20	カンノレン酸カリウム	ソルダクトン注	5-ア-①			3	
21	ガンマグロブリン	ベニロン、ヴェノグロビンIH	5-ア-①		ベニロンIなど	3	血液型不適合
22	グリセロール	グリセオール	5-ア-①			4	
23	グルコン酸カルシウム	カルチコール	5-ア-①			3	
24	クロルプロマジン塩酸	コントミン	5-ア-①			4	
25	ケタミン塩酸	ケタラール	5-ア-①			4	
26	酢酸オクレオチド	サンドスタチン注	5-ア-①		臨床試験中	3	ジアゾキサイド抵抗性高インスリン血症
27	ジアゼパム(静注)	ホリゾン、セルチン注	5-ア-①			4	
28	シメチジン	タガメット注	5-ア-①			3	
29	臭化パンクロニウム	ミオブロック	5-ア-①		ロクロリウム臭化物(エスラックス)	3	
31	スピロノラクトン	アルダクトンA	5-ア-①			3	
32	チアミラールナトリウム	イソゾール	5-ア-①			4	
33	チオペンタールナトリウム	ラボナール	5-ア-①			4	
34	テオフィリン	テオドールドライシロップ	5-ア-①		アプネカット	1	未熟児無呼吸発作
35	酢酸デキサメタゾン	デカドロンA注	5-ア-①			4	低出生体重児でCP増加
36	リン酸デキサメタゾンナトリウム	デカドロン注	5-ア-①			4	低出生体重児でCP増加
41	ニトログリセリン	ミリスロール注	5-ア-①			2	

46	人ハプトグロビン	ハプトグロビン	5−アー①			3	
47	ヒドロコルチゾン	コートリル錠	5−アー①			4	低出生体重児で CP 増加
48	コハク酸ヒドロコルチゾンナトリウム	ソルコーテフ	5−アー①			4	低出生体重児で CP 増加
49	リン酸ヒドロコルチゾンナトリウム	水溶性ハイドロコートン注射液	5−アー①			4	低出生体重児で CP 増加
50	塩酸ピリドキサール	ｱﾃﾞﾛｷｻﾞｰﾙ、ピロミジン散	5−アー①			2	
51	塩酸ピリドキシン	ビーシックス注	5−アー①			2	Gasping
52	ファモチジン	ガスター注	5−アー①			3	
58	フェンタニール	フェンタネスト	5−アー①		フェンタニル	2	麻酔導入
60	プロスタグランディン E2	プロスタルモン E 錠	5−アー①		プロスタルモン E2 錠	？？	
67	マンニトール	マンニトール	5−アー①			4	
74	コハク酸プレドニゾロンナトリウム	プレドニン注	5−アー①			2	
75	リン酸ベタメサゾンナトリウム	リンデロン(0.4%)注	5−アー①			2	
76	ベタメサゾン	リンデロン(0.01%)シロップ	5−アー①			2	
87	総合アミノ酸製剤	アミゼット B[注]アミゼット B:100 mL 中 L-イソロイシン 850 mg. L-ロイシン	5−アー①		プレアミン P	1	

1	Ⅷ因子製剤	コンファクトF	5−イ−①			4?	
2	Ⅸ因子製剤	ノバクトM	5−イ−①			4	
7	ⅩⅢ因子製剤	フィブロガミン	5−イ−①			3	
3	AT−Ⅲ	アンスロビン P、ノイアート	6−ア			3	
78	クロモグリク酸ナトリウム	インタール吸入液	6−ア			4	
79	腹膜透析用電解質液		6−ア			4	
86	総合アミノ酸製剤	アミパレン[注]アミパレン:100 mL 中 L−ロイシン 1.4 g. L−イソロイシン	6−ア			3	
88	脂肪乳剤	イントラファット・リポス・リピット	6−ア			1	
89	微量元素製剤	エレメンミック	6−ア			3	
90	リン酸一カリウム	コンクライトP	6−ア			4	
91	アスパラギン酸カリウム	アスパラK注	6−ア			5	
92	総合ビタミン剤	パンビタン	6−ア			4	
93	高カロリー輸液用総合ビタミン剤	ソービタ、マルタミン、ネオラミンマルチ	6−ア			4	
5	G-CSF	ノイトロジン、グラン	6−イ			3	
30	重炭酸ナトリウム	メイロン	6−イ			2	
40	トラゾリン塩酸	イミダリン注	6−イ		なし		

43	バルプロ酸ナトリウム	デパケン	6−イ			3	
53	フェニトイン	アレビアチン注	6−イ		ホストイン	3	てんかん重積状態
54	フェノバルビタール	フェノバール筋	6−イ			4	
56	フェノバルビタール	10%フェノバルビタール散	6−イ			4	
57	フェノバルビタールナトリウム	ワコビタール坐薬	6−イ			2	
65	ペントバルビタール	ネンブタール注射液	6−イ		なし		
66	抱水クロラール	エスクレ坐薬	6−イ			4	
69	ミルリノン	ミルリーラ注	6−イ			3	
70	メシル酸ガベキサート	FOY	6−イ			4	
71	メシル酸ナフォモスタット	フサン	6−イ			3	
77	アセタゾラミド	ダイアモックス注	6−イ			3	
81	抱水クロラール	抱水クロラール末	6−イ			4	
37	ドキサプラム	ドプラム	7		臨床試験	5	審査中
72	メフェナム酸	ポンタールシロップ	7			2	
6	NO	工業用一酸化窒素ガス	該当無し		アイノフロー	1	PPHN
10	アミノフィリン(静注)	アプニション注	承認			1	未熟児無呼吸発作
34	テオフィリン(経口)	アプネカット	承認			1	未熟児無呼吸発作
44	ビタミンK2メナテトレン製剤	ケイツーN	承認			1	ビタミンK欠乏性疾患予防

45	ビタミンK2メナテトレン製剤	ケイツーSyr	承認			1	ビタミンK欠乏性疾患予防
59	プロスタグランディンE1	注射用プロスタンディン20μg	承認			1	動脈管依存性疾患における動脈管開存
85	総合アミノ酸製剤	プレアミンP	承認			1	低蛋白血症時のアミノ酸補給

表２　H14 年度報告書　新生児汎用適応外使用の抗菌剤抗ウイルス剤 26 品目調査（H25 年度）

	薬品名	（2）必要性の分類	商品名（例示）	添付文書記載(2013)
1	アシクロビル	1. 他に治療法がない	ゾビラックス	1
2	アルベカシン	1. 他に治療法がない	ハベカシン	3
3	アルベカシン	6－a. 他の治療法がある、他の治療法の方が治療効果が優れている		
4	アンピシリン	1. 他に治療法がない	ビクシリン	1
5	アンフォテリシンB	1. 他に治療法がない	ファンギゾン	3
6	アンフォテリシンB	1. 他に治療法がない	（アンビゾーム）	3
7	イミペナム	2－a. 他に治療法がある、治療効果がこの治療法が優れている	チエナム	3
8	イミペナム	6－a. 他の治療法がある、他の治療法の方が治療効果が優れている		
9	エリスロマイシン	1. 他に治療法がない	エリスロシン	2
10	ゲンタマイシン（筋注）	6－a. 他の治療法がある、他の治療法の方が治療効果が優れている	ゲンタシン注	3
11	ゲンタマイシン〔静注）	1. 他に治療法がない		
12	セファゾリン	2－a. 他に治療法がある、治療効果がこの治療法が優れている	セファメジンα	3
13	セフォタキシムナトリウム	2－a. 他に治療法がある、治療効果がこの治療法が優れている	クラフォラン	3
14	セフスロジン	6－a. 他の治療法がある、他の治療法の方が治療効果が優れている	―	
15	セフメタゾール	1. 他に治療法がない	セフメタゾン	3*
16	ノルフロキサシン	7. 症例がいないため	バクシダール	3*

17	ノルフロキサシン	7. 症例がいないため		
18	パニペネム・ベタミプロン	1. 他に治療法がない	カルベニン	3
19	ピペラシリン	1. 他に治療法がない	ペントシリン(ゾシン)	3(3)
20	フルコナゾール	1. 他に治療法がない	ジフルカン	1
21	ホスホマイシン〔内服)	7. 症例がいないため	ホスミシン	4
22	ホスホマイシン	2－a. 他に治療法がある、治療効果がこの治療法が優れている	ホスミシン注	3
23	ミコナゾール	1. 他に治療法がない	フロリードF注	3
24	ムピロシンカルシウム	1. 他に治療法がない	バクトロバン鼻腔用	3
25	ガンシクロビル	1. 他に治療法がない	デノシン(バリキサ)(ホスカルネット)	3(3)(3)
26	ピリメタミン・サルファドキシン合剤	7. 症例がいないため	―	

表３　追加薬品リスト

No	*薬品名*	*商品名*	*医薬品集の記載（2003）* 注)	*添付文書の記載（2013）* 注)	*適応のない新生児での対象疾患*
1	アムリノン	カルトニック	3	3	急性心不全
2	アルプロスタジルアルファデクス	アピスタンディン	3	3	PPHN
3	安息香酸ナトリウム	局法		4	高アンモニア血症、OTC 欠損症など
4	ウルソデオキシコール酸	ウルソ顆粒　5%	4	4	胆汁うっ滞
5	塩化レボカルニチン	エルカルチン	3	4	プロピオン酸血症　メチルマロン酸血症
6	塩酸オルプリノン	コアテック	3	3	心不全、肺高血圧症
7	塩酸プロカインアミド	アミサリン	4	4	PSVT、頻脈性不整脈
8	塩酸ベラパミル	ワソラン	4	5	PSVT、頻脈性不整脈
9	塩酸メキシレチン	メキシチール	4	3	PSVT、頻脈性不整脈
10	塩酸モルヒネ	塩酸モルヒネ注射薬	4	2	鎮痛・鎮静
11	塩酸ラニチジン	ザンタック注	4	3	消化管出血
12	肝不全用アミノ酸	アミノレバン	3	3	肝不全
13	濃グリセリン・果糖	グリセオール	4	4	脳浮腫
14	グリセロリン酸カルシウム	グリセロリン酸カルシウム	4	4	低出生体重児
15	コハク酸メチル プレドニゾロンナトリウム	ソル・メドロール	4	4	
16	酢酸フレカイニド	タンボコール	3	3	頻脈性不整脈

17	ジアゾキサイド	ジアゾキサイド	輸入薬品	1	高インスリン血症による低血糖
18	ジクロロ酢酸ナトリウム	リバオール内服	試薬	4	高乳酸血症
19	ジソピラミド	リスモダン注	3	3	PSVT、頻脈性不整脈
20	硝酸イソソルビド	ニトロール注	4	3	心不全
21	セコバルビタールナトリウム	アイオナール・ナトリウム	4	2	鎮静に使用
22	フェニル酢酸ナトリウム	試薬		なし	高アンモニア血症
23	メシル酸フェントラミン	レギチーン	4	4	二次性高血圧
24	リン酸ピリドキサール	ピリドキサール	4	2	ビタミンB6欠乏症
25	50%糖液		4	4	低血糖が持続する時にミルクに入れて投与
26	塩化カリウム		4	4	K, Cl, Na の経口補充にミルクに入れて使用
27	塩化ナトリウム		4	4	K, Cl, Na の経口補充にミルクに入れて使用
28	アスパラK		5	5	内服で使用
29	硫酸銅	試薬			メンケス
30	硫酸マグネシウムブドウ糖	マグセント	4	4	PPHN, HIE
31	窒素（N2）	工業用？		なし	低酸素療法（肺血流量増加型の先天性心疾患）

アンケート報告者からの追加リスト (抗菌剤・抗ウイルス剤)

	薬品名	*商品名*	*医薬品集の記載 (2003)* 注)	*医薬品集の記載 (2013)* 注)	*適応のない新生児での対象疾患*
1	アンピシリンナトリウム・スルバクタムナトリウム	ユナシン	3	3	
2	塩酸セフォゾプラン	パンスポリン	3	3	
3	塩酸リンコマイシン	リンコシン	3	2.3	
4	セフォペラゾンナトリウム・スルバクタムナトリウム	スルペラゾン	3	3	
5	ベンジルペニシリンカリウム	結晶ペニシリンGカリウム	4	3	先天梅毒に静注で使用
6	メトロニダゾール	メトロニダゾール、フラジール	4	3	
7	メロペネム三水和物	メロペン	3	3	
8	塩化メチルロザニリン	ピオクタニン		?	皮膚カンジダ感染症

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

8 July 2012
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Human Medicines Development and Evaluation
Human Medicines Special Areas Sector

5-year Report to the European Commission

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

Prepared by the
European Medicines Agency with its Paediatric Committee

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Table of contents

1. Summary

The objective of the report is to present five years after the entry into force of the Paediatric Regulation, a factual analysis of data collected by the EU Member States and the EMA. The report aims at measuring the initial impact of the Paediatric Regulation in line with its objectives of achieving high-quality ethical paediatric clinical research, increasing availability of authorised medicines that are appropriate for children and producing better information on medicines.

- Paediatric research and development

The Paediatric Committee (PDCO) is responsible for the scientific evaluation of paediatric investigation plans (PIP), which is one of the main pillars of the Paediatric Regulation to foster paediatric research and development. The evaluation of PIPs was completed for 682 medicines up to the end of 2011. Among the opinions adopted, 476 were on the agreement of a PIP (70%) and 30% of a full waiver. Waivers indicate that the use of the medicine in the targeted condition was not of paediatric relevance or interest, or likely to be unsafe. Around 75% of PIPs were for medicines that were not yet authorised at the time of evaluation. All PIP and waiver opinions are made public.

The EMA/PDCO engaged in multiple interactions with external experts on scientific questions raised by paediatric development to improve the plans. The PDCO provided expertise to almost all EMA Scientific Advice / Protocol Assistance procedures addressing paediatric questions, i.e. about 70 per year. In total, about 150 companies benefited from Scientific Advice on paediatric questions, provided by either Member States directly or the EMA/CHMP.

New development approaches included in particular extrapolation of efficacy, required explicitly in 22% of PIPs to protect children against unnecessary trials. Simultaneously, the PDCO required studies in areas with historically no or only very limited paediatric research. Unfortunately, the submission of PIP and waiver proposals was delayed compared to the legal requirements; this did not improve over the years and represents missed opportunity for early regulatory dialogue.

Transparency of ongoing and planned paediatric research is another tool to avoid unnecessary replication of trials. The EudraCT database was developed to include protocol-related information of clinical trials, and this information was made publicly accessible in 2010 as mandated by the Paediatric Regulation. Paediatric trials that are part of an agreed PIP are increasingly visible in EudraCT, with 110 such trials authorised by the end of 2011 and already 21 more submitted for authorisation in 2012 (uploaded into EudraCT as of March 2012). Overall, the number of paediatric trials newly registered in EudraCT is at a constant level of about 350 per year since 2007, while the corresponding numbers of trials with adult participants decreased by about 6% per year from 2007 to 2011 (see limitation of data).

Trials with neonates represent high unmet needs and were requested wherever necessary by the PDCO, including in many cases where these would have been neglected in the past. However, studies with neonates are not necessary for all medicines or in all diseases; studies in this age group were required overall in about one third of the agreed PIPs. EudraCT provides information on temporarily halted or prematurely terminated trials with the paediatric population; monitoring of these situations did not indicate increased concerns on safety or efficacy during clinical trials since the entry into force of the Paediatric Regulation.

The development of 20 off-patent medicines for paediatric use in 15 projects was funded by the EU Framework programme, and the first 7 corresponding PIPs were agreed.

The European Network for Paediatric Research at the EMA (Enpr-EMA), established in 2009, has set up collaboration with 18 networks based on research quality criteria. Concerning support to research and

development, only some Member States have special provisions for paediatrics in addition to the general provisions for research.

- Medicines available to children

By the end of 2011, 29 PIPs (excluding duplicates) had been completed in compliance with the PDCO Decisions. After assessment of the results, the plans led to new paediatric indications (24 medicines) and to new pharmaceutical forms appropriate for children (7 medicines). However, data from 5 completed PIPs provided important information which did not support the use in children and this information was detailed in the Product Information for the benefit of health care professionals.

Between 2008 and 2012, 10 new medicinal products (new active substance) were centrally authorised and received a paediatric indication (out of 113 new active substances in total), under the requirements of the Paediatric Regulation. For 1 of the 10 products, a Paediatric Use Marketing Authorisation (PUMA) had been requested and was granted.

For medicines already authorised centrally or nationally, 18 and 12 respectively, received a new paediatric indication developed under the Paediatric Regulation between 2008 and 2012. Such new indications have increased since 2009, whereas new indications not linked to the Paediatric Regulation have decreased, as expected.

Regarding the development of pharmaceutical forms for use in children, the PIP propoals raised concerns in the majority of cases; issues were mostly related to excipients and/or to appropriateness of formulations to ensure their safe and acceptable use in children. The EMA/PDCO is monitoring how these issues are going to be addressed as well as how PIPs progress in practice.

Annual reports on deferred paediatric studies of authorised medicines indicate that the majority of PIPs are running as programmed. Paediatric research is ongoing at the same rate across therapeutic areas such as oncology, vaccines and immunology-rheumatology-transplantation as estimated by the first trial in agreed PIPs. As expected due to data acquired during medicine development, agreed PIPs need to be modified. The number of modifications of agreed PIPs per year, is about half of that of newly agreed PIPs for that year. The analysis of the reasons for modifications shows variability, for example time lines were changed by one year or less in about half of the modifications.

- Information on medicines and other outcomes

Information on the use of paediatric medicines was improved with the addition of new study data and new recommendations into the Summary of Product Characteristics (SmPC). Contrary to the assumption that very few paediatric data had ever been collected in the past, a huge number of paediatric study data were submitted by Marketing Authorisation Holders to competent authorities (Article 45 of the Paediatric Regulation). Results from more than 18,000 completed paediatric studies of about 1000 active substances have been submitted, including those published in the literature, and are undergoing assessment, in waves. For nationally authorised medicines, the assessment is co-ordinated by the CMD(h) and is ongoing for 248 active substances, prioritised according to the highest paediatric needs. By the end of 2011, the assessment of studies of 149 active substances had been completed, which resulted in 65 SmPC changes.

Rewards for completion of paediatric development in compliance with agreed PIPs are intended to compensate the work done by Marketing Authorisation Holders. By the end of 2011, National Patent Offices in 16 Member States had granted 6-month extensions of the Supplementary Protection Certificate to 11 medicines, resulting in a total of 105 national SPC extensions (not all medicines received the extension in every Member State), as per Article 36(1) of the Paediatric Regulation. In addition, one Paediatric Use Marketing Authorisation benefits from the 10-year protection.

As part of the implementation of the Paediatric Regulation the EMA engaged in projects with external stakeholders and international collaboration. As early as in 2007, a Paediatric Cluster was formed by the EMA and the FDA as part of the confidentiality arrangements. Up to the end of 2011, the cluster held 54 teleconferences, with exchange of information on paediatric development of common interest. Japan and Health Canada joined the teleconferences in 2009 and 2010 respectively. Further international partners of the EMA for the development of paediatric medicines, are the World Health Organization (WHO) with their initiative, Better Medicines for Children, and their Paediatric Medicines Regulators' Network (PmRN), and various academic groups. The EMA is also a partner in the Global Research in Paediatrics project (GRIP).

The EMA also engaged early in the implementation phase in interactions with trade associations and individual pharmaceutical companies (e.g. pre-submission meetings), in particular with Small and Medium Sized Enterprises, including through activities of the business pipeline.

- Conclusions

This report shows that the implementation has already had a positive impact in keeping with the main objectives of the Paediatric Regulation, and that paediatric development is increasing. Systematic paediatric development as set out in PIPs, and contribution to paediatric research and development by all stakeholders is leading to age-appropriate medicines and increasing paediatric information. In principle, PIP Decisions are in place for many authorised medicines that are relevant for children, but do not have a paediatric indication. Hopefully, long-standing gaps in knowledge will be filled in. Achieving the objectives of the Paediatric Regulation is a realistic goal based on the experience gathered so far, but sufficient time is needed as medicines development spans decades. Meanwhile, opportunities for improvement of the processes have been identified and are being addressed to increase the positive impact of the Paediatric Regulation and make medicines available with appropriate information to children.

Figure 1: Highlights of the impact of Paediatric Regulation after 5 years.

2006	2007-2011	End of 2011	Ongoing
Historical situation	**Activities driven by Paediatric Regulation**	**Achievements**	**Areas for improvements**
• Around 75% of all 317 centrally authorised medicines relevant for children, but only half (34%) with a paediatric indication	• Dramatic change with mandatory evaluation of potential paediatric use, for all new medicines and new indications • PDCO sees potential paediatric use in about 80% of medicines and agrees 476 PIPs • PDCO expertise contributes to EMA opinions on paediatric issues • Ongoing shared assessments by Member States of about 18,000 paediatric study reports	• Increasing number and proportion of paediatric trials conducted • PIPs completed for 29 active substances • Authorisation of 13 new medicines, 30 new indications and 9 new pharmaceutical forms for paediatric use, linked to PIPs • Rewards obtained for 12 medicines (SPC extensions for 11 medicines; 1 PUMA exclusivity) • Enpr-EMA established and operational	• Neglected therapeutic areas (e.g., paediatric oncology) • Missed regulatory dialogue opportunities (e.g., late PIP applications) • Simplified procedures; decreased level of details in PIPs • Support to applicants • Increased involvement of patients and learned societies

PIP: Paediatric investigation plan. PUMA: Paediatric Use Marketing Authorisation, SPC: Supplementary Protection Certificate. Enpr-EMA: European Network of Paediatric Research at the EMA.

2. Introduction

Regulation (EC) No. 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (hereinafter 'the Paediatric Regulation') was adopted on 12 December 2006. It was published in the Official Journal of the European Communities on 27 December 2006 and entered into force on 26 January 2007.

In 2013 the Commission has to present *to the European Parliament and the Council a general report on experience acquired as a result of the application of this Regulation (Article 50 (2) of the Paediatric Regulation).*

In order to support the Commission in drafting this report, a working group of the Paediatric Committee has prepared the present document together with the European Medicines Agency secretariat. The document discusses the achievements of the Paediatric Regulation from the view point of the EMA/PDCO. The working group members were: Daniel Brasseur, Maria Jesús Fernández Cortizo, Karl-Heinz Huemer, Dirk Mentzer, Marianne Orholm, Francesca Rocchi, Sylvie Benchetrit, Tsveta Schyns-Liharska, Anne-Sophie Henry-Eude, Ralf Herold and Franca Ligas.

The report includes indicators of activities and outcomes that were agreed in 2011 with the European Commission (list in Annex 12.). These indicators aim to capture the objectives of the Paediatric Regulation, i.e. encouraging ethical high quality paediatric research, making more medicines available to children and increasing information on paediatric medicines. The indicators are therefore presented in this sequence, going from research and development, to availability of medicines for children, to more information for use of medicines for children, complemented by a report on other projects and activities to supports applicants and reduce administrative burdens, and finally to lessons learned. The report includes examples and qualitative information on the impact of the Paediatric Regulation.

The report covers the period from January 2007 to December 2011 ("reporting period"). Data from previous years and data without the application of the Paediatric Regulation are provided as reference, where possible. Throughout the report, the term "children" refers to the whole paediatric population as defined in the Paediatric Regulation (from birth to less than 18 years of age), if not otherwise noted.

Various data sources were used for this report, including national surveys, datasheets of the CMD(h), various EMA business databases, the EudraCT databases as well as data collections of projects necessary to the implementation of the Paediatric Regulation. The surveys were conducted with the EU competent authorities and patent offices of the Member States, and their contributions to the implementation of the Paediatric Regulation and to the report are acknowledged.

As much as possible, the report refers to active substances, to summarise across marketing authorisations, duplicates and marketing authorisation holders (NB: the numbers of PDCO Opinions and EMA Decisions included about 13% duplicates). The report does not include data for generic, biosimilar, hybrid, homeopathic, traditional herbal and well-established medicinal products - which are excluded from the scope of the mandatory development - unless otherwise mentioned. Recitals and Articles refer to the Paediatric Regulation, if not otherwise stated.

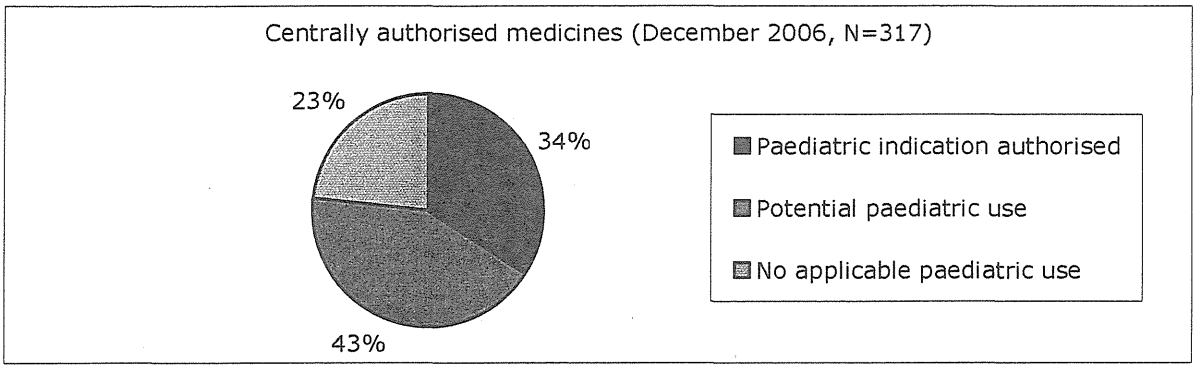
The report is limited by the variable quality of data; this is explained for each indicator.

3. Historical situation for medicines for children up until 2006 - achievements by end of 2011

At the time the Paediatric Regulation came into force (26 January 2007) in the European Union (EU), 50% or more of medicines used in children had never been studied in this population (Conroy et al. 2000), and not necessarily in the same indication or even the same disease in adults (for more details see document EMEA/17967/04 Rev 1 on EMA website).

By the end of 2006, paediatric clinical research was addressed by the guideline ICH E11, which came into force in 2002 following a previous EU guideline (1995). With respect to minors involved in research, the EU Clinical Trial Directive 2001/20/EC was adopted in 2001, transposed in 2004 and covered the research oversight and protection of clinical trials participants. A small number of EMA scientific guidelines (e.g., Addendum on Paediatric Oncology [CPMP/EWP/569/02] and Medicinal products in the treatment of Asthma [CPMP/EWP/2922/01]) explicitly called for paediatric medicines development.

Figure 2: Situation by December 2006: Proportion of medicines among the 317 centrally authorised medicines, for which a potential paediatric indication was identified, already authorised or not applicable in relation to the indication authorised for adults.



Source: EMA analysis of SmPCs in the authorised conditions.

Historically, few paediatric clinical trials which supported medicines development were submitted to regulatory authorities. Some paediatric therapeutic areas and subsets such as neonates were particularly neglected and paediatric clinical research infrequently contributed to medicines development. The lack of paediatric data resulting from the lack of trials on the use of medicines in children is the classical reason cited for the predominance of off-label use in children (e.g., Choonara 2000). There was also a lack of commercial interest into paediatric medicine development due to the length and perceived difficulty of studies, the small fragmented market and the ability to prescribe off-label adult medicines to children.

There was also a consequential lack of age-appropriate formulations. Paediatric health care professionals had to use at best magistral formulas and extemporaneous preparations, which have risks of their own, such as dosing inaccuracy or errors, excipient toxicity, and modified bioavailability and resulted in a higher frequency and seriousness of adverse reactions.

The information on medicines, in particular the Summary of product characteristics, did not systematically identify information relating to special populations such as children. For example, it was often not clear for paediatric health care professionals, whether a paediatric use was authorised, whether there were insufficient data or existing data showed negative effects of the medicine when used in children; often existing information was not even included (e.g., Boos 2003).

The Paediatric Regulation was necessary to make systematic evaluations of the potential paediatric use of medicines by a scientific expert committee, the Paediatric Committee (PDCO). The Committee was established to agree Paediatric Investigation Plans (PIP), deferrals and waivers. A PIP is a development plan aiming at generating the data necessary for a paediatric indication. A deferral allows postponing the initiation and/or the completion of the measures in the PIP so as not to delay the marketing authorisation in adults and to perform studies in children when it is safe to do so. A waiver of the paediatric development can be granted for all (full waiver) or subsets (partial waiver) of the paediatric population on the basis of the lack of efficacy or safety of the medicine, when the disease or condition only occurs in adults, or when the medicine does not have significant therapeutic benefit over existing therapies.

- Major milestones of the implementation of the Paediatric Regulation (summary)

The Paediatric Committee was established and held its first meeting on 1-2 July 2007. It has met monthly since then. Innovative transparency measures were set up and the outcome of the PDCO scientific evaluations of applications for PIPs and waivers were made public each month.

The European Commission Guideline on content and format of applications (2008/C 243/01) was published in September 2008.

Regulatory procedures and the scientific evaluation were set up at the EMA to implement the legal requirements. All were prepared on time, and the deliverables were released without delay..

For the coordination and prioritisation of assessment of paediatric trials completed before the Paediatric Regulation came into force, the Co-ordination Group for Mutual Recognition and Decentralised Procedures - (CMD(h)) set up work-sharing procedures and published the first outcomes in June 2009 (Article 45). Similar procedures for Article 45 and 46 were set up for CHMP in respect of centrally approved products at the same time.

The European Network for Paediatric Research at the EMA (Enpr-EMA) was set up following the adoption of the strategy in 2008 by the EMA Management Board, launched in 2009 and has met regularly since 2010.

The European Union Clinical Trials database (EudraCT) was modified and made publicly accessible (EU-CTR) in March 2011 for paediatric trials included in a PIP or submitted under Article 46. Interventional clinical trials are accessible as soon as the trial is authorised in a first EU Member State, or has received an unfavourable opinion of an Ethics committee. Paediatric trials included in a PIP but performed completely outside of the EU are also available. Since October 2011, the available results of studies submitted under Article 45 are publicly accessible in a separate database.

The results of the survey of all paediatric uses of medicinal products among all Member States in Europe were published in December 2010 (Article 42) and this is the foundation for the inventory of therapeutic needs (Article 43).

The EU funding of projects investigating off-patent medicinal products commenced in 2007 and funding was available every year since then (except in 2011). The EMA / PDCO have annually revised and published a priority list for studies into off-patent paediatric medicinal products to support the research proposals and their evaluation by the European Commission.

4. Better and safer research with children

This chapter reports on the activities and achievements linked to the Paediatric Regulation in terms of its first objective, which is, attaining and conducting better and safer research and development of medicinal products in children. The chapter covers indicators related to the frequency and extent of research and development as well as related to scientific quality and participant safety. Clinical research with children is necessary to develop and make safe and efficacious medicines available for that population.

4.1. Impact of the Paediatric Committee on paediatric development

A multidimensional programme is necessary for the development of better medicines for children, incorporating paediatric therapeutics into the overall development programme, where relevant. The number of PIP submissions and agreed opinions by the PDCO reflect the fulfilment of the legal requirements of the Regulation by the MAHs, i.e., to provide either the results of studies in compliance with an agreed PIP, or their deferral, or a waiver for such studies when filing for marketing authorisation or for certain authorisation variations/line extensions (Article 7 or 8 of the Paediatric Regulation).

EMA Decisions agreeing a PIP (476) represented 70% and EMA Decisions agreeing a full waiver (206) represented 30% of all 682 EMA Decisions by the end of 2011. This does not include modifications of agreed PIPs and negative opinions. At the time of PIP agreement, 356 (75%) of these EMA Decisions were for medicines that were not yet authorised in the EU (Article 7).

It should be noted that the time span between agreeing a PIP and granting a paediatric indication may be several years, taking into account the normal length of medicines development in adults, and considering the time needed for a parallel or deferred paediatric development. The progress of agreed PIPs is addressed in a later section (5.5.).

Whereas Figure 2 shows that only approximately 30% of medicines applied for and obtained a (single subset) paediatric indication before the Paediatric Regulation came into force, the present situation is the reverse, with approximately 70% of all PIPs evaluated by the PDCO proposing or being required to develop indications for the whole or some subsets of the paediatric population.

Table 1 shows the frequency with which paediatric therapeutic areas are addressed by agreed PIPs. Relatively few PIPs were submitted exclusively for the therapeutic area of neonatology, although this subpopulation is known to have the highest need for medicines development. In fact, the neonate is covered under each therapeutic area and about one in four agreed PIPs include specifically the neonatal subpopulation. This is reported in more detail in the following section.

Limitations: In addition to Table 1, Annex I section 15.1. presents the number of EMA Decisions by year and therapeutic area; in both tables, please note that a single PIP may address more than one therapeutic area and, consequently the sum across therapeutic areas may exceed the total number of EMA Decisions.

The relative frequencies of therapeutic areas cannot readily be compared with unmet paediatric therapeutic needs and priorities for medicines for paediatric use. Although the relative frequencies indicate that a reassuringly broad range of paediatric uses is addressed, the prominence of the areas endocrinology-gynaecology-fertility-metabolism and cardiovascular diseases may well be related to the prominence of medicines for such diseases developed in adults.

Table 1: Therapeutic areas addressed by the Paediatric Investigation Plans (PIPs) agreed by the PDCO (a PIP may be for more than one therapeutic area).

Therapeutic areas	Proportion of PIPs (%)
Endocrinology-Gynaecology-Fertility-Metabolism	11
Infectious Diseases	11
Oncology	11
Immunology-Rheumatology-Transplantation	9
Cardiovascular Diseases	8
Haematology-Haemostaseology	8
Vaccines	7
Dermatology	6
Neurology	5
Gastroenterology-Hepatology	5
Pneumology - Allergology*	4
Other	4
Oto-rhino-laryngology	3
Pain, Anaesthesiology	3
Uro-nephrology	3
Psychiatry	2
Neonatology** - Paediatric Intensive Care	2
Other	3

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

Future directions: The impact of the application of requirements of the Paediatric Regulation to medicines developed for adults will need to be further monitored. Section 5.7. offers preliminary reports on the correspondence between agreed PIPs and unmet paediatric needs, exemplified by the survey of all paediatric uses in the EU.

The figures do not predict the proportion of agreed PIPs that eventually progress to completion of the studies and submission of the results, nor whether an authorisation in children can be granted or not. Although attrition rates as high as 50% are cited for phase 3 of medicinal product development, such high rates may not apply to the PIPs agreed so far, because a sizeable proportion of PIP applications were made late in the overall development, or were for already authorised medicines (about 25%).

To understand better the impact of the PDCO on defining the required paediatric development as set out in PDCO opinions agreeing PIPs, the development approaches and characteristics of paediatric trials were compared systematically, analysing the applicants' proposals and the PDCO opinions, as well as the modifications requested by the PDCO during its evaluation to ensure the generation of the necessary data to establish a paediatric indication. Such information informs applicants on PDCO expectations, and allows better focus in the applications. To some extent, the PDCO has performed such analyses, and already published expectations in articles, guidelines and workshops.

4.2. Addressing unmet therapeutic needs: example of neonates

Whenever relevant, neonates should be included in the clinical development of a medicinal product in order to address their unmet therapeutic needs. Neonates present additional challenges compared to older paediatric age subsets, because they are the most vulnerable population, with the highest dependency on others to respect ethical principles, and because of specific disease characteristics affecting the neonatal population.