 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 21. 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 22. 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 22. Paediatric trials which were prematurely terminated or temporarily halted

Number of trials*	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: *The 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 23. ; of note, in more than half of the cases no reason was reported (or is marked as "other" or "not specified").

Table 23. 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.

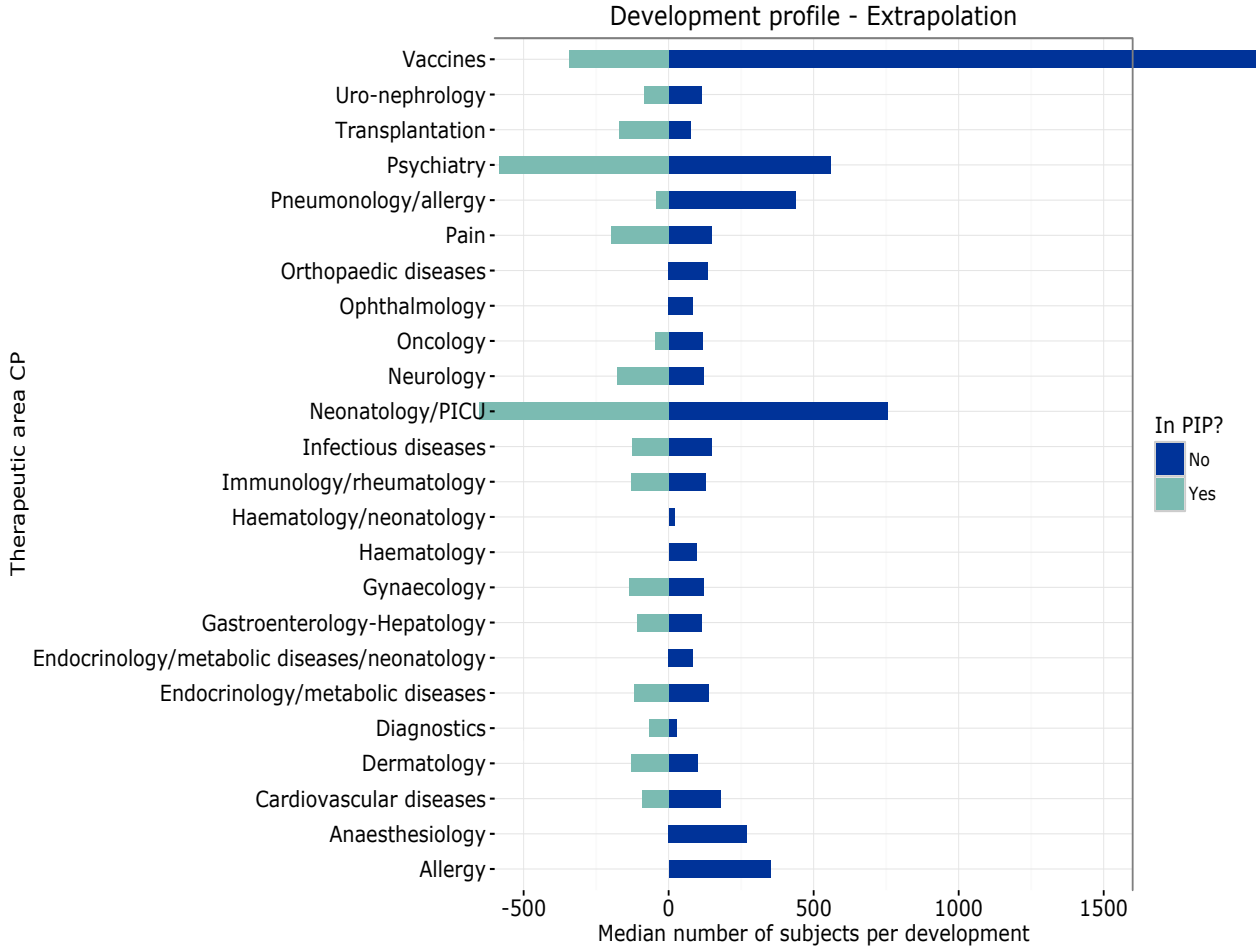
The EMA established an extrapolation expert group including clinicians, pharmacologists, pharmacometricians and statisticians from the EMA, NCAs and from academia.

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 13.). 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 13. 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 24.).

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 24. 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 25. 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 25. Full and partial product-specific waivers based on safety grounds

			Waiver						
Therapeutic area	**Full waiver**	**Partial 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 26. 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 26. 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 83 oncology PIPs[5] (83 / 859 = 10% of all PIP decisions as of December 2015), and these are for 68 anti-cancer medicines. These 68 anti-cancer medicines represent more than 30 different mechanisms of action (based on the ATC code and the scientific assessment by the PDCO). The main cancer types being studied in 41 out of the 68 PIPs for anti-cancer medicines are those which primarily affect paediatric patients (e.g. acute lymphoblastic leukaemia, Ewing sarcoma, medulloblastoma, neuroblastoma, rhabdomyosarcoma). In fact, 14 out of these 41 PIPs are intended to identify and to investigate a childhood cancer as therapeutic target for the medicines' mechanism of action.

Based on compliance opinions issued by the PDCO for anti-cancer medicines, 7 developments in PIPs have been completed (7 / 68 = 10%). These are: ipilimumab, vandetanib, bevacizumab (high-grade glioma), bevacizumab (rhabdomyosarcoma), recombinant asparaginase, everolimus (astrocytoma), imatinib (acute lymphoblastic leukaemia). Three 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, sunitinib).

The assessments by the CHMP of the paediatric indications of some of these medicines are ongoing (ipilimumab). Due to findings in adult clinical trials a number of anti-cancer medicine developments were discontinued (recombinant human monoclonal antibody of the IgG1 class to insulin-like growth factor-1 receptor, cediranib, cilengitide, cyclophosphamide, elacytarabine, enzastaurin, ombrabulin).

3.13.2. Authorisations of anti-cancer medicines

In total, five 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 27.).

5 http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fpip_search.jsp&mid=WC0b01ac058001d129&searchkwByEnter=false&alreadyLoaded=true&isNewQuery=true&keyword=Enter+keywords&searchType=Invented+name&taxonomyPath=&treeNumber=&currentCategory=Oncology

Table 27. Active substances of centrally authorised medicines for paediatric oncology indications.

Authorised before 2007	Authorised from 2008 onwards
Busulfan[IND]	Everolimus[IND PIP]
Clofarabine	Mifamurtide[NEW]
Nelarabine	Mercaptopurine** [NEW]
-	Asparaginase* [NEW]
-	Asparaginase (recombinant) [PIP NEW]
-	Temozolomide[IND]
-	Imatinib[IND PIP]
-	Dinutuximab [PIP NEW]
-	Daunorubicin[IND]
-	Etoposide[IND]
-	Idarubicin[IND]

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. * Asparaginase 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), 48 anti-cancer medicines have been authorised via the centralised procedure after the Paediatric Regulation came into force.[6] Twenty-seven out of these 48 (56%) 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 11 out of these 27 new anti-cancer medicines, the pharmaceutical companies also proposed PIPs (see also next section). The remaining 21 out of the 48 (44%) 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 14 PIPs fit this description (Table 28.).

6 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 28. Overview of "voluntary" PIPs (cut-off date December 2015) 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

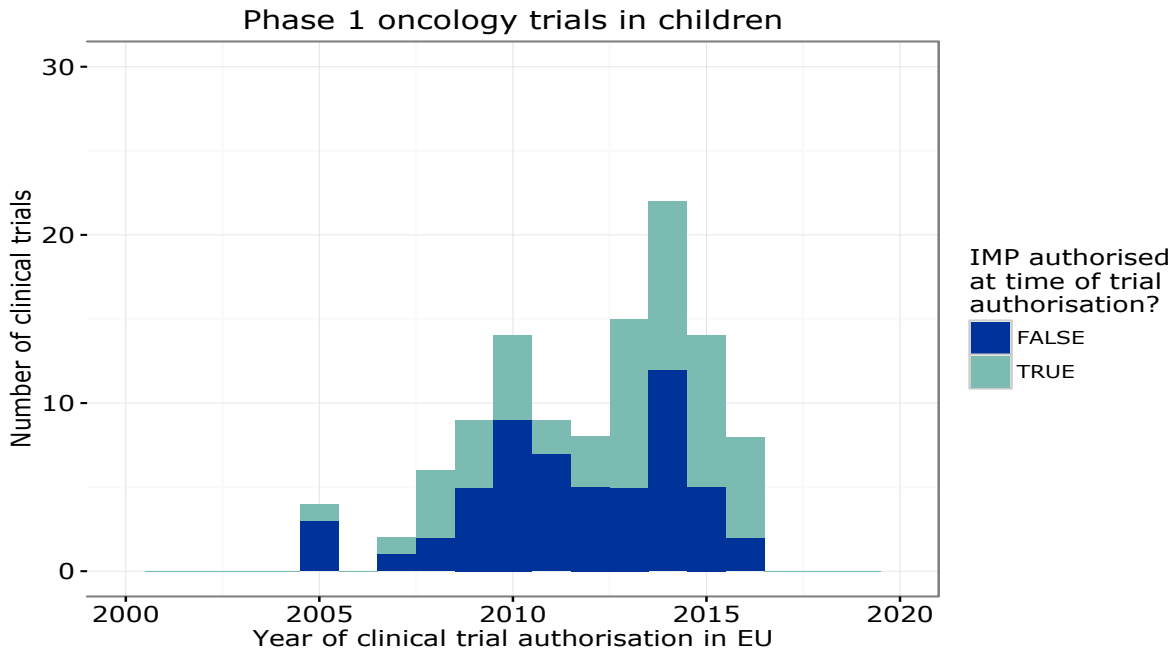
Source: EMA website.

3.13.4. Early phase paediatric oncology trials

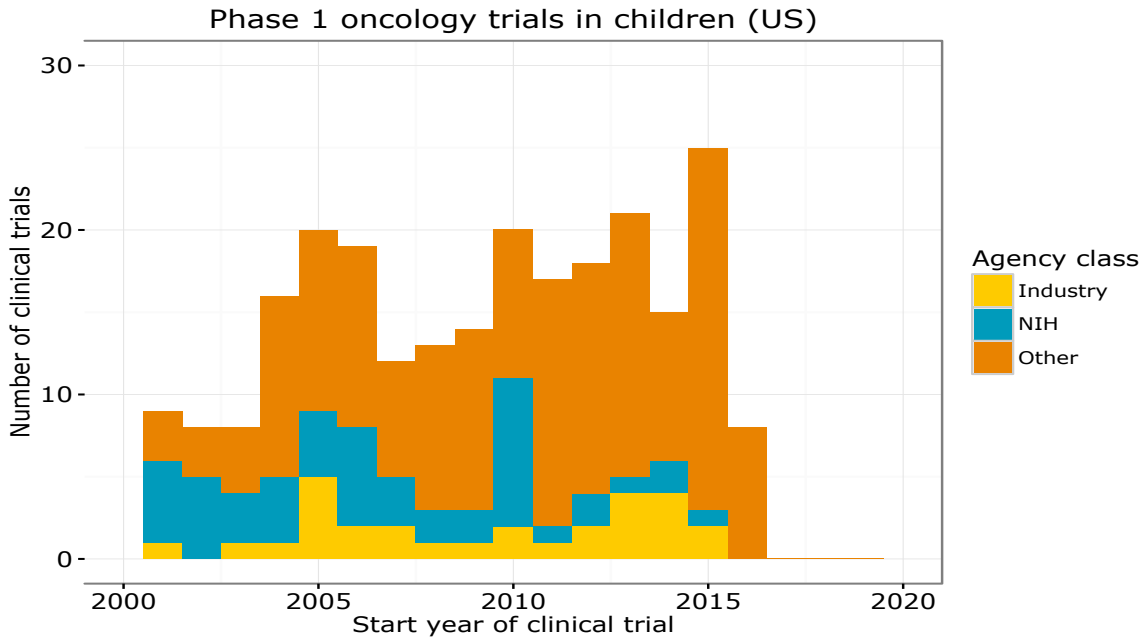
Given the limited relevance to children of information from adult trials of anti-cancer medicines, there is interest in conducting early phase trials in children based on biological rationale and animal toxicology and efficacy data, rather than on adult trials (see also Addendum on Paediatric Oncology, 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 14. 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 2015 the committee handled more than 550 requests to confirm the applicability of a class waiver to a development; most of these (60%) 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 29.).

Table 29. 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	• 44 conditions (including 22 cancers)	• 8 conditions (no cancer)
For specific classes of medicines within a certain condition	• 2 classes of medicines that are likely unsafe in children and that are used to treat 1 condition in adults	• 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.

So far, 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, it is too early to draw any conclusions only six months after the class waiver revision, in particular 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, 38 networks are listed in the fully searchable Enpr-EMA database with 20 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 30.).

Table 30. 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

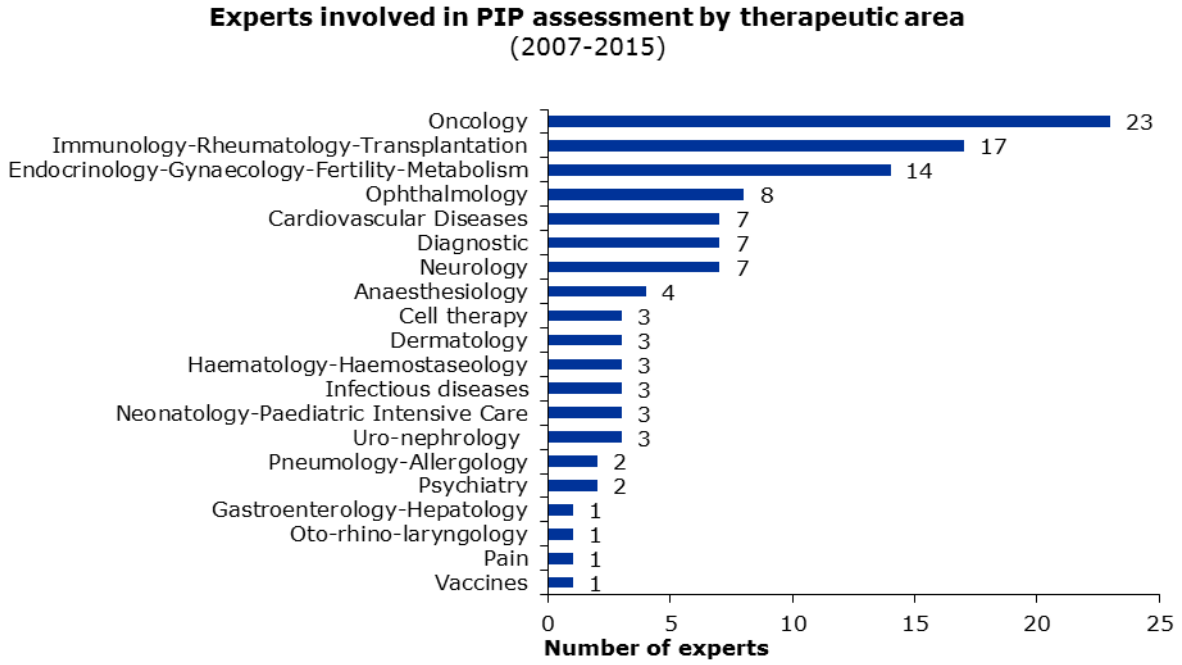
External experts are consulted by the PDCO in order to ensure that paediatric development programmes are in line with up to date clinical practice and scientific knowledge.

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 15.), 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 15. 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 31.). 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 31. 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**

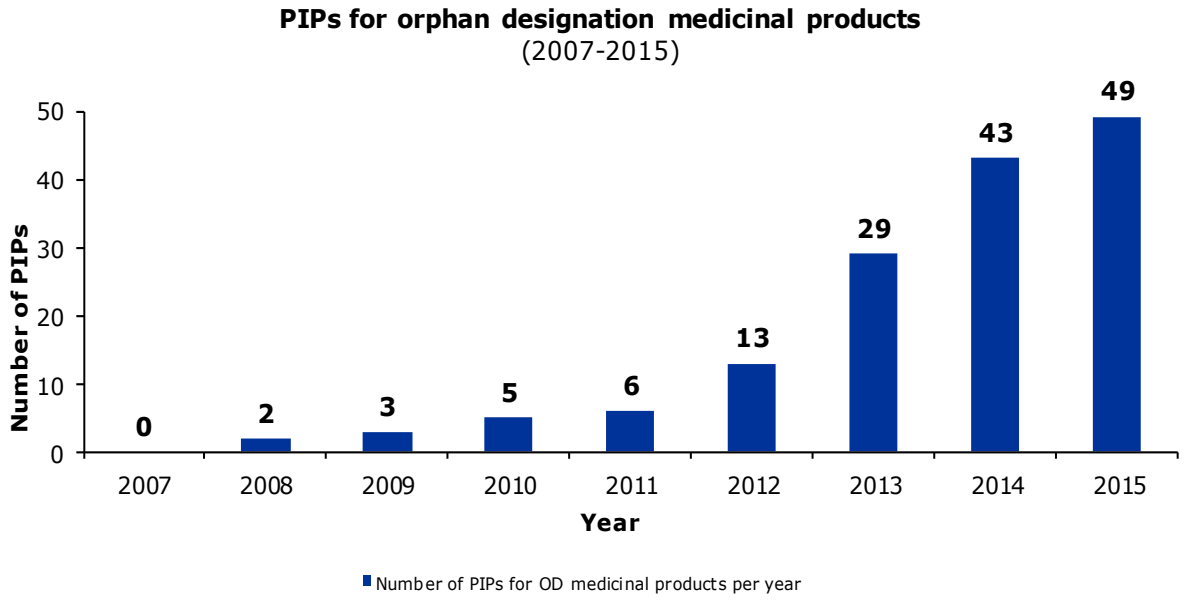
Source: EMA internal data.

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 16.) have been agreed for medicinal products which have also received an orphan designation. 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 16. 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 32. 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 33.). 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 33. 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 34.).

Table 34. Missed opportunities in PIPs related to timing of submission

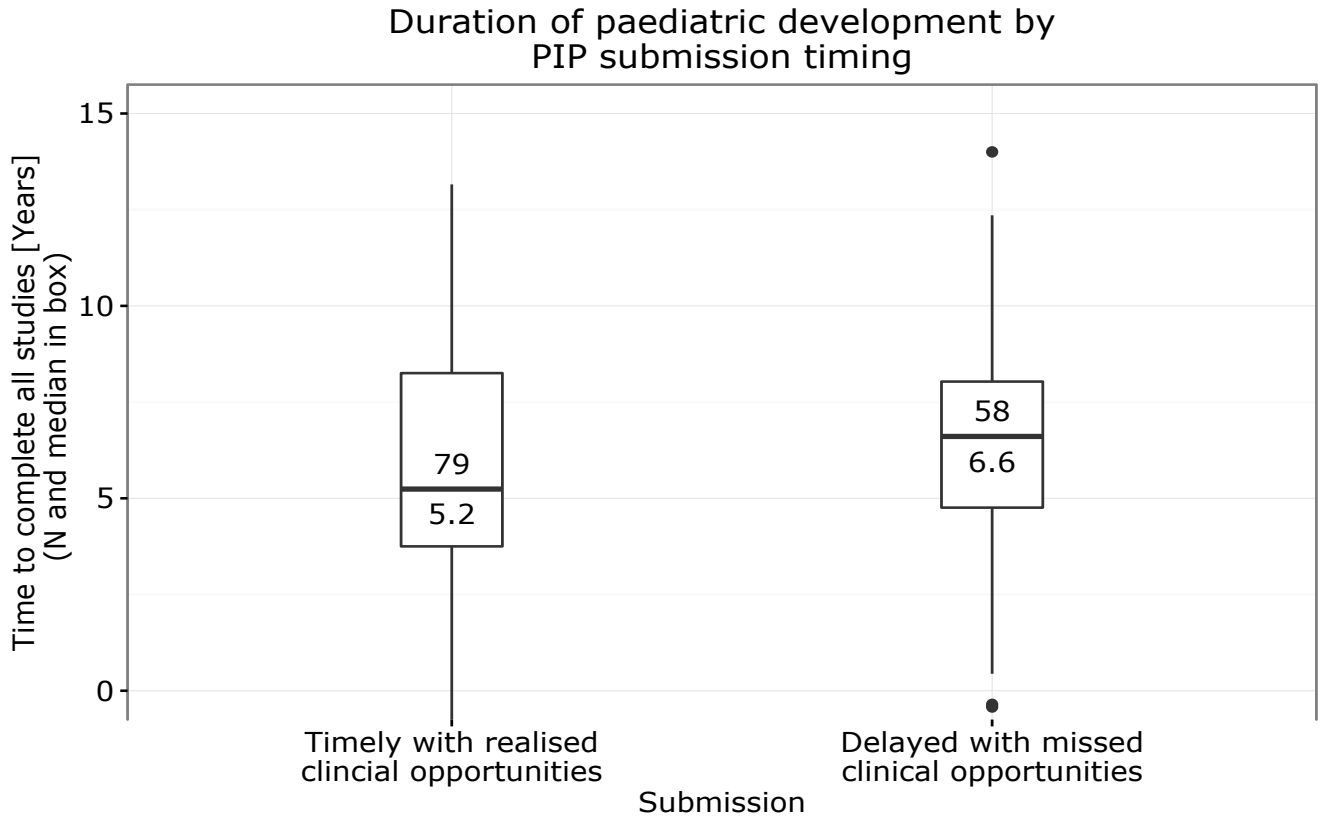
Missed opportunity	Number and proportion among late submissions (N=295)
Formulation	17 (6%)
Nonclinical	17 (6%)
Clinical	57 (19%)
Modelling/Simulation	2 (1%)
Joint paediatric adult trials	6 (2%)
Any opportunity as listed above	64 (22%)

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 17.); 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 17. 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.

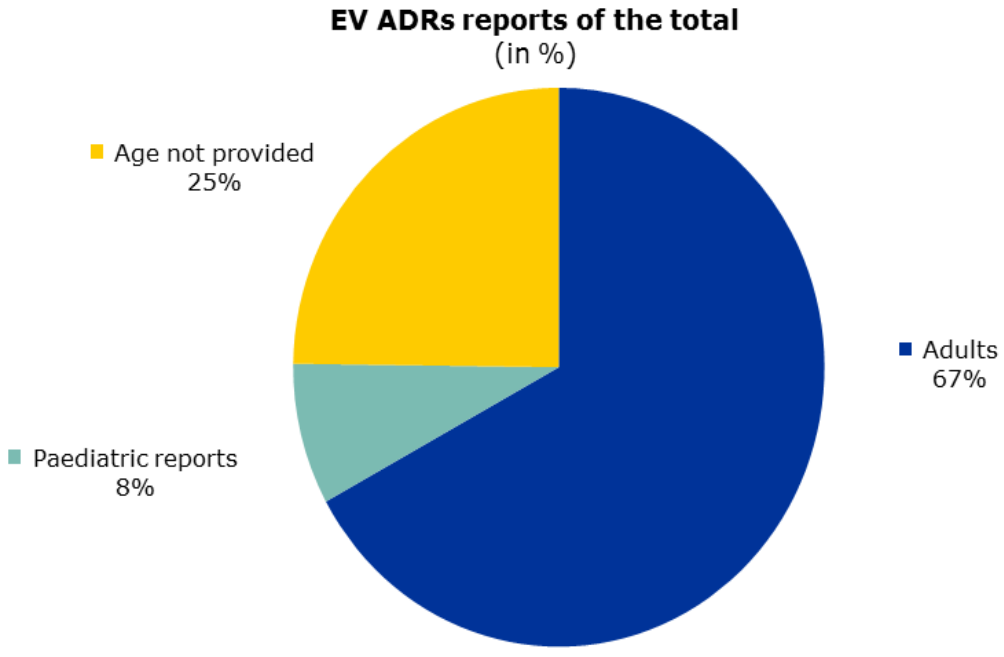
EudraVigilance and safety signals

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 18.) (Blake KV et al, 2016).

Figure 18. 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 35. 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 35. Number of contributions (rapporteurships/peer reviewerships) 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 two 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

Abbreviation/term	Explanation
iCAN	International Children's Advisory Network
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

Abbreviation/term	Explanation
	Section 4.8 Undesirable effects Section 5.1 Pharmacodynamics properties 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)