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Annex

10-year Report to the European Commission

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1. New medicines for children

1.1. New medicines, new indications and new pharmaceutical forms

1.1.1. Centrally authorised medicines

New medicines

- Eighty-nine new medicinal products were centrally authorised from 2007 to 2015 with a paediatric indication at the time of the initial marketing authorisation. Forty-nine of these were linked to the Paediatric Regulation.
- Out of these medicines, ten were authorised for use in the paediatric population only.

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

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

[1] Adult and paediatric

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

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

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

Source: EMA database (SIAMED)

New paediatric indications

- Eighty-five new paediatric indications for already authorised products were approved from 2007 to 2015. Sixty-four of these were linked to the Paediatric Regulation.

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

Year	Active substance (INN)	Trade name	Subject of extension	MAH
2007	Levetiracetam	Keppra	Extension of the indication to include adjunctive therapy in the treatment of primary generalised tonic-clonic (PGTC) seizures in adults and adolescents from 12 years of age with idiopathic generalized epilepsy	UCB Pharma SA
2007	Pneumococcal saccharide conjugated vaccine, adsorbed	Prevenar	Extension of the indication to include new information on efficacy against disease caused by Streptococcus pneumoniae serotypes 4, 6B, 9V, 14, 18C, 19F and 23F in otitis media.	Wyeth Lederle Vaccines S.A.
2007	Pneumococcal saccharide conjugated vaccine, adsorbed	Prevenar	Extension of indication from active immunisation against bacteraemic pneumonia to active immunisation against pneumonia.	Wyeth Lederle Vaccines S.A.
2007	Infliximab	Remicade	Extension of indication to include treatment of severe active Crohn's disease in children aged 6 to 17 years.	Janssen Biologics B.V.
2007	Darbepoetin alfa	Aranesp	Extension of indication for CRF patients, which currently restricts the use of Nespo to paediatric subjects >/= 11 years of age	Amgen Europe B.V.
2007	Fosamprenavir	Telzir	Extension of indication of Telzir in combination with ritonavir for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults in combination with other antiretroviral medicinal products to include paediatric populations.	ViiV Healthcare UK Limited
2007	Lamivudine / zidovudine	Combivir	Extension of indication to include paediatric patients and replacement of film coated tablets by scored film coated tablets.	ViiV Healthcare UK Limited
2008	Desloratadine	Aerius	Extension of indication from 'chronic idiopathic urticaria' to 'urticaria'.	Merck Sharp & Dohme Ltd.
2008	Insulin glulisine	Apidra	Extension of indication to include 6 years old and older children based on the results of 2 paediatric studies.	Sanofi-aventis Deutschland GmbH

Year	Active substance (INN)	Trade name	Subject of extension	MAH
2008	Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)	Gardasil	Extension of indication to include the prevention of high-grade vaginal dysplastic lesions (VaIN 2/3).	Sanofi Pasteur MSD, SNC
2008	Adalimumab	Humira	Extension of indication to include treatment of active polyarticular juvenile idiopathic arthritis in adolescents from 13 to 17 years of age.	Abbott Laboratories Ltd.
2008	Caspofungin	Cancidas	Extension of the indication to include the paediatric population.	Merck Sharp & Dohme Ltd.
2008	Etanercept	Enbrel	Extension of indication to include the treatment of chronic severe plaque psoriasis in children and adolescents from the age of 8 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.	Pfizer Ltd.
2009	Miglustat	Zavesca	Extension of indication to include the treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease.	Actelion Registration Ltd.
2009	Tacrolimus	Protopic	Extension of indication to 'maintenance treatment' further to completion of one study in adult patients and one in paediatric patients.	Astellas Pharma Europe B.V.
2009	Tipranavir	Aptivus	Extension of indication to include the treatment of HIV-1 infection in highly pre-treated adolescents 12 years of age or older with virus resistant to multiple protease inhibitors.	Boehringer Ingelheim International GmbH
2009	Omalizumab	Xolair	Extension of indication to children from 6 to <12 years of age as add-on therapy to improve allergic asthma control.	Novartis Europharm Ltd.
2009	Aripiprazole	Abilify	Extension of indication to include treatment of schizophrenia in adolescents 15 years and older.	Otsuka Pharmaceutical Europe Ltd.

Year	Active substance (INN)	Trade name	Subject of extension	MAH
2009	Levetiracetam	Keppra	Extension of indication to include the adjunctive treatment of partial seizures with or without secondary generalisation in children from 1 month to <4 years old.	UCB Pharma SA
2009	Peginterferon alfa-2b	PegIntron	Extension of indication of the combination therapy peginterferon alfa-2b and ribavirin to include treatment of the paediatric population.	Schering-Piough Europe
2009	Ribavirin	Rebetol	Extension of indication of the combination therapy peginterferon alfa-2b and ribavirin to include treatment of the paediatric population.	Schering-Piough Europe
2010	Abatacept	Orencia	Extension of indication to include the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis in paediatric patients 6 years of age and older who have had an insufficient response to other DMARDs including at least one TNF inhibitor.	Bristol-Myers Squibb Pharma EEIG
2010	Atazanavir sulphate	Reyataz	Extension of indication for Reyataz capsules to include the treatment of HIV-infected children and adolescents above the age of 6 in combination with other antiretroviral medicinal products.	Bristol-Myers Squibb Pharma EEIG
2010	Measles, mumps and rubella vaccine (live)	M-M-RVAXPRO	Extension of indication to include administration to healthy children from 9 months of age.	Sanofi Pasteur MSD, SNC
2011	Nitric oxide	Inomax	Extension of indication to include the treatment of pulmonary hypertension peri- and post heart surgery in children.	INO Therapeutics AB
2011	Adalimumab	Humira	Extension of indication to include treatment of active polyarticular juvenile idiopathic arthritis in the paediatric population aged from 4 to 12 years.	Abbott Laboratories Ltd.
2011	Tenofovir disoproxil fumarate	Viread	Amendment of indication based on the 48-week results of a safety and efficacy study GS-US-104-0321 in treatment-experienced adolescents aged 12 to 18 years old.	Gilead Sciences International Ltd.

Year	Active substance (INN)	Trade name	Subject of extension	MAH
2011	Paliperidone	Invega	Extension of indication to include treatment of psychotic or manic symptoms of schizoaffective disorder.	Janssen-Cilag International N.V.
2011	Sildenafil	Revatio	Extension of indication in paediatric patients aged 1 year to 17 years old with pulmonary arterial hypertension.	Pfizer Ltd.
2011	Human normal immunoglobulin	Kiovig	Extension of indication to include treatment of multifocal motor neuropathy (MMN). Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation (HSCT) in adults and children.	Baxter AG
2011	Tocilizumab	Roactemra	Extension of indication to include treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids.	Roche Registration Ltd.
2011	Pneumococcal polysaccharide conjugate vaccine (adsorbed)	Synflorix	Extension of indication to increase the upper age limit of infants and children from 2 years to 5 years.	GlaxoSmithKline Biologicals S.A.
2011	Etanercept	Enbrel	Extension of indication to include lower age range for polyarticular juvenile idiopathic arthritis (JIA) "from the age of 4 years" to "from the age of 2 years".	Pfizer Ltd.
2011	Etanercept	Enbrel	Extension of indication to include lower age range for paediatric plaque psoriasis from "from the age of 8 years" to "from the age of 6 years".	Pfizer Ltd.
2011	Insulin detemir	Levemir	Extension of indication as add-on therapy to liraglutide treatment.	Novo Nordisk A/S
2011	Insulin detemir	Levemir	Extension of indication to children aged 2-5 years	Novo Nordisk A/S
2011	Eculizumab	Soliris	Extension of indication to include atypical haemolytic uremic syndrome (aHUS). Additional vaccination and antibiotic prophylaxis recommendation have also been added in section 4.2 for treatment of aHUS in adults and children.	Alexion Europe SAS

Year	Active substance (INN)	Trade name	Subject of extension	MAH
2011	Human papillomavirus vaccine (types 16, 18) (recombinant, adjuvanted, adsorbed)	Cervarix	Extension of indication to children from 9 years.	GlaxoSmithKline Biologicals S.A.
2012	Aztreonam	Cayston	Extension of indication to children from 6 years	Gilead Sciences International Limited
2012	Etanercept	Enbrel	Extension of JIA indication to include children and adolescents with extended oligoarticular JIA from the age of 2 years, children and adolescents with enthesitis-related arthritis from the age of 12 years and children and adolescents with psoriatic arthritis from the age of 12 years	Pfizer Limited
2012	Deferasirox	Exjade	Extension of indication for the treatment of chronic iron overload requiring chelation therapy in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older	Novartis Europharm Limited
2012	Adalimumab	Humira	Extension of indication to children from 6 years with Crohn's disease	AbbVie Ltd
2012	Insulin glargine	Lantus	Extension of indication for paediatric population age 1 to less than 6 years old	sanofi-aventis Deutschland GmbH
2012	Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)	Prevenar 13	Extension of indication to include children and adolescents 6 to 17 years of age.	Pfizer Limited
2012	Darunavir	Prezista	Extension of indication from the age of 3 years	Janssen-Cilag International NV
2012	Measles, mumps, rubella and varicella vaccine (live)	Proquad	Extension of indication from 9 months under special circumstances	Sanofi Pasteur MSD, SNC
2012	Infliximab	Remicade	Extension of indication to children 6-17 years with ulcerative colitis	Janssen Biologics B.V.

Year	Active substance (INN)	Trade name	Subject of extension	MAH
2012	Tenofovir disoproxil	Viread	Extension of indication to include treatment-experienced adolescents 12 to < 18 years of age.	Gilead Sciences International Limited
2013	Aripiprazole	Abilify	Extension of indication to include the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.	Otsuka Pharmaceutical Europe Ltd
2013	Human papillomavirus vaccine (types 16, 18) (recombinant, adjuvanted, adsorbed)	Cervarix	Addition of prevention of premalignant vulvar and vaginal lesions	GlaxoSmithKline Biologicals S.A.
2013	Imatinib	Glivec	Extension of the indication for the treatment of paediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ALL) integrated with chemotherapy.	Novartis Europharm Ltd
2013	Canakinumab	ILARIS	Extension of indication of canakinumab for the treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids.	Novartis Europharm Ltd
2013	Japanese encephalitis vaccine (inactivated, adsorbed)	Ixiaro	Extension of indication to the paediatric segment (2 months of age and older)	Valneva Austria GmbH
2013	Eculizumab	Soliris	Extension of indication of Soliris in the Paroxysmal Nocturnal Hemoglobinuria (PNH) in children.	Alexion Europe SAS
2013	Pandemic Influenza Vaccine H5N1 Baxter	Pandemic Influenza Vaccine H5N1 Baxter	Extension of Indication to paediatric population for Pandemic Influenza Vaccine H5N1 Baxter.	Baxter AG

Year	Active substance (INN)	Trade name	Subject of extension	MAH
2013	Human normal immunoglobulin	Privigen	Extension of indication to immunomodulation in adults, and children and adolescents (0-18 years) in Chronic inflammatory demyelinating polyneuropathy	CSL Behring GmbH
2013	Darunavir	Prezista	Extension of the indication in the HIV infected treatment naive patients aged 12 to 18 years.	Janssen-Cilag International NV
2013	Tocilizumab	RoActemra	Extension of indication of tocilizumab for the treatment in combination with methotrexate (MTX) of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX	Roche Registration Limited
2013	Zonisamide	Zonegran	Extension of the indication "adjunctive treatment of partial seizures with or without secondary generalisation" to include adolescents and children aged 6 years and above.	Eisai Ltd
2013	Etravirine	INTELENCE	Extension of indication to children from 6 years	Janssen-Cilag International NV
2013	Raltegravir	Isentress	Extension of indication to children from 2 years	Merck Sharp & Dohme Ltd
2013	Peginterferon alfa-2a	Pegasys	Extension of indication to children from 5 years	Roche Registration Limited
2013	Anakinra	Kineret	Extension of indication in adults and children for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS)	Biovitrum AB
2013	Pneumococcal polysaccharide conjugate vaccine (adsorbed)	Synflorix	Extension of the indication for the prevention of pneumonia caused by Streptococcus pneumoniae in infants and children from 6 weeks up to 5 years of age	GlaxoSmithKline Biologicals S.A.
2013	Prepandemic influenza vaccine (h5n1) (whole virion, inactivated, prepared in cell culture)	Vepacel	Extension of the indication for the treatment of children and adolescent from the age of 6 months onwards	Nanotherapeutics Bohumil, s.r.o.
2013	Everolimus	Votubia	Extension of indication to include treatment of patients < 3 years of age with TSC who have SEGA.	Novartis Europharm Ltd

Year	Active substance (INN)	Trade name	Subject of extension	MAH
2014	Entecavir	Baraclude	Extension of indication to include treatment of chronic HBV infection in paediatric patients from 2 to <18 years of age with compensated liver disease and evidence of active viral replication and persistently elevated serum ALT levels.	Bristol-Myers Squibb Pharma EEIG
2014	Filgrastim	Grastofil	Extension of indication to include children.	Apotex Europe BV
2014	Adalimumab	Humira	Extension of indication to include the treatment of paediatric subjects with active polyarticular juvenile idiopathic arthritis (JIA) from 4 to 17 years of age to 2 to 17 years of age.	AbbVie Ltd
2014	Paliperidone	Invega	Extension of indication to add the treatment of schizophrenia in adolescents 15 years and older.	Janssen-Cilag International NV
2014	Raltegravir	Isentress	Extension of indication to toddlers and infants from 4 weeks to less than 2 years of age	Merck Sharp & Dohme Ltd
2014	Ivacaftor	Kalydeco	Extension of Indication to include additional gating (class III) mutations in the CFTR gene: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N and S549R.	Vertex Pharmaceuticals (Europe) Ltd
2014	Catridecacog	NovoThirteen	Extension of indication to include the treatment of bleeding in children with congenital factor XIII A-subunit deficiency below 6 years of age.	Novo Nordisk A/S
2014	Darunavir	Prezista	Extension of indication to use darunavir once daily in children aged 3 to 12 years ≥ 15 kg who are treatment-naïve or treatment-experienced with no darunavir resistance-associated mutations (DRV RAMs)	Janssen-Cilag International NV
2014	Voriconazole	Vfend	New indication in prophylaxis of invasive fungal infections in high risk hematopoietic stem cell transplant recipients	Pfizer Limited
2014	Denosumab	XGEVA	Extension of indication to add treatment of giant cell tumour of bone in adults or skeletally mature adolescents.	Amgen Europe B.V.

Year	Active substance (INN)	Trade name	Subject of extension	MAH
2015	Palonosetron	Aloxi	Extension of indication to include paediatric patients 1 month of age and older	Helsinn Birex Pharmaceuticals Ltd.
2015	Lamivudine / abacavir	Kivexa	Lower the threshold for use in paediatric patients from >40kg to >25 kg	ViiV Healthcare UK Limited
2015	Sapropterin	Kuvan	Extension of indication for the 'treatment of hyperphenylalaninaemia (HPA) in adults and paediatric patients of 4 years of age and over with phenylketonuria (PKU) who have shown to be responsive to such treatment' to include the paediatric population of all ages.	Merck Serono Europe Limited
2015	Ustekinumab	Stelara	Extension of Indication to add treatment of moderate to severe plaque psoriasis in paediatric patients from the age of 12 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies	Janssen-Cilag International NV
2015	Bosentan	Tracleer	Extension of Indication to include treatment of symptomatic pulmonary arterial hypertension in paediatric patients aged from 3 months to 18 years.	Actelion Registration Ltd
2015	Tigecycline	Tygacil	Extension of Indication to include the restricted use of Tygacil in paediatric patients ≥8 years to <18 years of age for Tygacil	Pfizer Ltd.
2015	Human coagulation factor viii / human von willebrand factor	Voncento	Extension of indication to include prophylactic treatment of patients with VWD	CSL Behring GmbH
2015	Daptomycin	Cubicin	Extension of indication to extend the age range for the indication "complicated skin and soft-tissue infections" (cSSTI), to include paediatric patients from 1 to 17 years of age	Novartis Europharm Limited

Year	Active substance (INN)	Trade name	Subject of extension	MAH
2015	Rilpivirine	Edurant	Extension of Indication to include treatment of ARV treatment-naïve paediatric patients aged 12 to <18 years of age	Janssen-Cilag International N.V.

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

New pharmaceutical forms or routes of administration

Fourteen centrally authorised products had either a new pharmaceutical form (10/14) and/or a new route of administration (1/14) or a new strength (3/14) authorised that was of paediatric interest. It should be noted that even though a new strength could be of interest to the paediatric population, the addition of a new strength does not fall under Article 8 of the Paediatric Regulation.

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

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

Year	Active substance (INN)	Trade name	Subject of extension	MAH
2011	Moroctocog alfa	ReFacto AF	Addition of new pharmaceutical form: 500, 1000 and 2000 IU powder and solvent for solution for injection in pre-filled syringe.	Pfizer Ltd
2011	Mycophenolate mofetil	Myclausen	Addition of a new pharmaceutical form and strength 250 mg hard capsules (two presentations)	Herbert J. Passauer GmbH & Co. KG
2011	Nevirapine	Viramune	Addition of new strengths: 50 mg, 100 mg and 400 mg + a new pharmaceutical form: Prolonged-release tablet	Boehringer Ingelheim International GmbH
2011	Rufinamide	Inovelon	New pharmaceutical form: 40 mg/ml, oral suspension.	Eisai Ltd
2011	Oseltamivir	Tamiflu	Addition of the new strength: 6 mg/ml, powder for oral suspension	Roche Registration Ltd.
2012	Darunavir	Prezista	Addition of 100mg/ml oral suspension	Janssen-Cilag International NV
2012	Tenofovir disoproxil	Viread	Addition of reduced-strength tablets (150-, 200-, and 250-mg strengths) and a TDF granules formulation	Gilead Sciences International Limited
2013	Etravirine	INTELENCE	Addition of 25 mg strength	Janssen-Cilag International NV
2013	Raltegravir	Isentress	Addition of chewable tablets	Merck Sharp & Dohme Ltd
2013	Peginterferon alfa-2a	Pegasys	Addition of 90 microgram strength	Roche Registration Limited
2013	Anakinra	Kineret	Addition of 100mg/0.67 ml strenght	Biovitrum AB
2014	Raltegravir	Isentress	Addition of granules for oral suspension	Merck Sharp & Dohme Ltd
2014	Palivizumab	Synagis	Addition of oral liquid 100mg/ml	AbbVie Ltd
2015	Ritonavir	Norvir	Line extension of a new oral powder formulation of Norvir	AbbVie Ltd
2015	Ivacaftor	Kalydeco	Line extension to the Marketing Authorisation to include a new pharmaceutical form (granules) in two new strengths (50 mg and 75 mg unit doses) to enable administration of Kalydeco to patients aged 2 to less than 6 years of age.	Vertex Pharmaceuticals (Europe) Ltd

Source: EMA database (SIAMED)

1.1.2. Nationally authorised medicines (including DCP and MRP)

New medicines

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

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

[2] Adult and paediatric

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

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

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

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

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

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

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

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

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

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

Year of MA	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric-only or mixed[2] use
2011	Mycophenolate mofetil	Mycophenolate mofetil Stada 250 mg kemény kapszula, Mycophenolate mofetil Stada 500 mg filmtabletta, Mycophenolate mofetil Pharm V Solutions500 mg filmtabl, Mycophenolate mofetil Actavis 250 mg kemény kapsz, Mycophenolat Mofetil-ratiopharm 250 mg k. Kapsz, Mycophenolat Mofetil-Ratiopharm 500 mg ftbl.	Stada Arzneimittel AG, Pharm V Solutions Ltd., Actavis Group PTC ehf., Ratiopharm GmbH	Hungary	Mixed
2008	Neisseria meningitidis group A Neisseria meningitidis group C Neisseria meningitidis group Y Neisseria meningitidis group W135	Mencevax ACWY powder and solvent for solution for injection in prefilled syringe, Meningitec Meningococca	GSK d.o.o.	Slovenia	Mixed
2008	Neisseria meningitidis group A Neisseria meningitidis group C Neisseria meningitidis group Y Neisseria meningitidis group W135	Meningitec Meningococca	John Wyeth and Brother Limited	Italy	Not reported

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

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

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

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

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

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

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

Source: NCA questionnaire

New paediatric indications

Table 5. New paediatric indications[3] (variations of existing marketing authorisations)

Year of variation	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric indication
2007	Atovaquone / Proguanile hydrochloride	Malarone	Glaxosmithkline	Italy	Not reported
2007	Fluoxetine hydrochloride	Prozac and associated names	Eli Lilly Italia Spa	Italy	Not reported
2007	Oxybutynin hydrochloride	Various	Various	Italy United Kingdom	Not reported
2007	Pantoprazole	Peptazol	Recordati Industria Chimica E Farmaceutica S.P.A.	Italy	Not reported

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

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

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

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

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

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

Year of variation	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric indication
2013	Baclofen	Baclofen	Sintetica Italia	Spain	
2013	Nitric oxide	Noxap		Spain	Persistent pulmonary hypertension
2014	Rupatadine	Rupatall	J Uriach & Cia	BelgiumCzech Republic Estonia Finland Lithuania Poland Spain	Allergic rhinoconjunctivitis
2014	Valganciclovir	VALCYTE	Roche	Czech Republic Estonia Finland Poland Portugal RomaniaSlovenia	
2014	Adenosine	Adenocor	Sanofi	Hungary	
2014	Gadoteric acid	Dotarem	Guerbet Roisyy	Hungary Slovenia	
2014	Rosuvastatin	Crestor	AstraZeneca	Italy, PortugalRomania	Primary hypercholesterolaemia
2014	Tiotropine	Spiriva Respimat	Boehringer Ingelheim International GmbH	Poland	
2014	Atomoxetine	Strattera	Eli Lilly	UK	
2015	Gadobutrol	Gadovist	BAYER	Austria Cyprus Germany Sweden	diagnostic
2015	Metronidazole	Supplin	Sandoz GmbH	Lithuania	
2015	atomoxetine	Strattera	Eli Lilly	Czech Republic	

Source: NCA questionnaire

New pharmaceutical forms or routes of administration

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

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

Year	Active substance (INN)	Trade name	MAH	MS(s)	Paediatric formulation / route of administration
2011	Rizatriptan	Maxalt	Merck Sharp & Dohme	Lithuania	Tablet, oral lyophilisate, oral use
2009	Somatropin	Zomacton	Ferring	Italy	
2010	Valsartan	Diovan and associated names	Novartis Pharma GmbH	Austria Cyprus Czech Republic Estonia Finland Italy Romania Slovenia Spain Sweden United Kingdom	Paediatric formulation: oral solution, divisibility of the tablet
2012	Rupatadine	Rupafin	J. Uriach & Cia.	Slovenia Estonia Italy	Oral solution
2014	Atomoxetine	Strattera	Eli Lilly	Denmark Estonia United Kingdom Czech Republic	Oral solution
2015	Meningococcal group C oligosaccharide conjugated to Corynebacterium diphteriae CRM197 protein (MenC-CRM)	MENJUGATE	NOVARTIS VACCINES AND DIAGNOSTICS	France	

Source: NCA questionnaire

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

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

Initial marketing authorisations		**Already authorised products (type II variations or line extensions)**					**Other paediatric changes to SmPC (sections)**								
Year	Initial MA with a clear paediatric indication (section 4.1)	New paediatric indication (section 4.1)	Update to 4.1 (not new indication)	New paediatric posology (section 4.2)	Update to 4.2 (not new posology)	New pharmaceutical form or stregth for children (line extension)	4.3	4.4	4.5	4.7	4.8	4.9	5.1	5.2	5.3
2004	6	5	0	7	0	2	0	11	0	0	5	1	4	2	1
2005	2	6	0	10	4	1	2	7	2	0	5	1	7	7	1
2006	13	3	0	4	5	5	0	7	0	0	13	1	9	9	0
Sum 2004 - 2006	**21**	**14**	**0**	**21**	**9**	**8**	**2**	**25**	**2**	**0**	**23**	**3**	**20**	**18**	**2**
2012	10	11	3	12	27	1	0	19	2	0	25	1	20	18	1
2013	21	17	0	11	16	1	1	12	7	1	26	3	27	18	0
2014	14	10	3	12	20	1	1	17	8	0	18	2	16	13	1
Sum 2012 - 2014	**45**	**38**	**6**	**35**	**63**	**3**	**2**	**48**	**17**	**1**	**69**	**6**	**63**	**49**	**2**

Source: EMA database (SIAMED)

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

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

Year	Active substance (INN)	Trade name	Application type	Linked to a PIP
2005	Interferon alfa-2b	IntronA	TYPE_II	N/A
2005	Ertapenem	Invanz	TYPE_II	N/A
2005	Levetiracetam	Keppra	TYPE_II	N/A
2005	Insulin detemir	Levemir	TYPE_II	N/A
2005	Ribavirin	Rebetol	TYPE_II	N/A
2006	Clofarabine	Evoltra	INITIAL_MA	N/A
2006	Deferasirox	Exjade	INITIAL_MA	N/A
2006	Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)	Gardasil	INITIAL_MA	N/A
2006	Human normal immunoglobulin	Kiovig	INITIAL_MA	N/A
2006	Measles, mumps and rubella vaccine (live)	M-M-RVAXPRO	INITIAL_MA	N/A
2006	Galsulfase	Naglazyme	INITIAL_MA	N/A
2006	Somatropin	Omnitrope	INITIAL_MA	N/A
2006	Measles, mumps, rubella and varicella vaccine (live)	Proquad	INITIAL_MA	N/A
2006	Rotavirus vaccine, live, attenuated	Rotarix	INITIAL_MA	N/A
2006	Rotavirus vaccine, live	RotaTeq	INITIAL_MA	N/A
2006	Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)	Silgard	INITIAL_MA	N/A
2006	Buprenorphine / naloxone	Suboxone	INITIAL_MA	N/A
2006	Somatropin	Valtropin	INITIAL_MA	N/A
2006	Imatinib	Glivec	TYPE_II	N/A
2006	Levetiracetam	Keppra	TYPE_II	N/A
2006	Oseltamivir	Tamiflu	TYPE_II	N/A

Source: EMA database (SIAMED)

1.3. Paediatric Use Marketing Authorisation (PUMA)

Table 9. Agreed PIPs for potential PUMAs

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

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

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

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

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

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

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

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

Source: EMA database (PedRA)

1.4. Statements of compliance in marketing authorisations

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

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

1.4.1. Statements of compliance (CAPs)

Table 10. Statements of complicance for CAPs

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

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

Source: EMA databases (SIAMED, PedRA)

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

Table 11. Statement of compliance for NAPs, DCP/MRP

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

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

Year	Active substance (INN)	Trade name	MAH
2015	LANREOTIDE	Somatuline Autogel	IPSEN LIMITED
2015	IVERMECTIN	Soolantra 10 mg/g cream	GALDERMA (UK) LIMITED
2015	TAPENTADOL HYDROCHLORIDE	PALEXIA	GRUNENTHAL LIMITED

Source: NCA questionnaire

1.4.3. PDCO opinions on PIP compliance

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

Table 12. Number of positive PDCO opinions on PIP compliance per year

Year	2007	2008	2009	2010	2011	2012	2013	2014	2015
Number of PDCO compliance opinions	0	5	8	9	9	4	16	31	17

Source: EMA database (PedRA)

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

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

Table 13. PDCO opinions on PIP compliance

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

Active substance (INN)	Therapeutic area	Company name	Compliance opinion date
Lopinavir / ritonavir	Infectious diseases	AbbVie Ltd.	17/07/2015
Canakinumab	Immunology-rheumatology-transplantation	Novartis Europharm Ltd	19/06/2015
Sieved freeze-dried allergen extract of Dermatophagoides pteronyssinus / sieved freeze-dried allergen extract of Dermatophagoides farinae	Pneumology - allergology	Stallergenes S.A.	19/06/2015
Everolimus	Immunology-rheumatology-transplantation	Novartis Europharm Limited	22/05/2015
Solifenacin (succinate)	Uro-nephrology	Astellas Pharma Europe B.V.	22/05/2015
Eculizumab	Immunology-rheumatology-transplantation	ALEXION EUROPE SAS	22/05/2015
Von Willebrand Factor / human coagulation Factor VIII	Haematology-hemostaseology	CSL Behring GmbH	22/05/2015
Fluticasone Propinate / formoterol fumarate dihydrate	Pneumology - allergology	Mundipharma Research Limited	13/02/2015
Atazanavir (sulphate)	Infectious diseases	Bristol-Myers Squibb Pharma EEIG	13/02/2015
Human normal immunoglobulin	Immunology-rheumatology-transplantation	Baxter Innovations GmbH	16/01/2015
Anakinra	Immunology-rheumatology-transplantation	Swedish Orphan Biovitrum AB (publ)	12/12/2014
Pandemic influenza vaccine (H1N1) (split virion, inactivated, adjuvanted), containing antigen equivalent to Influenza A/California/7/2009 (Produced at Quebec manufacturing site)	Vaccines	GlaxoSmithKline Biologicals S.A.	12/12/2014
Purified antigen fractions of inactivated split virion Influenza virus type A, H1N1 A/California/7/2009	Vaccines	GlaxoSmithKline Biologicals S.A.	12/12/2014
Tigecycline	Infectious diseases	Pfizer Limited	12/12/2014

Active substance (INN)	Therapeutic area	Company name	Compliance opinion date
Autologous CD34+ cells transduced ex vivo with retroviral vector (GIADAI) containing human adenosine deaminase gene from cDNA	Immunology-rheumatology-transplantation	GlaxoSmithKline Trading Services Limited	14/11/2014
Eltrombopag	Infectious diseases / oncology / gastroenterology-hepatology / haematology-hemostaseology	Novartis Pharmaceuticals UKLtd	14/11/2014
Glycopyrronium bromide	Neurology	Proveca Limited	14/11/2014
Insulin detemir	Endocrinology-gynaecology-fertility-metabolism	Novo Nordisk A/S	14/11/2014
Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), inactivated poliovirus and Haemophilus type b (meningococcal protein conjugate) vaccine (adsorbed)	Vaccines	Sanofi Pasteur MSD	10/10/2014
Ivabradine hydrochloride	Cardiovascular diseases	LES LABORATOIRES SERVIER	10/10/2014

Active substance (INN)	Therapeutic area	Company name	Compliance opinion date
Pneumococcal Polysaccharide Serotype 5 - Diptheria-CRM197 conjugate / Pneumococcal Polysaccharide Serotype 7F - Diptheria-CRM197 conjugate / Pneumococcal Polysaccharide Serotype 23F - Diptheria-CRM197 conjugate / Pneumococcal Polysaccharide Serotype 1 - Diptheria-CRM197 conjugate / Pneumococcal Polysaccharide Serotype 3 - Diptheria-CRM197 conjugate / Pneumococcal Polysaccharide Serotype 6B - Diptheria-CRM197 conjugate / Pneumococcal Polysaccharide Serotype 18C - Diptheria-CRM197 conjugate / Pneumococcal Polysaccharide Serotype 9V - Diptheria-CRM197 conjugate / Pneumococcal Polysaccharide Serotype 14 - Diptheria-CRM197 conjugate / Pneumococcal Polysaccharide Serotype 19A - Diptheria-CRM197 conjugate / Pneumococcal Polysaccharide Serotype 6A - Diptheria-CRM197 conjugate / Pneumococcal Polysaccharide Serotype 4 - Diptheria-CRM197 conjugate / Pneumococcal Polysaccharide Serotype 19F - Diptheria-CRM197 conjugate	Vaccines	Pfizer Limited	10/10/2014
Sapropterin dihyrochloride	Endocrinology-gynaecology-fertility-metabolism	Merck Serono Europe Ltd	10/10/2014
Aprepitant	Oncology	Merck Sharp & Dohme (Europe) Inc.	10/10/2014
Fosaprepitant dimeglumine	Oncology	Merck Sharp & Dohme (Europe) Inc.	10/10/2014

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

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

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

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

Active substance (INN)	Therapeutic area	Company name	Compliance opinion date
Alanine isoleucine serine potassium acetate arginine leucine taurine magnesium acetate, tetrahydrate aspartic acid lysine monohydrate threonine calcium chloride, dihydrate Cysteine / cystine methionine tryptophan sodium glycerophosphate, hydrated glutamic acid ornithine hydrochloride tyrosine glucose, monohydrate glycine phenylalanine valine olive oil, refined histidine proline sodium chloride soya-bean oil, refined	Nutrition	BAXTER World Trade SA/NV	16/10/2009
Purified diphtheria toxoid, Purified tetanus toxoid, Five component acellular pertussis [Purified Pertussis Toxoid (PT), Purified Filamentous Haemagglutinin (FHA), Purified Fimbriae Types 2 and 3 (FIM) and Purified Pertactin (PRN)], Inactivated poliomyelitis vaccine (Vero) – Type 1 (Mahoney), Type 2 (MEF-1) and Type 3 (Saukett), Purified polyribosylribitol phosphate capsular polysaccharide of Haemophilus influenzae type b covalently bound to Tetanus protein (PRP-T)	Vaccines	Sanofi Pasteur MSD	18/09/2009
Valsartan	Cardiovascular diseases	Novartis Europharm Limited	21/08/2009

Active substance (INN)	Therapeutic area	Company name	Compliance opinion date
Alanine, Arginine, Aspartic acid, Cysteine/Cystine, Glutamic acid, Glycine, Histidine, Isoleucine, Leucine, Lysine monohydrate, Methionine, Ornithine hydrochloride, Phenylalanine, Proline, Serine, Taurine, Threonine, Tryptophan, Tyrosine, Valine, Sodium chloride, Potassium acetate, Magnesium acetate, tetrahydrate, Calcium chloride, Sodium glycerophosphate, Glucose, Olive oil, refined, Soya-bean oil, refined	Nutrition	BAXTER World Trade SA/NV	24/07/2009
Colesevelam hydrochloride	Endocrinology-gynaecology-fertility-metabolism	Genzyme Europe B.V	24/07/2009
Abatacept	Endocrinology-gynaecology-fertility-metabolism	Bristol-Myers Squibb Pharma EEIG	29/05/2009
Anastrozole	Endocrinology-gynaecology-fertility-metabolism	AstraZeneca AB	03/04/2009
Losartan potassium	Cardiovascular diseases	Merck, Sharp & Dohme (Europe) Inc	06/02/2009
Zoledronic acid	Endocrinology-gynaecology-fertility-metabolism	Novartis Europharm Limited	12/12/2008
Peginterferon alfa-2b	Infectious diseases / gastroenterology-hepatology	Schering-Plough Europe	17/10/2008
Ribavirin	Infectious diseases / gastroenterology-hepatology	Schering-Plough Europe	17/10/2008
Caspofungin acetate	Infectious diseases	Merck Sharp & Dohme (Europe) Inc.	04/06/2008

Source: EMA database (PedRA)

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

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

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

Table 14. Medicines and companies that have received the 6-month extension of the supplementary protection certificate (SPC)

Active substance (INN) (Invented name)	**MAH**	**SPC extension granted in MS (year)**	**SPC extension pending in MS (year)**
Abatacept (Orencia)	Bristol-Myers Squibb Pharma EEIG	Austria (2011) Denmark (2010) Estonia (2011) Finland (2011) France (2010) Germany (2010) Ireland (2010) Luxembourg (2010) The Netherlands (2010) Portugal 2010) Slovenia (2011) Sweden (2011) United Kingdom (2011) Bulgaria (2012) Italy (2012) Romania (2012)	Greece (2010) Lithuania (2011) Luxembourg (2011) Spain (2010) Czech Republic (2014) Hungary (2014)
Adalimumab (Humira)	AbbVie Ltd	Austria (2015) Denmark (2015) France (2015) Germany (2015) Hungary (2015) Ireland (2015) Italy (2015) Luxembourg (2015) Netherlands (2015) Poland (2015) Slovenia (2015) Sweden (2015) UK (2015)	Bulgaria (2015) Greece (2015) Romania (2015) Slovakia (2015) Spain (2015)

Active substance (INN) (Invented name)	MAH	SPC extension granted in MS (year)	SPC extension pending in MS (year)
Anastrazole (Arimidex and associated names)	AstraZeneca AB	Austria (2010) Belgium (2010) Denmark (2010 Finland (2 March 2010) France (11 June 2010) Germany (19 July 2010) Ireland (29 June 2010) Italy (16 March 2010) Luxembourg (27 July 2010) The Netherlands (1 April 2010) Sweden (27 April 2010) United Kingdom (10 June 2010)	Romania (2010, 2011; *SPC granted after appeal*)
Aripiprazole (Abilify)	Otsuka Pharmaceutical Europe Ltd	Italy (2014)	Denmark(2012) Germany (2012) Romania(2012) Sweden(2012) The Netherlands(2012) United Kingdom(2012) France (2013) Spain (2015)
Atorvastatin (Sortis and associated names)	Pfizer	Austria (year not reported, possibly 2011) Denmark (2011) Germany (2011) Ireland (2011) Italy (2011) Luxembourg 2011) Sweden (2011) The Netherlands (2011) United Kingdom (2011)	France (2010)
Paclitaxel (Abraxane)	Celgene Europe Limited		Germany (2015)
Entecavir (Baraclude)	Bristol-Myers Squibb Pharma EEIG	Denmark (2014) Finland (2014) Ireland (2014) Italy (2014) Austria (2015) Greece (2015) Hungary (2015) Luxembourg (2015) Poland (2015) Romania (2015) Spain (2015)	Belgium (2014) France (2014) Germany (2014) Netherlands (2014) Sweden (2014) UK (2014)

Active substance (INN) (Invented name)	MAH	SPC extension granted in MS (year)	SPC extension pending in MS (year)
Bevacizumab (Avastin)	Roche Registration Ltd		Czech Republic (2015) Hungary (2015) Slovakia (2015)
Bosentan (Tracleer)	Actelion Registration Ltd	Denmark (2015) Finland (2015) France (2015) Germany (2015) Hungary (2015) Ireland (2015) Italy (2015) Netherlands (2015) Romania (2015) Spain (2015) Sweden (2015)	Belgium (2014) Slovakia (2014) UK (2014) Austria (2015) Greece (2015) Luxembourg (2015) Slovakia (2015)
Caspofungin (Cancidas)	Merck Sharp and Dohme	Austria (2010) Belgium 2010) Finland (2011) Greece (2010) Italy (2010) Portugal 2010) Slovenia (2010) Denmark (2009) France (2009) Germany (2009) Ireland (2009) The Netherlands (2009) Sweden (2009) United Kingdom (2009) Romania (2012) Bulgaria (2013) Czech Republic (2013) Slovakia (2013) Luxembourg (2015)	Czech Republic (2010, 2011) Hungary (2010, 2011) Poland (2011) Spain (2010)
Clopidogrel (Plavix and associated names)	Sanofi BMS	Denmark (2012) Finland (2011) Germany (2011) Portugal (2011) Sweden (2011) Belgium (2012) Denmark (2012) Ireland (2012) Italy (2012) Spain (2012)	Austria (2012) Ireland (2011) Italy (2011) The Netherlands (2011) United Kingdom (2011)
Colesevelam (Cholestagel)	Genzyme Europe BV		United Kingdom(2012) The Netherlands (2014)

Active substance (INN) (Invented name)	MAH	SPC extension granted in MS (year)	SPC extension pending in MS (year)
Colistimethate(Colobreathe)	Forest Laboratories UK		Germany (2013)
Darunavir (Prezista)	Janssen-Cilag International NV	Denmark (2015) Finland (2015) France (2015) Greece (2015) Ireland (2015) Italy (2015) Luxembourg (2015) Spain(2015) Sweden (2015)	UK (2014) Austria (2014) Germany (2015)
Etanercept (Enbrel)	Pfizer Limited	France(2012) Ireland (2012) Italy (2012) Sweden (2012) The Netherlands (2012) Finland (2013) France (2013) Germany (2013) Greece (2013) United Kingdom (2013) Belgium (2014) Bulgaria (2015)	Austria (2012) Bulgaria (2012) Denmark (2012) Luxembourg (2012) Spain (2012)
Ezetimibe (Ezetrol and associated names)	Merck Sharp & Dohme	Denmark (2015) Italy (2015) Netherlands (2015) Sweden (2015)	Austria (2015) Czech Republic (2015) Finland (2015) France (2015) Germany (2015) Greece (2015) Ireland (2015) Slovakia (2015) Spain (2015) UK (2015)
Human papillomavirus vaccine (Gardasil)	Sanofi Pasteur MSD	France (2014) Italy (2014) UK (2014) Austria (2015) Denmark (2015) Greece (2015) Ireland (2015) Luxembourg (2015) Spain (2015) Sweden (2015)	Belgium (2014) Germany (2014) Ireland (2014) Netherlands (2014)

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

Active substance (INN) (Invented name)	MAH	SPC extension granted in MS (year)	SPC extension pending in MS (year)
Ivabradine (Corlentor/ Procoralan)	Les Laboratoires Servier	Denmark (2015) France (2015) Italy (2015) Sweden (2015) UK (2015)	Austria (2015) Germany (2015) Greece (2015) Ireland (2015) Luxembourg (2015) Spain (2015)
Latanoprost (Xalatan and associated names)	Pfizer	Austria (year not reported, possibly 2011) Denmark (2011) Finland (2011) Germany (2011) Ireland (2011) Italy (2011) Luxembourg (2011) Portugal (2011) Sweden (2011) The Netherlands (2011) United Kingdom (2011)	Spain (2010)
Losartan (Cozaar and associated names)	Merck Sharp & Dohme BV	Austria (2010) The Netherlands (2009) Germany(2009) Denmark (2009) Finland (2009) France (2009) Ireland (2009) Italy (2009) Sweden (2009) United Kingdom (2009) Luxembourg (2009)	Cyprus (2010)
Montelukast (Singulair)	Merck Sharp & Dohme	Denmark (2012) Ireland (2011) Slovenia (2011) Sweden (2011) The Netherlands (2011) United Kingdom (2012) Germany (2012) Italy (2012) Luxembourg (2012) Spain (2012)	The Netherlands (2011)

Active substance (INN) (Invented name)	MAH	SPC extension granted in MS (year)	SPC extension pending in MS (year)
Nevirapine (Viramune)	Boehringer	Denmark (2012) Portugal (2011) Sweden (2011) Belgium(2012) Germany (2012) Italy (2012) Luxembourg (2012) Spain (2012) The Netherlands (2012) United Kingdom (2012)	
Rizatriptan (benzoate) (Maxalt and associated names)	Merck Sharp & Dohme	Belgium (2012) Denmark (2012) France(2012) Germany (2012) Ireland (2012) Italy (2012) Luxembourg (2012) Spain (2012) Sweden (2012) The Netherlands(2012) United Kingdom (2012) Austria (2013) Czech Republic (2015)	Portugal (2012) Czech Republic (2013)
Rosuvastatin (Crestor and associated names)	AstraZeneca AB	Denmark (2015) France (2015) Germany (2015) Italy (2015) Luxembourg (2015) Netherlands (2015) Sweden (2015)	Austria (2015) Greece (2015) Hungary (2015) Spain (2015) UK (2015)
Rupatadine (Rupafin)	J. Uriach y Compañía, S.A.	Italy (2014) Netherlands (2014) Austria (2015) Spain (2015)	Belgium (2014) Czech Republic (2014) France (2014) Ireland (2014) Slovakia (2014) UK (2014) Germany (2015) Greece (2015) Luxembourg (2015)
Sitagliptin (Januvia)	Merck Sharp and Dohme (Europe), Inc.		Czech Republic (2014) Hungary (2014)
Sugammadex (Bridion)	Merck Sharp & Dohme		Czech Republic (2014)

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

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

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

Source: NPO questionnaire

2. Paediatric research and development

2.1. Paediatric investigation plans

2.1.1. Addressing unmet paediatric needs

Table 15. Paediatric medicine development in PIPs correlated with survey of all paediatric needs.

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

[4] Procedure for example FP6, FP7, PIP etc.

Paediatric therapeutic area	Paediatric need	Active substance or class	Addressed by[4]	Comments
Gastroenterology	Treatment of reflux disease	Proton pump inhibitors H2-receptor antagonists	Rabeprazole (EMEA-000055-PIP01-07), esmeprazole (EMEA-000331-PIP01-08)	
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	PIPs agreed for Vortioxetine (EMEA-000455-PIP02-10), Agomelatine (EMEA-001181-PIP01-11)
Dermatology	Treatment of atopic eczema	Glucocorticosteroids, topical use	Prednicarbate / octenidine dihydrochloride (EMEA-000993-PIP01-10)	PIPs agreed for monoclonal antibodies
Endocrinology	Prevention of pregnancy	Oral contraceptives	Ulipristal (EMEA-000305-PIP01-08), Levonorgestrel (EMEA-000606-PIP01-09), Nomegestrol / estradiol (EMEA-000250-PIP01-08), Estetrol / drospirenone (EMEA-001332-PIP01-12), Drospirenone (EMEA-001495-PIP01-13), Estetrol / levonorgestrel (EMEA-001513-PIP01-13)	
Endocrinology	Various uses	Dexamethasone, systemic use	No PIP	
Endocrinology	Not specified	Multivitamin preparations	No PIP	

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

2.2. Paediatric research incentives

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

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

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

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

Table 16. Funded off-patent medicines projects (starting by 31 December 2015) and agreed PIPs, if existing.

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

Acronym	Year	Objectives (active substance in bold)	PIP
CloSed	2013	The objectives of this project are a) to develop an age appropriate formulation of **clonidine** suitable for sedation of children in PICU b) to conduct a randomised, phase III, double-blind, active-controlled parallel group clinical trial of clonidine vs midazolam in patients from birth to 18 years to establish the efficacy and safety, including long-term outcomes and dose-dependent effects of clonidine and c) to establish an European consensus guideline for sedion of critically ill children. The ultimate goal is to use these data and to apply for a PUMA. On this basis a Paediatric Investigation Plan (PIP) has been approved by the EMA in February 2013 and is reflected in the work plan of CloSed.	EMEA-001316-PIP01-12-M01
DEVELOPAKURE	2012	To fund the clinical development of **nitisinone** for the treatment of Alkaptonuria	PIP agreed for the treatment of tyrosinemia type 1
KIEKIDS	2011	To develop an innovative, age-adapted, flexible and safe paediatric formulation of **ethosuximide** for the treatment of absence and of myoclonic epilepsies in children	NA
NEO-CIRC	2011	To provide safety and efficacy data for **dobutamine**, to perform pre-clinical studies, to develop biomarker of hypotension and to adapt a formulation for newborns	NA
TAIN	2011	To develop a neonatal formulation of **hydrocortisone** for the treatment of congenital and acquired adrenal insufficiency and for use in oncology (brain tumours and leukaemia)	NA
DEEP	2010	To evaluate PK & PD of **deferiprone** in 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
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
TINN2	2010	To evaluate PK & PD of **azithromycin** against urea plasma and in BPD in neonates.	NA
NEMO	2009	Evaluates the efficacy safety, PK, PD, mechanisms of action of **bumetanide** in neonatal seizures, including the effect on neurodevelopment and to develop and adapt a bumetanide formulation suitable for newborns in order to apply for a Paediatric Use Marketing Authorisation (PUMA).	NA
NeoMero	2009	European multicentre network to evaluate pharmacokinetics, safety and efficacy of **meropenem** in neonatal sepsis and meningitis	EMEA-000898-PIP01-10

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

Source: European Commission, note: NA = Not available

2.2.2. National funding

Austria

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

Belgium

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

Finland

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

France

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

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

Germany

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

Hungary

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

Italy

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

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

The Netherlands

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

Lithuania

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

Malta

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

Poland

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

Spain

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

Slovenia

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

United Kingdom

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

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

2.3. Paediatric clinical trials

2.3.1. Selection of fields and trials

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

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

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

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

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

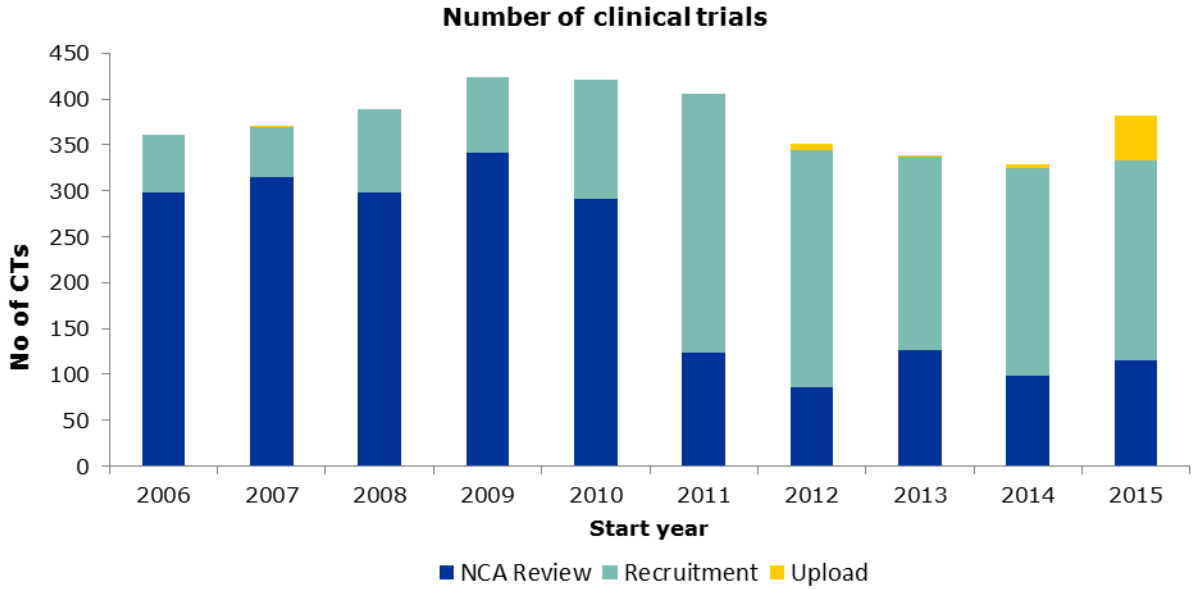
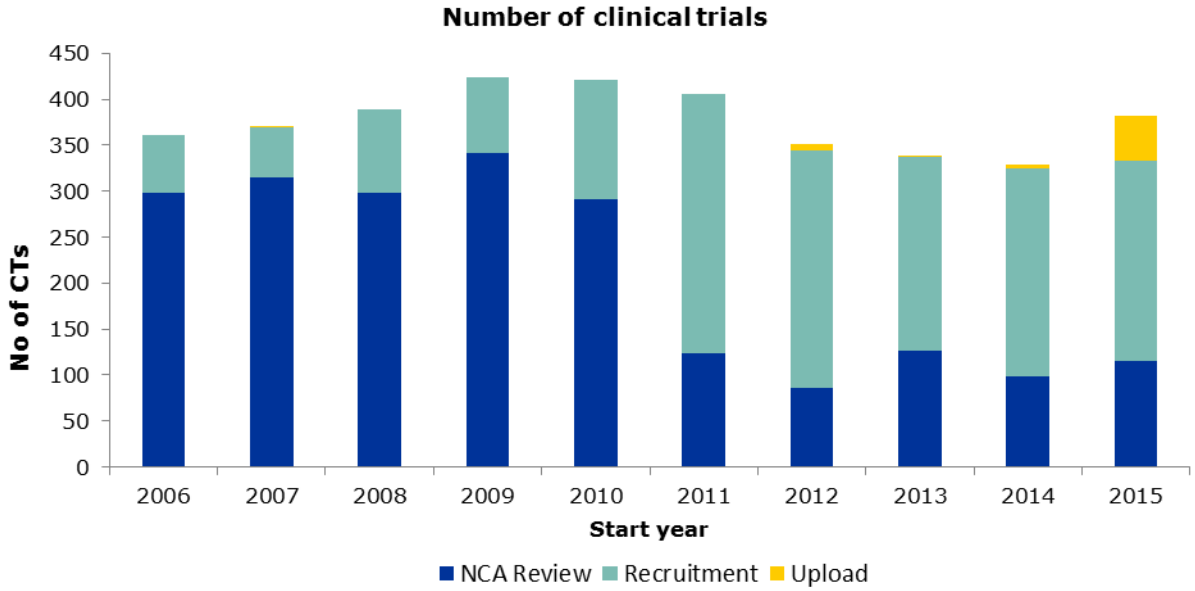


Figure 1. Number of paediatric trials by start year, indicating the source of the information for the date of start.



Source: EudraCT database.

2.3.2. Number of paediatric clinical trials

Table 17. Paediatric clinical trials by year of authorisation (or, if not available, by year of protocol upload into EudraCT)

Trials	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Paediatric[1] trials	340	362	341	407	391	373	401	344	435	720
Total number of trials	4274	4855	4642	4565	4138	3976	3867	3580	3585	3937
Proportion of paediatric trials of all trials (%)	8.0	7.5	7.3	8.9	9.4	9.4	10.4	9.6	12.1	18.3
Exclusively[2] paediatric trials	196	188	184	241	230	218	256	211	281	453

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

Source: EudraCT database.

2.3.3. Clinical trials by phase and design

Table 18. Overview of authorised clinical trials with the paediatric population by start date[1].

Type	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Paediatric[2] trials	361	370	389	424	421	406	352	339	329	382
Paediatric trials planned as										
Phase 1	28	29	29	31	53	41	40	51	37	47
Phase 2-3	239	266	257	298	278	304	263	246	252	270
Phase 4	93	84	105	95	94	73	67	63	52	79
Controlled (various types of control)	259	254	265	276	262	247	209	197	198	207
Active controlled	44	59	60	68	75	66	44	60	61	53
Placebo controlled / placebo use	97	105	116	112	102	108	100	92	82	94
Paediatric trials planned to be conducted										
in EEA only	298	314	299	337	325	302	284	294	287	312
in and outside of EEA	4	11	14	28	26	39	21	19	9	13
only outside of EEA	59	45	76	59	70	65	47	26	33	57
Reference: All trials (adults, elderly and / or children)	3898	4528	4360	4321	3895	3854	3525	3317	3305	3320

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

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

Source: EudraCT database

2.3.4. Number of children in clinical trials

Table 19. Number of children planned to be enrolled in clinical trials, by year of protocol upload into EudraCT database

CTA Load Year	Preterm newborns	Newborns	Infants and toddlers	Children	Adolescents	Total
2006	0	0	540	2669	439	**3648**
2007	0	98	134	637	36528	**37397**
2008	210	125	54714	719	1162	**56930**
2009	207	64	56	4463	5329	**10119**
2010	126	252	2457	4542	5951	**13328**
2011	2285	1295	13780	30381	21672	**69413**
2012	1694	2284	61882	23614	21757	**111231**
2013	4695	1505	17647	27656	18228	**69731**
2014	3342	2114	39179	61743	40324	**146702**
2015	2539	1666	121971	52532	39631	**218339**

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

Basic filters used for EudraCT analyses

All trials (adults and/or children):

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

Paediatric trials:

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

Exclusively paediatric trials (no adults included):

	First Past the Post(FPP) Flag is equal to / is in Yes	
and		F.1.1.2 Preterm Newborn Infants is equal to / is in Yes
	or	F.1.1.3 Newborns (0-27 days) is equal to / is in Yes
	or	F.1.1.4 Infants and Toddlers (28 days - 23 months) is equal to / is in Yes
	or	F.1.1.5 Children (2-11 years) is equal to / is in Yes
	or	F.1.1.6 Adolescents (12-17 years) is equal to / is in Yes
	or	F.1.1 Age Range <18 yrs is equal to / is in Yes
and		N. Latest/Older Review is equal to / is in Yes
	or	N. Latest/Older Review is null
and	F.1.2 Adults (18-64 years) is not equal to / is not in Yes	
and	F.1.3 Elderly (>= 65 years) is not equal to / is not in Yes	

Add-on filters used for EudraCT analyses

Trials included in an agreed PIP:

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

Phase 1 trials:

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

Phase 2-3 trials:

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

Phase 4 trials:

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

Controlled trials:

E.8.1 Controlled is equal to / is in Yes

Trials with active control:

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

Trials with placebo control:

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

Trials with sites inside EU only:

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

Trials with sites inside and outside EU:

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

Trials with site outside EU only:

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

Consideration for all EudraCT analyses per authorisation date

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

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

2.4.1. Enpr-EMA milestones

Table 20. Main Enpr-EMA milestones (2007-2015)

Year	Milestones
2007	• Consultation of Paediatric Committee on network strategy • Public consultation on network strategy
2008	• Adoption of Enpr-EMA Implementing Strategy by EMA Management Board • Call for European Paediatric Research Networks to identify additional networks
2009	• First networks workshop • Proposed organisational structure of Enpr-EMA • Finalisation of proposal for recognition criteria
2010	• Second networks workshop • Agreement on and publication of recognition criteria • Agreement of organisational structure and composition of Enpr-EMA Coordination Group (CG)

2011	• Official launch of Enpr-EMA at first annual workshop open to all stakeholders, i.e. networks, industry and patients organisations • Publication of list of networks becoming member of Enpr-EMA • Workshop on emerging networks in the therapeutic areas of cardiology, endocrinology and gastroenterology to fill the identified gap of networks
2012	• Nomination of a representative of the EMA Patient and Consumer Working Party (PCWP) as observer member of the Enpr-EMA CG. Survey among all networks, to analyse how paediatric networks in Europe support the engagement of young people in research: results showed that only a minority (3 networks) had dedicated resources and strategies to achieve this objective. A need for training on how to establish and maintain young person's advisory groups was identified • Establishment of collaboration with micro, small and medium-sized enterprises and Enpr-EMA network members through the Agency's SME office • Publication of first annual Enpr-EMA newsletter

2013	• Publication of an online searchable Enpr-EMA Network Database providing easy access to data about each individual registered network and their expertise in paediatric research.
	• Establishment of Enpr-EMA Working Groups (WGs), including network and industry representatives, tasked with addressing the most important needs identified during the fifth annual open workshop, such as
	  • Joint WG on public-private partnership
	  • WG on ethics
	  • WG on neonatology
	  • Joint Enpr-EMA/ENCePP WG on paediatric pharmacovigilance
	• Corporate Enpr_EMA response during public consultation on the EU guideline on the format and content of PIP and waiver applications. It was proposed to add a recommendation to consult Enpr-EMA members, i.e. networks, in the development of a PIP. (This recommendation is now included in the guideline.)
	• Corporate Enpr_EMA response during public consultation on the revised Clinical Trial Regulation
	• Nomination of a representative of the EMA Health Care Professional Working Party (HCPWP) as observer member of the Enpr-EMA CG.
	• Establishment of task force and core groups of 3 emerging paediatric networks (cardiology: Task Force of the AEPC (Association for European Paediatric Cardiology); gastroenterology: PEDDCReN (Paediatric European Digestive Diseases Clinical Research Network); endocrinology/diabetes: EUCADET (European Children and Adolescent Diabetes and Endocrine Trial)).
	• Provision of practical tips and training on strategies and guidance to involve young people and families in the activities of the Enpr-EMA networks.

2014	• Existing European young persons' advisory groups linked up with established North American ones into a Communicating International Network for worldwide involvement of young people in research (iCAN). • A framework was established to allow industry representatives from EFPIA and EUCOPE as observers within the Enpr-EMA CG for ad-hoc topics in order to improve communication and collaboration with industry. • A plenary discussion on future approaches to funding of paediatric clinical trials was held during the November PDCO meeting, with representatives from the European Commission and EFPIA/IMI as well as the Enpr-EMA chair/co-chair and representatives from Enpr-EMA networks.
2015	• Participation of several neonatal Enpr-EMA networks in the "International Neonatal Consortium" (official launch May 2015) • Participation of young people advisory groups (YPAGs) from several Enpr-EMA network members at the first international summit of the International Children's' Advisory Network (ICAN) • Representatives from the YPAG of the Scottish clinical research network presented to the PDCO plenary as well as to EMA staff at the 20th EMA anniversary lunch event their work and proposals how YPAGs could be involved in the activities of the Agency and its committees. • Publication of a table listing requirements to obtain Informed Consent for paediatric clinical trials in the various EU member states • Publication of an article summarising the results of a survey among industry and networks: "Pharmaceutical industry and paediatric clinical trial networks in Europe – How do they communicate?" (Lepola et al. 2016)

Source: Enpr-EMA records

2.4.2. Enpr-EMA networks

Table 21. presents all Enpr-EMA networks and their therapeutic areas. Networks have been classified according to 4 categories:

Category 1 networks fulfilling all minimum criteria for membership;

Category 2 networks potentially fulfilling all minimum criteria but in need of clarifying issues before becoming a member;

Category 3 networks currently not yet fulfilling minimum criteria;

Category 4 networks that do not run paediatric clinical trials but have expertise in clinical trial methodology, or support infrastructure, etc.

Table 21. Enpr-EMA registered networks and their therapeutic areas

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

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

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

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

Table 22. Enpr-EMA survey results 2015

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

[5] e.g. definition of therapeutic needs, standard of care
[6] e.g. feasibility of requested trials
[7] e.g. acceptability of clinical endpoints

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

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

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

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

2.5. External experts, workshops and scientific guidelines

2.5.1. Expert meetings and workshops

Table 23. Main expert meetings and workshops organised by the EMA in 2006-2015

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

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

Source: EMA website and internal records

Table 24. Expert meetings and workshops by therapeutic area

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

Source: EMA website and internal records

Table 25. Workshops per therapeutic area

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

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

Source: EMA website and internal records

2.5.2. Guidelines

Table 26. EMA Guidelines with PDCO input

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

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

Source: EMA website

3. Other initiatives

3.1. Publications relating to the Paediatric Regulation

3.1.1. Publications by EMA/PDCO on the Paediatric Regulation

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