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11. Glossary/Abbreviations

- Age groups: newborns: from birth to 28 days of age, infants: from 1 month to less than 12 months, toddlers: from 1 year to less than 2 years of age, children: from 2 years to less than 12 years, adolescents: from 12 years to less than 18 years (see also "Paediatric population" below, reference: ICH E11)
- CT: clinical trial as defined in Directive 2001/20/EC
- EudraCT: European Union drug regulating authorities' clinical trials database. Public access is via the "EU Clinical Trials Register", https://www.clinicaltrialsregister.eu/
- EuTCT: European Union Telematics Controlled Terms System, http://eutct.ema.europa.eu/
- Paediatric population: the population aged between birth and 18 years (Article 2.1)
- PUMA: Paediatric use marketing authorisation, with Article 30 of Regulation (EC) 1901/2006 in conjunction with Article 8(3) of Directive 2001/83/EC, as amended, as the legal basis for the marketing authorisation
- SmPC: Summary of Product Characteristics. In case of variations of the SmPC, new paediatric data are to be reflected in SmPC section(s) 4.5, 4.8, 5.1 and / or 5.2. Recommendations in relation to any paediatric use are in section(s) 4.1, 4.2 and / or 4.4. The SmPC has the following sections:
  - Section 4.1 Indication(s)
  - Section 4.2 Posology and method of administration
  - Section 4.4 Special warnings and precaution for use
  - Section 4.5 Interactions
  - Section 4.8 Undesirable effects
  - Section 5.1 Pharmacodynamics properties
  - Section 5.2 Pharmacokinetic properties
- US BPCA and PREA legislation: Best Pharmaceuticals for Children Act and Pediatric Research Equity Act

12. Indicators used for this report

The following indicators were agreed in 2011 with the European Commission.

12.1. Better and safer research and development

1. Number of Clinical trials (CTs):
    1.1. requested by the PDCO as a result of the assessment of a PIP and that were not initially proposed in the PIP at the time of submission
    1.2. suppressed from the PIP upon request from PDCO
2. Number of juvenile toxicity studies requested by the PDCO as a result of the assessment of a PIP and that were not initially proposed in the PIP at the time of submission / number of juvenile toxicity studies suppressed from the PIP upon request from PDCO
3. Decrease in number of children to be included in CTs upon request from PDCO further to the assessment of PIP
4. Number of scientific advices given at National and EMA level for paediatric use only, or for paediatric and adult use
5. Comparison between 2010 and 2011 to see if PIP are submitted earlier in the development
6. List of funding at National level and at EU level (DG Research)
7. Development of the paediatric network according to Article 44 of the paediatric regulation
8. Number of publications and workshops on paediatric aspects published by the EMA / EMA staff
9. EudraCT: number of CTs stopped and reason, number of CTs conducted in EU or outside of EU

12.2. More medicines available for children in the EU

1. Number of new products authorised, with Paediatric indication only or paediatric and adult indication
2. Number of variations to extend the therapeutic indication to include paediatric population
3. Number of article 29 referrals to extend the therapeutic indication to include paediatric population
4. Number of PIPs for a later PUMA agreed
5. Number of annex II procedure to add a new paediatric pharmaceutical form or a new route of administration for children
6. Number of products with new paediatric information in the dosage recommendation section of the SmPC (section 4.2)
7. List of medicines available for children as prepared according to Article 42 of the paediatric regulation
8. List of therapeutic needs for children as prepared according to Article 43 of the paediatric regulation. A link between these identified therapeutic needs and new paediatric indications granted could be done in the report.
9. Off label use could be investigated liaising with Member States, academia.

12.3. More information on children in the SmPC

1. Number of statements on deferrals and waivers included in the SmPC
2. Number of variations leading to additional information on paediatric population in SmPC including and identifying number of Article 45 and 46 of the paediatric regulation leading to a change in the SmPC
3. Number of assessments according to of Article 45 and 46 of the paediatric regulation performed even if not leading to changes in the SmPC

- Number of failure to show any paediatric indication according to Article 36 of the paediatric regulation that leads to information added in the SmPC

13. Description of methods and data sources for the report

Unless stated otherwise, data on Paediatric investigation plans (PIPs) and waivers refer to EMA Decisions, excluding withdrawn applications or prematurely terminated procedures for agreement of a PIP and / or a waiver. Modifications of PIPs do not count as another EMA Decision. Data on PIPs and waivers are presented by the year of the PDCO opinion. In principle, there is one EMA Decision for one PDCO opinion on one application for agreement of a PIP and / or waiver. The number of EMA Decisions, however, is higher than the number of different active substances, because duplicate applications can be made for the same active substance. Separate applications were also made, for example, for conditions that were and those that were not orphan designated. Second and subsequent applications account for only 13% of all EMA Decisions. Therefore the report uses the number of all applications and EMA Decisions as denominator, recognising this may change in future reports.

Some analyses specially consider or exclude 118 "allergen products" (allergen extract products for the specific immunotherapy of allergic rhinitis and rhinoconjunctivitis), for which a high number of applications were handled in 2009 and 2010 subsequent to a change of pharmaceutical law in a Member State (Germany) (see Eichler and Soriano, 2011, and http://bit.ly/znsbX8).

The survey queries to Member States and National Patent Offices are provided in the annexes.

Data from EudraCT are based on data submitted in the Clinical Trial Authorisation (CTA) application form (EudraLex Vol. 10, Chapter I, http://bit.ly/b54eUC), fields A.7, E.7, F.1.1.2 to F.1.3, F.4.

14. Additional data: Historical situation for medicines for children by 2006

Figure 4: Case example on lack of availability of centrally authorised medicines for paediatric oncology

Through the centralised procedure, 29 new anti-cancer medicines were authorised between December 2000 and January 2007, for the treatment of 21 different diseases.

- For the 7 of the diseases that occur in adults and children, 6 out of the 7 medicines have a paediatric indication.
- 18 out of the 23 medicines without a paediatric indication have a paediatric interest, based on a clinical or strong biological and / or non-clinical rationale, and should be evaluated in the paediatric population.

Source: modified from (Vassal 2009)

15. Additional data: Better and safer research with children

15.1. Number of agreed PIPs

Table 13: Number of agreed PIPs addressing therapeutic areas

Therapeutic area addressed	2008	2009	2010	2011	Sum
Infectious Diseases	4	22	29	33	88
Endocrinology-Gynaecology-Fertility-Metabolism	4	23	21	32	80
Immunology-Rheumatology-Transplantation	4	19	26	28	77
Oncology	6	17	12	33	68
Vaccines	4	18	21	21	64
Pneumology-Allergology	3	10	108*	35*	156
Cardiovascular Diseases	7	16	11	20	54
Haematology-Haemostaseology	1	7	19	24	51
Dermatology	1	9	16	13	39
Neurology	3	6	11	15	35
Gastroenterology-Hepatology	5	4	14	10	33
Psychiatry	2	4	4	10	20
Pain	1	11	2	5	19
Uro-nephrology		3	7	8	18
Other	1	4	10	5	19
Oto-rhino-laryngology		2	1	10	13
Ophthalmology	1	4	4	3	12
"Neonatology"** - Paediatric Intensive Care		2	3	3	8
Diagnostic use		2		3	5

Source: EMA Paediatric Business database using query. * Including 118 allergen products (Eichler and Soriano 2011) ** Applications that specifically address a use in neonates or in paediatric intensive care, only; PIPs agreed for other therapeutic areas however may also include neonates in the development.

15.2. Scientific advice

Summary of Scientific Advices provided by the MEA:

- Questions related to paediatric development were addressed in 133 EMA Scientific Advice procedures (including follow-up advices and Protocol Assistance). Number of such advices per year: 21 (2007), 23 (2008), 30 (2009), 32 (2010) and 27 (2011)
- Approximately 70 companies benefited from the European Medicines Agency free paediatric Scientific Advice during the years 2007 through 2011. Out of the 133 advices, 24 were obtained by a small, micro or medium-sized enterprise (SME) company.

In Table 14, the phases of the clinical development may refer to the stage of the adult development, even if the majority of paediatric related SAs were for paediatric-only questions, because almost all of the advices were for medicines developed for both adult and paediatric use.

It appears that advice is asked increasingly later during the development, which could be speculated to be the result of the PDCO evaluation of a proposed PIP taking place earlier in the overall development.

Table 14: Scientific advices (SA) and Protocol Assistances (PA) provided by the EMA SAWP per year

Number	2006	2007	2008	2009	2010	2011
Reference: Scientific advices in total	201	214	265	311	332	355
Reference: Protocol assistance in total	58	73	56	77	68	78
Reference: Sum of above	259	277	321	388	400	433
Paediatric only, SA	NA	14	13	14	19	21
Paediatric only, FU SA	NA	4	5	9	4	2
Paediatric only, PA	NA	0	5	4	6	3
Paediatric only, FU PA	NA	3	0	3	3	1
"Mixed" (Paediatric and adult), SA	NA	NA	6	21	25	12
Mixed, FU SA	NA	NA	1	8	6	7
Mixed, PA	NA	NA	1	12	12	7
Mixed, FU PA	NA	NA	1	3	5	4
Sum of paediatric-only and mixed advices and follow-up advices	NA	21	32	74	80	57
Paediatric quality issues	ND	7	7	7	13	6
Paediatric pre-clinical issues	ND	15	12	22	16	13
"Paediatric population" issue in development	ND	17	20	21	27	23
Paediatric only, SA+FU+PA+FU, Phase I	NA	3	7	4	8	1
Paediatric only, SA+FU+PA+FU, Phase II	NA	4	10	9	11	5
Paediatric only, SA+FU+PA+FU, Phase III	NA	9	15	15	14	10
Paediatric only, SA+FU+PA+FU, Phase IV	NA	0	1	2	5	0

Source: EMA Scientific Advice database. ND = Not documented

15.3. Guidelines

Summary:

- The PDCO contributed to the development and publication of 12 guidelines
- Some guidelines already included sections that specifically addressed the development for use in children; for others, the PDCO developed paediatric addenda to address the recommendations for paediatric development

Table 15: EMA Guidelines in which the PDCO was involved

Publication date	Title	Document reference
22/01/2009	Requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD) in adults and for use in the treatment of asthma in children and adolescents	CPMP/EWP/4151/00 Rev. 1
25/06/2009	Guideline on the Investigation of medicinal products in the term and preterm neonate	
01/11/2009	Guideline on the Clinical Development of Medicinal Products for the Treatment of Cystic Fibrosis	CHMP/EWP/9147/08
01/01/2010	Addendum to the note for guidance on evaluation of medicinal products indicated for treatment of bacterial infections to specifically address the clinical development of new agents to treat disease due to Mycobacterium tuberculosis	CHMP/EWP/14377/08
01/01/2010	Guideline: Reflection Paper On Ethanol Content In Herbal Medicinal Products	EMA/HMPC/85114/2008
01/01/2010	Clinical investigation of medicinal products in the treatment of epileptic disorders	CPMP/EWP/566/1998 Rev. 2 Corrigendum
01/03/2010	Guideline on Alcohol Dependence after public consultation as well as an overview of the comments on this GL	CHMP/EWP/20097/2008
01/07/2010	Clinical investigation of medicinal products for the treatment of attention-deficit/hyperactivity disorder (ADHD)	CHMP/EWP/431734/2008
01/02/2011	Guideline on medicinal products for the treatment of insomnia	EMA/CHMP/16274/2009
01/08/2011	Guideline on clinical investigation of recombinant and human plasma-derived factor IX products	CHMP/BPWP/144552/09
01/08/2011	Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products	CHMP/BPWP/144533/09
01/08/2011	Guideline on the treatment of Premenstrual Dysphoric Disorder	EMA/CHMP/607022/2009

Publication date	Title	Document reference
01/09/2011	Reflection paper on the necessity of initiatives to stimulate the conduct of clinical studies with herbal medicinal products in the paediatric population	EMA/HMPC/833398/2009
01/02/2012	Paediatric addendum to the CHMP guideline on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension	CHMP/EWP/213972/10

15.4. Clinical trials with the paediatric population

Table 16: Overview of clinical trials with the paediatric population by year of authorisation (or, if not available, by the year of upload of the protocol-related data into EudraCT)

Number of	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**
Paediatric trials (trials with the paediatric population)	251	310	354	340	402	374	302
Paediatric trials planned as							
◦ Phase 1	17	18	23	25	30	50	28
◦ Phase 2-4	227	286	336	310	365	324	281
◦ Controlled (various types of control)	186	226	250	240	268	244	189
◦ Active controlled	40	33	56	59	60	85	42
◦ Placebo controlled / placebo use	85	92	103	107	117	93	91
Paediatric trials planned to be conducted							
◦ in EEA only	171	220	229	243	271	232	169
◦ in and outside of EEA	80	90	125	97	131	142	133
◦ only outside of EEA					1		
Reference: All trials (adults, elderly and / or children)	3314	3912	4734	4495	4412	4002	3488

Source: EudraCT using pre-defined query counting the first authorised trial only, in case of conduct in more than one Member State. Data were uploaded by the National Competent Authorities.

It was assumed that the extraordinary high number of adult participants planned to be enrolled (Table 6) could correspond to large post-authorisation (Phase 4) trials and pharmaco-epidemiological studies that were uploaded into EudraCT, but may not have required authorisation. The following table has been created excluding all entries in EudraCT that were only marked as "phase 4" trials.

Table 17: Number of subjects planned to be enrolled in clinical trials registered in EudraCT. As Table 6, but excluding trials marked as "phase4" only.

Number of subjects	2005	2006	2007	2008	2009	2010	2011	2012
Preterm newborns					22		1,059	
Newborns			98		59	6	184	24
Infants and toddlers	13	330	98	15	54,560	1,847	7,629	1,390
Children	163	1,810	248	178	869	845	14,203	1,379
Adolescents	183	50	85	129	1,449	1,276	14,964	810
Sum of above	**359**	**2,190**	**529**	**322**	**56,959**	**3,974**	**38,039**	**3,603**
Reference: in utero			98				210	
Reference: adults including elderly	5,003	9,834	49,642	14,555	85,298	98,116	408,396	56,877

15.5. Analysis of clinical trials with the neonatal population in applications and PDCO opinions agreeing paediatric investigation plans

Material and methods: A retrospective analysis of the opinions for Paediatric Investigation Plans (PIPs) adopted by the PDCO from 2007 until end of 2011 (first opinion adopted in January 2008), was performed.

Opinions represent complete data sets without missing data. Applications withdrawn before opinion were not included in the analysis of outcomes. Applications which failed the validation step were not included in the analysis. Duplicates of medicines share a single development, therefore in these cases a single PIP was considered in our analysis. As the opinion is produced several months after the application, the starting date for the analysis of opinions was 23 January 2008, including the very first opinions adopted under this legislation, seven months after the establishment of the Paediatric Committee; the cut-off date is 31 December 2011.

We analysed, to which extent the neonatal age group was covered in agreed PIPs. It was analysed for how many PIP-opinions the PDCO had requested the inclusion of neonates in the clinical development programme where initially the applicants had requested a waiver for that age group. It was analysed which types of studies the PDCO asked that neonates were investigated in. In particular it was looked at, which types of studies neonates were asked to be enrolled in, when initially a waiver for that age group had been requested.

In addition, a closer look was taken at more specific clinical trial parameters proposed to and requested by the PDCO for the procedures that reached an opinion during the first 10 months between 23 January 2008 and 17 October 2008 and during the latest 10 months between March 2011 and December 2011. The content of scientific opinions adopted by the Paediatric Committee was compared to the proposals submitted by industry. We analysed the changes in the age groups to be included, changes to the need for randomisation, changes to blinding, and inclusion of an active or a placebo comparator.

First, global results are presented in section 4.2. of the core report.

Table 18: Sum of number of studies with neonates required in PDCO opinions per year of opinion, presented by type of study for PIP applications proposing a study or a waiver for neonates. A PDCO opinion can have more than one study with neonates.

Number of types of studies with neonates required in PDCO opinions	**Sum**
PK (PD) and tolerability studies	
• application proposed any neonate study	34
• application proposed waiver for neonates	24
Controlled safety and efficacy studies	
• application proposed any neonate study	32
• application proposed waiver for neonates	15
Non-controlled safety and activity studies	
• application proposed any neonate study	15
• application proposed waiver for neonates	9

Table 19: Jan-Oct 2008: Age groups which were covered by PIP applications, additionally requested by the PDCO and eventually covered in PDCO opinions (adapted from Olski et al., 2011 REF)

Age group	Covered in PIP application	Additionally requested by PDCO	Covered in PDCO opinion
12 to less than 18 years	76% (41/54)	7¥	81% (44/54)
6 to less than 12 years	67% (36/54)	7	74% (40/54)
2 to less than 6 years	46% (25/54)	5	54% (29/54)
Subset of 2 to less than 6 years	9% (5/54)	3	13% (7/54)
28 days to less than 2 years	28% (15/54)	7*	35% (19/54)
Subset of 28 days to less than 2 year	17% (9/54)	3	17% (9/54)
Birth to less than 28 days	15% (8/54)	7	26% (14/54)

¥ in 1 PIP, the PDCO requested to cover the entire age group instead of only a subset of the age group
* in 3 PIP, the PDCO requested to cover the entire age group instead of only a subset of the age group

Table 20: Mar-Dec 2011: Age groups which were covered by PIP applications, additionally requested by the PDCO and eventually covered in PDCO opinions

Age group	Covered in PIP application	Additionally requested by PDCO	Covered in PDCO opinion
12 to less than 18 years	79% (65/82)	2	80% (66/82)
6 to less than 12 years	87% (71/82)	5	93% (76/82)
2 to less than 6 years	87% (62/82)	4	80% (66/82)
28 days to less than 2 years	44% (36/82)	7	50% (41/82)
Birth to less than 28 days	24% (20/82)	6	32% (26/82)

When initially a study comprised the neonatal age group as part of a larger trial that encompassed many age groups, the request for modification by the PDCO could have resulted in a separation of the trial and the request for a trial specifically for the neonatal age range. This could not be analysed specifically. However, based on the data collected, an attempt was made to estimate in how many cases the neonatal age group was part of a larger trial encompassing older patients and in how many cases separate trials for neonates exclusively were part of the opinion. This data was retrieved for analysis also subdivided by size of the trial.

However, as a qualitative finding, there were a number of medicine developments for which the PDCO required to study neonates separately from older children, in an additional study exclusively for neonates, even though the PIP application proposed to study these age groups together in a single study.

For the number of newborns that were requested per study, there is no apparent pattern that they were enrolled particularly in large or small trials when looking at the entire time span 2008-2011.

There is also no clear trend towards inclusion into larger or smaller trials, when looking at PIP-opinions where a waiver initially requested for newborns.

Study design features such as blinding and type of control were compared between PIP proposals by applicants and PDCO opinions, analysing all age groups during the same time periods used in the preceding section (Jan-Oct 2008 and Mar-Dec 2011).

The requests of the PDCO appear to remain consistent over time, however with a slight decrease in active-controlled trials during the last 10 months compared to the first 10 months, including 2 dose-comparative parallel-group trials.

Table 21: Jan-Oct 2008: Number of trials for specific design features as proposed by the applicants and as additionally required in PDCO opinion (Olski et al. EJCP, 2011 REF)

Number of trials	Proposed by applicant	Additionally required in PDCO opinion	Sum
Double-blind	33 (53%)	11 (47.8%)	44 (52%)
Placebo control	12 (19%)	12 (52.2%)	24 (28%)
Active control	35 (57%)	6 (26.1%)	41 (48%)
Active and placebo control	4 (7%)	0	4 (5%)
Sum	62 (100%)	23 (100%)	85 (100%)

Table 22: Mar-Dec 2011: Number of trials for specific design features as proposed by the applicants and as additionally required in PDCO opinion

Number of trials	Proposed by applicant	Additionally required in PDCO opinion	Sum
Double-blind	70 (34%)	9 (15%)	79 (32%)
Blinded	86 (42%)	22 (36%)	101 (41%)
Placebo control	55 (27%)	10 (16%)	65 (27%)
Active control	38 (18%)	11 (18%)	50 (20%)
Active and placebo control	3 (1%)	2 (1%)	5 (2%)
Sum	207 (100%)	61 (100%)	245 (100%)

However, when following the number of neonates included in trials over the last 4 years, there appears to be a trend from 2008 towards 2011 of including a larger number of newborns in trials, in particular, when looking at the number of neonates included in 2011.

Is the increased number of newborns enrolled especially in 2011 a result of proposals by applicants or a result of requests from the PDCO? The detailed analysis of applications vs. opinions in 2011 (Mar-Dec) supports the notion that the PDCO's requests to companies played a significant part in enrolling more newborns in larger trials. The PDCO increased the number of trials with more than 100 neonates from 5 to 7. It increased the number of trials with 11 to 50 neonates from 0 to 3.

Table 23: Number of newborns included in studies as proposed and agreed by the PDCO (from Mar-Dec 2011). The values for the number of neonates are separated depending on how the age range was specified in the opinion

	0-28 days	0-2 yrs*	0-6 yrs*	0-12 yrs*	0-18 yrs*
As proposed by applicants					
1-10 patients	0	1*	2*	0	0
11-20 patients	0	3*	6*	2*	0
21-50 patients	0	2*	4*	0	2*
51-100 patients	0	0*	0	2*	0
> 100 patients	5	0*	0	0	4*
In opinions agreed by PDCO					
1-10 patients	0	3*	1*	0	0
11-20 patients	1	3*	7*	0	1*
21-50 patients	2	1*	7*	0	2*
51-100 patients	0	0	0	0	1*
> 100 patients	7	0	0	0	5*

*: These fields contain more than just the neonatal age group, as a broader age range was specified in the opinion.

15.6. List of projects on off patent medicines funded by the European Commission through the EU Framework programme

Health: area 4.2 results, Off-patent medicines calls 2, 3, 4 and 5.

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

Table 24: Funded off patent medicines projects (start up to 01 January 2012) and agreed PIPs, if available. Information on the projects is available on this web page: http://bit.ly/wUPuOb. Agreed PIPs for active substances addressed in projects are available via this web page: http://bit.ly/xTshyn.

No.	Acronym	Year start	Objectives (active substance[s] in bold)	Agreed PIP
1	KIEKIDS	2011	To develop an innovative, age-adapted, flexible and safe paediatric formulation of **ethosuximide** for the treatment of absence and of myoclonic epilepsies in children	NA
2	NEO-CIRC	2011	To provide safety and efficacy data for **dobutamine**, to perform pre-clinical studies, to develop biomarker of hypotension and to adapt a formulation for newborns	NA
3	TAIN	2011	To develop a neonatal formulation of **hydrocortisone** for the treatment of congenital and acquired adrenal insufficiency and for use in oncology (brain tumours and leukaemia)	NA
4	DEEP	2010	To evaluate PK & PD of **deferiprone** in in 2-10 years old children in order to produce an approved Paediatric Investigational Plan to be used for regulatory purposes	EMEA-001126-PIP01-10
5	HIP Trial	2010	Evaluates the efficacy safety, PK, PD of **adrenaline** and **dopamine** in the management of neonatal hypotension in premature babies and to develop and adapt a formulation of both suitable for newborns in order to apply for a Paediatric Use Marketing Authorisation (PUMA)	EMEA-001105-PIP01-10
6	TINN2	2010	To evaluate PK & PD of **azithromycin** against urea plasma and in BPD in neonates.	NA
7	NEMO	2009	Evaluates the efficacy safety, PK, PD, mechanisms of action of **bumetanide** in neonatal seizures, including the effect on neurodevelopment and to develop and adapt a bumetanide formulation suitable for newborns in order to apply for a Paediatric Use Marketing Authorisation (PUMA).	NA
8	NeoMero	2009	European multicentre network to evaluate pharmacokinetics, safety and efficacy of **meropenem** in neonatal sepsis and meningitis	EMEA-000898-PIP01-10
9	PERS	2009	Focuses on two indications, the use of **risperidone** in children and adolescents with conduct disorder who are not mentally retarded, and the use of risperidone in adolescents with schizophrenia	EMEA-001034-PIP01-10
10	EPOC	2008	To evaluate pharmacokinetics and pharmacodynamics of	NA

No.	Acronym	Year start	Objectives (active substance[s] in bold)	Agreed PIP
			doxorubicin	
11	LOULLA & PHILLA	2008	Development of oral liquid formulations of **methotrexate** and 6-**mercaptopurine** for paediatric acute lymphoblastic leukaemia (ALL).	NA / NA
12	NeoOpioid	2008	Compares **morphine** and **fentanyl** in pain relief in pre-term infants	EMEA-000712-PIP01-09
13	NEUROSIS	2008	Efficacy of **budesonide** (BS) in reducing bronchopulmonary dysplasia (BPD)	EMEA-001120-PIP01-10
14	O3K	2008	Oral liquid formulations of **cyclophosphamide** and **temozolomide**	EMEA-000530-PIP02-11 / NA
15	TINN	2008	Aims to evaluate PK & PD of **ciprofloxacin** and **fluconazole** in neonates	NA

NA = Not available

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

Table 25: Investigator-driven clinical trials of off-patent antibiotics

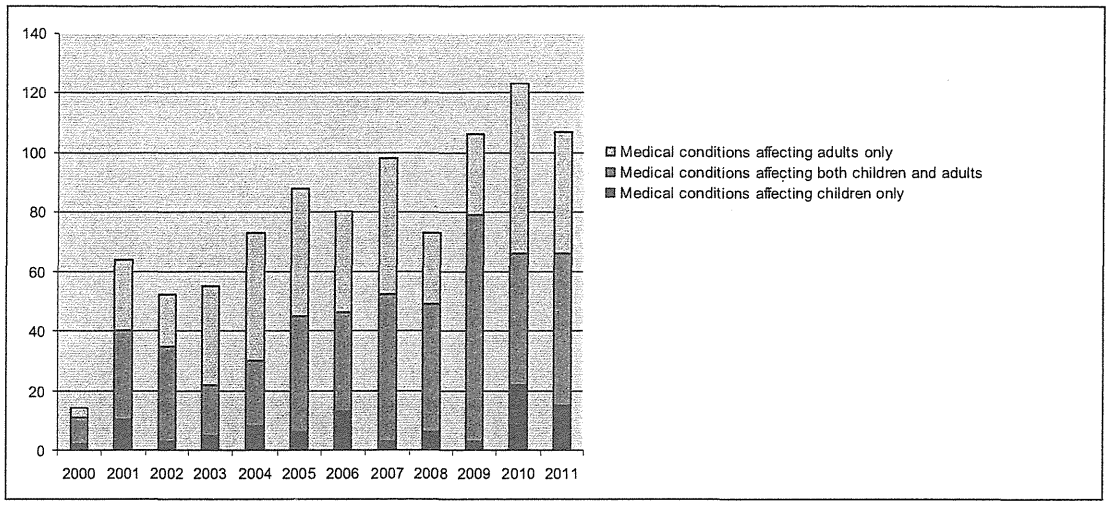
No.	Acronym	Year start	Objectives (active substance[s] in bold)	Agreed PIP
1	MAGICBULLET	2012	Optimisation of treatment with off-patent antimicrobial agents of ventilator-associated pneumonia (VAP)	NA
2	AIDA	2011	Assessment of clinical efficacy by a pharmacokinetic / pharmacodynamic approach to optimise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

NA = Not available

16. Additional data: More medicines available for children in the EU

16.1. Orphan medicine designation for paediatric uses

Figure 5: Total number of orphan designated medicines by year



16.2. Paediatric medicine development in PIPs correlated with survey of all paediatric uses

Table 26: Therapeutic needs in the paediatric population according to the Survey of all paediatric uses (EMA/794083/2009) and projects addressing the needs

Paediatric therapeutic area	Paediatric use	Active substance / class of substances	Addressed by (FP6, FP7, PIP etc.)	Comments
Infectious diseases	Treatment of bacterial infections in very young children	• Macrolides • Betalactamines plus beta-lactamase inhibitors • Carbapenems	• No PIP • No PIP • Doripenem (EMEA-000015-PIP01-07)	PIPs agreed for quinolones
Cardiovascular diseases	Treatment of hypertension (primary and seconddary)	• Renin-angiotensin inhibitors • Beta-blocker	• Aliskiren (EMEA-000362-PIP01-08), Alizisartan (EMEA-000237-PIP01-08), Candesartan (EMEA-000023-PIP01-07) • No PIP	
Cardiovascular diseases	Treatment of arrhythmia	• Antiarrhythmics	• No PIP	
Gastroenterology	Treatment of reflux disease	• Proton pump inhibitors • H2-receptor antagonists	• Rabeprazole (EMEA-000055-PIP01-07), esmeprazole (EMEA-000331-	

Paediatric therapeutic area	Paediatric use	Active substance / class of substances	Addressed by (FP6, FP7, PIP etc.)	Comments
			PIP01-08) • No PIP	
Pulmonology / respiratory medicine	Treatment of asthma	• Antiasthmatics (including montelukast, salbutamol)	• Montelukast (EMEA-000012-PIP01-07) • Tulobuterol (EMEA-000763-PIP01-09)	PIPs agreed for long acting beta agonists
Psychiatry	Treatment of depressive disorder	• Selective serotonin reuptake inhibitors • Serotonin-norepinephrine reuptake inhibitors • Tricyclic antidepressants	• No PIP • Desvenlafaxine (EMEA-000523-PIP01-08, waiver) • No PIP	Others: LUAA21004 (EMEA-000455-PIP02-10)
Dermatology	Treatment of atopic eczema	• Glucocorticosteroids, topical use	• No PIP	
Endocrinology	Prevention of pregnancy	• Oral contraceptives	9 unique PIPs agreed (EMEA-000148-PIP01-07, EMEA-000305-PIP01-08, EMEA-000475-PIP01-08, EMEA-000474-PIP01-08, EMEA-000250-PIP01-08-M01, EMEA-000518-PIP01-08, EMEA-000526-PIP01-08, EMEA-000546-PIP01-09, EMEA-000606-PIP01-09, EMEA-000658-PIP01-09, EMEA-000305-PIP01-08-M01, EMEA-000250-PIP01-08-M02, EMEA-000305-PIP01-08-M02)	
Endocrinology	Various uses	• Dexamethasone, systemic use	• No PIP	
Endocrinology	Not specified	• Multivitamin preparations	• No PIP	