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Human Medicines Research and Development Support Division

Report to the European Commission

on companies and products that have benefited from any of the rewards and incentives in the Paediatric Regulation[1] and on the companies that have failed to comply with any of the obligations in this regulation

Year 2015

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[1] REGULATION (EC) No 1901/2006 of the EUROPEAN PARLIAMENT AND OF THE COUNCIL on medicinal products for paediatric use

Table of contents

Table of figures and tables

Acronyms, abbreviations

AEPC	Association for European Paediatric Cardiology
CC	Compliance check of PIP
CHMP	Committee for Medicinal Products for Human Use
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedure – Human
EAPS	European Academy of Paediatric Societies
EC	European Commission
EMA, the Agency	European Medicines Agency
Enpr-EMA	European Network of Paediatric Research at the European Medicines Agency
EPLTN	European Paediatric Liver Transplantation Network
ESPNIC Medicine Research Network	European Society of Paediatric Neonatal Intensive Care
EUCADET	European Children and Adolescent Diabetes and Endocrine Trial
EudraCT	European Clinical Trials Database
FDA	U.S. Food and Drug Administration
HIV	Human Immunodeficiency Virus
HMA	Heads of Medicines Agencies
IBD	Inflammatory bowel disease
ICAN Research	International Children's Advisory Network
INN	International non-proprietary name
IMI	Innovative Medicines Initiative
MA	marketing authorisation
MAH	marketing authorisation holder(s)
MCRN	Medicines for Children Research Network
MS	Member States
NCA	National Competent Authorities
NHS	National Health Service
NIHR	National Institute for Health Research
NPO	National patent offices
PA	Protocol Assistance
Paediatric Regulation	REGULATION (EC) No 1901/2006 of the EUROPEAN PARLIAMENT AND OF THE COUNCIL on medicinal products for paediatric use
PDCO	Paediatric Committee
PEDDCReN	Paediatric European Digestive Disease Clinical Research Network
PedRA	Pediatric Records Application
PIP	paediatric investigation plan(s)
PPRS	Pharmaceutical Price Regulation Scheme

PSP	Pediatric Study Plan
PUMA	paediatric use marketing authorisation
SA	CHMP scientific advice
SAWP	Scientific Advice Working Party
SmPC	summary of product characteristics
SPC	supplementary protection certificate

1. Synopsis

This annual report to the European Commission (EC) covers the 9th year following the implementation of the Paediatric Regulation.

A summary of the trends, major events and projects in 2015

- The PDCO assessed the highest number of applications to date (515), even though the total number of compliance checks decreased by 20% compared to 2014, see Table 1.

Table 1 - Number of applications assessed by PDCO

Application type	2007	2008	2009	2010	2011	2012	2013	2014	2015	Grand Total
Initial	109	313	301	322	192	184	214	172	210	2017
Modification	0	12	88	110	177	200	202	221	231	1241
Compliance check	0	12	36	49	59	59	64	92	74	445
Total p/a	109	337	425	481	428	443	480	485	515	3703

Source: PedRA.

- The number of Committee for Medicinal Products for Human Use (CHMP) scientific advices (SA) including paediatric questions continues to increase steadily from the start of the Paediatric Regulation and PDCO members are now contributing to such procedures in the majority of cases. This coordination leads to specialised input which has a positive impact on both SAs and PIPs.
- The number of clinical trials including children has increased significantly as has the proportion of clinical trials including children compared to the overall number of clinical trials.
- European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) enrolled more networks, bringing the number to 46. The ever increasing engagement of scientific networks has a positive impact on the development of paediatric medicines.
- Two additional inventories of paediatric needs were adopted by PDCO, providing information to applicants on unmet needs.
- A significantly higher number of active substances benefited from the six-month extension of the supplementary protection certificate (over 50% increase compared to 2014).
- Another orphan medicine has benefited from the additional specific reward (the first two benefited in 2014 from the additional two years of market exclusivity).
- Launch of pilot phase of early paediatric interaction meetings, intended to assist applicants at early stages of the development programme.
- Organisation of workshops relating to paediatric medicines in the areas of HIV, IBD and Extrapolation workshop for EU and Non-EU regulators.
- Publication of the opinion on revision of class waivers
- Drafting of the 10 year report to the EC by EMA staff and PDCO members.

2. Introduction

2.1. Scope of the report

REGULATION (EC) No 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use (Paediatric Regulation) entered into force on 26 January 2007.

Article 50(1) states*: "On the basis of a report from the Agency, and at least on an annual basis, the Commission shall make public a list of the companies and of the products that have benefited from any of the rewards and incentives in this Regulation and the companies that have failed to comply with any of the obligations in this Regulation. The Member States shall provide this information to the Agency."*

This report covers year 2015 and follows a similar structure as the previous reports prepared by the European Medicines Agency (EMA) for the EC.

2.2. Data collection and methodology

In October 2015, the Agency invited all Member States (MS) to contribute to the preparation of this report. The spreadsheet used for the compilation of data is attached in Annex 1.

The Agency also contacted the national patent offices (NPO) of each MS with regards to the medicinal products that had obtained a six-month extension of the supplementary protection certificate (SPC) in 2015. Information was also requested on medicinal products for which the extension of the SPC was pending.

The Agency received contributions from 24 out of 28 (86%) MS and from 23 out of 28 (82%) NPOs, see Annex 2. Participation of MS was slightly lower (7%) compared to 2014.

Since 2013, most of the data for EMA procedures are reported using automated analyses generated from the Agency's databases. As a consequence, some figures for years up to 2012 may be marginally different from those presented in the previous annual reports. These differences do not affect the conclusions.

In March 2016, companies identified as potentially infringing the Paediatric Regulation in 2015 were contacted in order to provide comments on the identified infringement before publication. The report was amended accordingly.

3. Companies and products that have benefited from the rewards and incentives in the regulation

3.1. Scientific advice

3.1.1. Advice from the EMA

In accordance with Article 26 of the Paediatric Regulation, the Agency provides free scientific advice on any question related to paediatric development. The advice is provided by the Scientific Advice Working Party (SAWP) and is adopted by the CHMP. For the requests on paediatric development, members of the PDCO routinely contribute to the provision of scientific advice through the SA procedures (**Table 2**, **Figure 1**).

The number of SA procedures including paediatric questions has been increasing steadily from the implementation of the Paediatric Regulation. In 2015, despite the lower number of scientific advice and protocol assistance compared previous years, more of them were of paediatric relevance: 109/510, (i.e. 21% - an increase from previous years: 16% in 2013, 20% in 2014). The majority (89%) of SA procedures with paediatric development involved a PDCO member as an expert.

Table 2 - Scientific advice (SA) and protocol assistance (PA), incl. follow-ups (by the EMA, SAWP and CHMP, p/a 2009-2015)

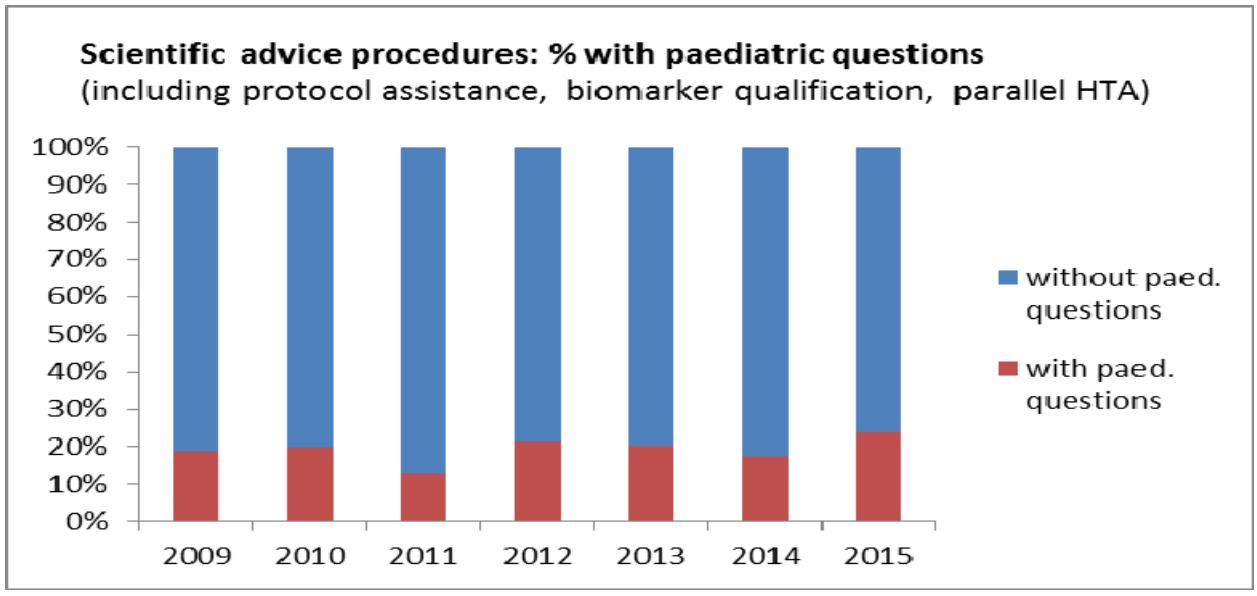
	2009	2010	2011	2012	2013	2014	2015
Total no. of advice (SA and PA)	388	400	433	420	473	551	510
No. of SA/PA/qualification of biomarker procedures incl. questions on paediatric development	74	80	57	91	96	97[1]	109[2]
Paediatric-only or mixed advice that involved a PDCO members as experts	68	80	55	91	93	88	97

Source: EMA databases.

[1] biomarker procedures with paediatric relevance n=7;

[2] includes parallel HTA n=2 and biomarker procedures n=8

Figure 1 - Scientific advice and protocol assistance percentage with paediatric questions



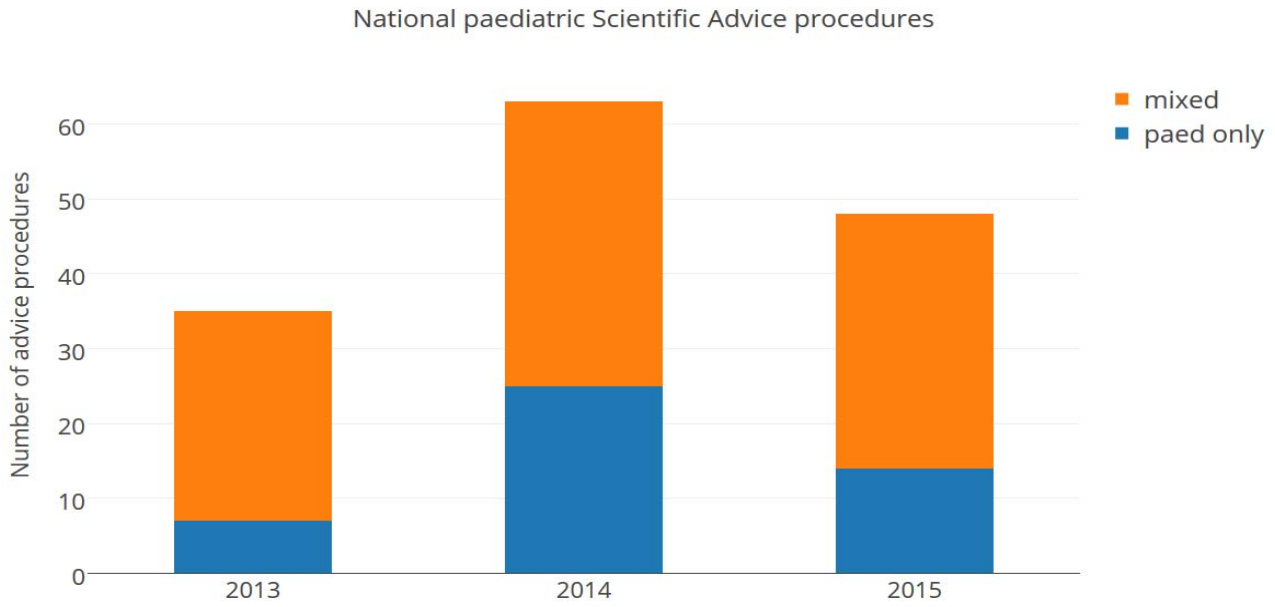
3.1.2. Advice from the National Competent Authorities

In 2015, a total of 48 either mixed adult-paediatric or paediatric only scientific advices were provided by MS (Table 3).

Table 3 - Number of national scientific advice provided by Member States in 2014 and 2015

	2014			2015		
Member state	**Paed. only**	**Mixed**	**Total**	**Paed. only**	**Mixed**	**Total**
Austria	0	2	**2**	1	1	**2**
Belgium	3	4	**7**	1	4	**5**
Bulgaria	0	0	**0**	0	0	**0**
Croatia	0	0	**0**			
Cyprus	0	0	**0**	0	0	**0**
Czech Republic	0	0	**0**	0	0	**0**
Denmark	2	0	**2**	0	1	**1**
Estonia	0	0	**0**	0	0	**0**
Finland	1	0	**1**	0	2	**2**
France	1	2	**3**			
Germany	12	16	**28**	6	12	**18**
Hungary	0	0	**0**	0	0	**0**
Ireland						
Italy	1	1	**2**	2	1	**3**
Latvia				0	0	**0**
Lithuania	0	0	**0**	0	1	**1**
Luxembourg						
Malta	0	0	**0**			
Poland	0	0	**0**	0	0	**0**
Portugal	1	0	**1**	0	0	**0**
Romania	0	0	**0**	0	0	**0**
Slovakia						
Slovenia	0	0	**0**	0	0	**0**
Spain	2	0	**2**	0	3	**3**
Sweden	0	0	**0**	0	0	**0**
The Netherlands	0	0	**0**			
United Kingdom	2	13	**15**	4	9	**13**
Total of advices	**25**	**38**	**63**	**14**	**34**	**48**

Figure 2 - National scientific advice procedures in 2013, 2014 and 2015

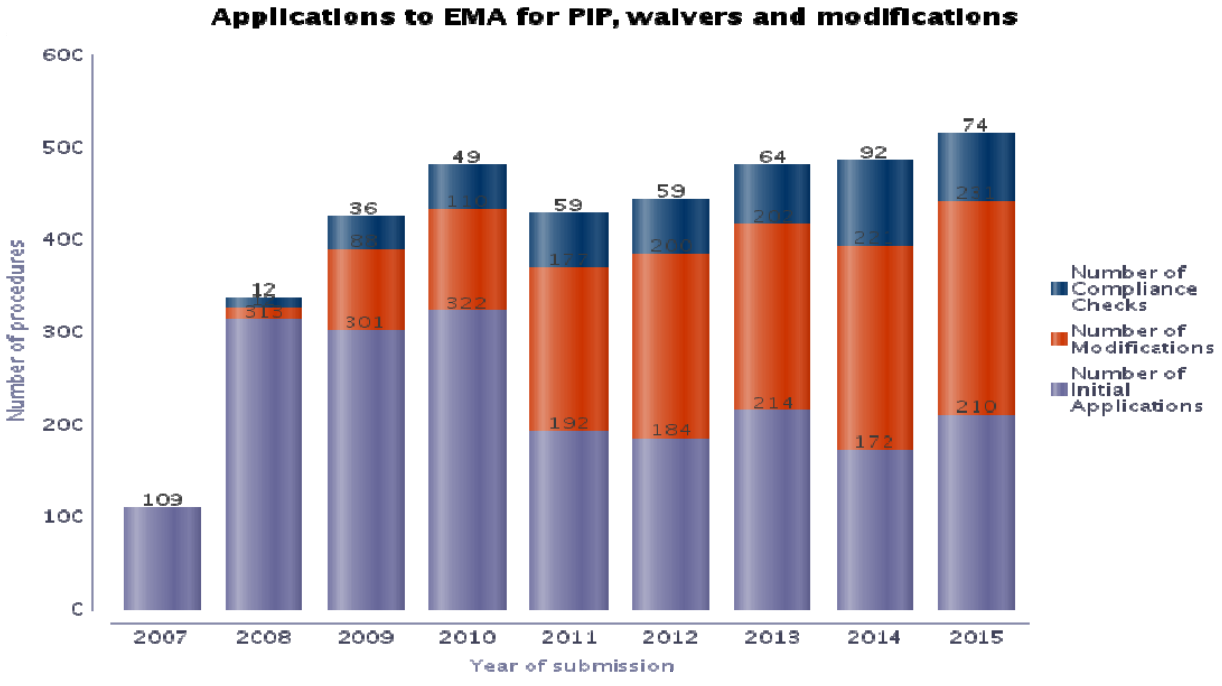


3.2. Paediatric investigation plans and waivers

3.2.1. Applications

The total number of applications for PIPs, waivers, compliance checks and modifications of agreed PIPs in 2015 (515) increased compared to 2014 (485) and 2013 (480). (see Figure 3). In 2015, 136 applications were received for PIPs, 231 for modifications, 74 for full waivers and 74 for compliance checks.

Figure 3 - Applications for PIPs, waivers, compliance checks and modifications of agreed PIPs



3.2.2. Opinions

The table below (**Table 4**) is a compilation of PDCO opinions per year since 2011. It includes opinions on PIPs, product specific waivers, waivers on own motion for PIP applications and modifications of an agreed PIP..

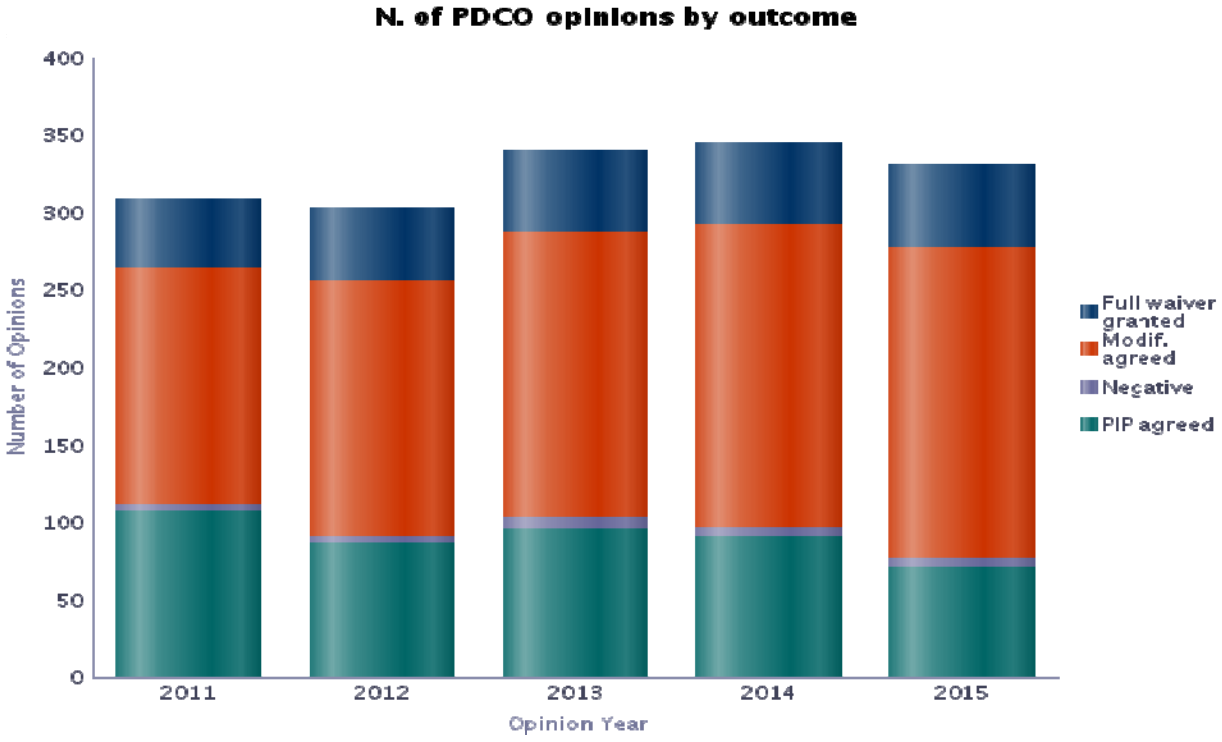
Table 4 - Opinions on paediatric investigations plans and waivers

Number of	2011	2012	2013	2014	2015
Positive opinions on PIP applications	**107**	**87**	**96**	**91**	**71**
Positive opinions on product-specific waivers	**44**	**47**	**51**	**46**	**47**
Positive opinions on a modification of an agreed PIP	**152**	**165**	**184**	**195**	**200**
Product-specific waivers granted on own motion for PIP applications	**1**	**0**	**1**	**5**	**6***
Negative opinions on PIP	**1**	**1**	**2**	**1**	**0**
Negative opinions on product-specific waivers	**2**	**2**	**2**	**1**	**3**
Negative opinions on modifications of an agreed PIP	**2**	**1**	**3**	**4**	**3**
Grand total of opinions	**309**	**303**	**340**	**345**	**331**

Source: PedRA, *one waiver on own motion was granted following a modification application

A summary of the data is provided in **Figure 4**.

Figure 4 - Number of opinions by outcome



3.2.3. Publication of PDCO opinions and EMA decisions

The EMA decisions on PDCO opinions are published without confidential information. They can be found on the EMA website, in a dedicated webpage. In 2015, 320 EMA decisions were issued.

3.2.4. Class waivers

The latest EMA decision on class waivers, dated 23 July 2015, can be found on the EMA website.

In 2015, 49 requests for class waivers applicability were assessed and their outcomes were adopted during monthly PDCO plenary meetings (**Table 5**):

- 86% of the requests were given a positive outcome; for each of these requests, the proposed indication in adults was assessed as being covered by the condition which is class waived in paediatric population.
- 14% of the requests were given a negative outcome, on the following conditions: treatment of coronary atherosclerosis, diagnosis of breast carcinoma, treatment of Alzheimer's disease, treatment of gastroenteropancreatic neuroendocrine tumours, treatment of pancreatic malignant neoplasms, adenocarcinoma of the pancreas, adenocarcinoma of the colon and rectum.
- 61% of the requests involved products used in oncology.
- The PDCO recommended that for 37% of the requests, the products may be developed for another condition for which a therapeutic need in children has been identified.

Table 5 - Requests of confirmation of applicability of a class waiver - 2015

	Confirmed	Not confirmed	Total
All requests	42	7	49
Of which in the therapeutic area of oncology	*25*	*5*	*30*
Potential use in children identified by PDCO in another condition	15	2	17

3.2.5. Modifications of agreed PIPs

In 2015, 200 PDCO opinions were adopted on modifications of agreed PIPs (out of a total of 331 PDCO opinions) compared to 195 in 2014.

The number of requests for modification of agreed PIPs continues to increase moderately but this is expected as the number of current "active" PIPs is still on the rise. It was foreseen that an agreed PIP would be subjected to modification procedures as the progress in the development of the product requires changes to the development plan.

The number and type of changes requested in modification procedures varies considerably, since a full modification procedure is required to change any key element, e.g. a single timeline for completion of a study.

However relative to the number of all existing agreed PIPs, the number of requests for modifications is actually decreasing, with a lower ratio of requests for modification per total number of agreed PIPs every year (ratio shown in **Figure 5**; data from Table 6).

Figure 5 - Ratio of modification requests per total of existing agreed PIPs

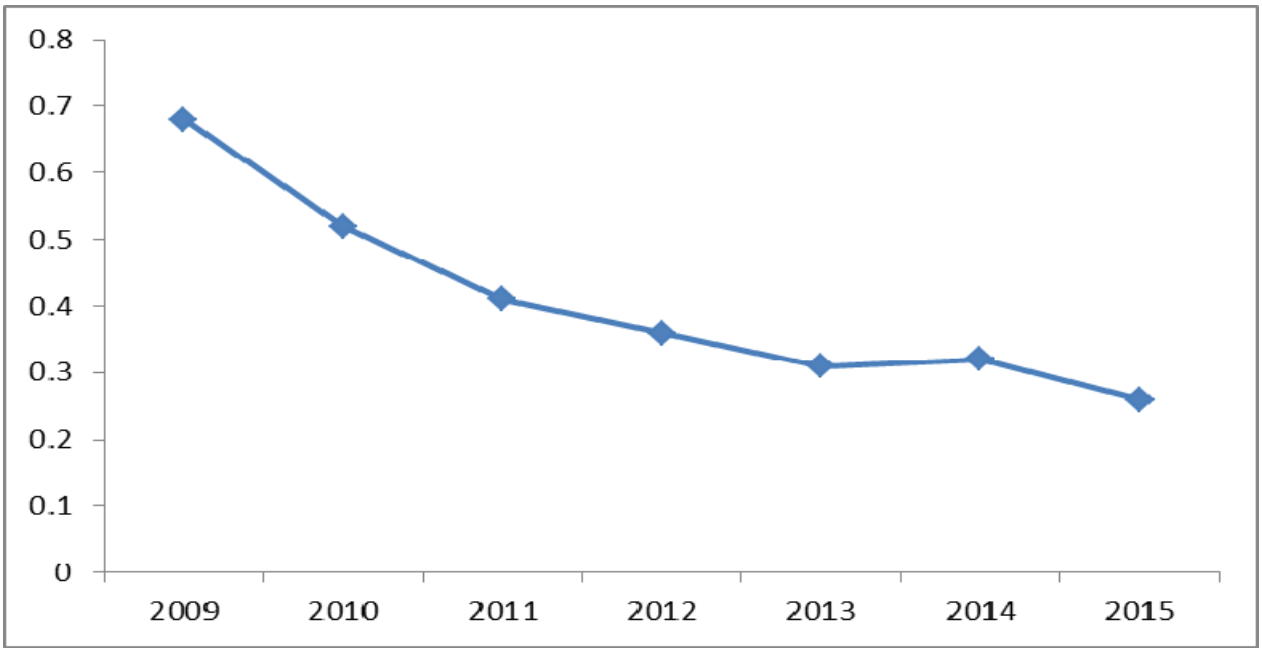


Table 6 - PIPs agreed and modifications requested - ratio of PIP modification requests to cumulative number of first PIPs

	Year							
Number of	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
PIPs agreed per year	76	122	185	116	95	92	91	76
PIPs agreed	76	198	383	499	594	686	777	853
Positive final CC	5	13	22	31	35	51	82	99
"Ongoing" PIPs	71	185	361	468	559	635	695	754
Modification requested	5	48	96	149	169	176	221	199
Ratio (modifications/cumulative total of ongoing PIPs in the previous year)		0.68	0.52	0.41	0.36	0.31	0.32	0.26

This suggests that the exercise in simplification of the PIP opinions, with a reduction of the level of detail in the key elements of the opinions, seems to result in reduction of the number of modification procedures per PIP which was one of the objectives of the simplification exercise.

3.2.6. Compliance checks

A compliance check (CC) can be done at the EMA or by NCAs, either as part of validation of applications for marketing authorisation; or validation of applications for variations/extensions of the MA; or on request of the applicant to the PDCO, prior to the submission of such applications. At the end of the regulatory procedure, a compliance statement is issued by the relevant authority (EC, EMA or NCA accordingly).

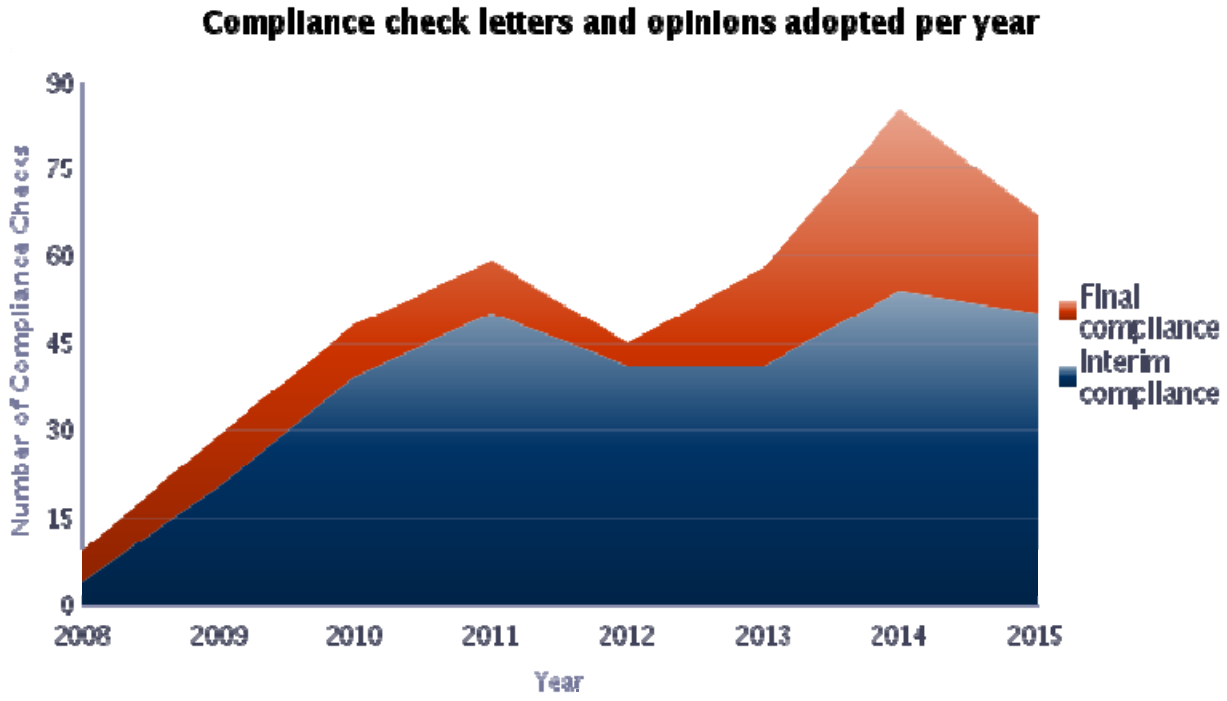
No NCA reported having checked compliance of a PIP in 2015.

In 2015, the PDCO adopted 17 positive opinions on full (final) compliance check (see Table 7 and **Figure 6**).

Table 7 - PDCO Opinions on compliance and outcome of interim compliance check

Type of CC	PDCO outcome	2008	2009	2010	2011	2012	2013	2014	2015	Total
Interim (partial)	Negative	0	2	0	3	1	1	1	**3**	**11**
	Positive	4	18	39	47	40	40	52	**47**	**287**
Full (final)	Negative opinion	0	1	0	0	0	1	0	**0**	**2**
	Positive opinion	5	8	9	9	4	16	31	**17**	**99**
Totals		**9**	**29**	**48**	**59**	**45**	**58**	**84**	**67**	**399**

Figure 6 - compliance check procedures



3.3. Compliance statement included in a marketing authorisation

3.3.1. Compliance statement for centrally-authorised medicinal products

In 2015, the EMA issued seven compliance statements related to regulatory submissions for authorised products in accordance with Article 7 and 8 (**Table 8**). This is the same amount as 2014 and an increase compared to 2013 (three).

Table 8 - compliance statement in centralised medicines

Company	Invented name	INN	Type of procedure
Merck Sharp & Dohme Limited	DUTREBIS	Lamivudine / raltegravir potassium	Initial MA
Sanofi Pasteur MSD	Gardasil 9	Human papillomavirus vaccine [types 6, 11, 16, 18, 31, 33, 45, 52, 58] (recombinant, adsorbed)	Initial MA

Company	Invented name	INN	Type of procedure
Instituto Grifols S.A.	Flebogamma DIF	Human normal immunoglobulin	Type II variation
Shire Pharmaceuticals Ireland Ltd	Resolor	Prucalopride	Type II variation
Alexion Europe SAS	Soliris	Eculizumab	Type II variation
Marklas Nederlands BV	Stayveer	Bosentan	Type II variation
Shire Pharmaceutical Contracts Limited	Tygacil	Tigecycline	Type II variation

3.3.2. Compliance statement for medicinal products authorised through national/decentralised/mutual recognition procedure

The access to the reward for both centralised and nationally-authorised products was similar in 2015 compared to 2014 (14 products in 2015 compared to 16 products in 2014).

Table 9 - compliance statement in national/decentralised/mutual recognition medicines

Company	INN	Invented name
Laboratoire Français du Fractionnement et des Biotechnologies	Human normal immunoglobulin	IQYMUNE
Bayer GmbH	Gadobutrol	Gadovist
ALK-Abelló A/S	allergen extract mixture 12 SQ-HDM	ACARIZAX
IPSEN LIMITED	LANREOTIDE	Somatuline Autogel
GALDERMA (UK) LIMITED	IVERMECTIN	Soolantra 10 mg/g cream
Eli Lilly	Atomoxetine	Strattera
GRUNENTHAL LIMITED	TAPENTADOL HYDROCHLORIDE	PALEXIA

3.4. Rewards

3.4.1. Extensions of the supplementary protection certificate

Extensions of the Supplementary Protection Certificate are granted by National Patent Offices (see Table 10).

In 2015, 28 active substances benefited from the six-month extension compared 13 in 2014 which represents an increase. Products may be mentioned in annual reports of several years because SPC expiration (and therefore extension) may not be simultaneous in all EU countries, and therefore a product may obtain SPC extension in different years according to the country.

Table 10 - List of companies/products receiving six-months extension in 2015

Company	Invented name(s)	INN	SPC extension granted in 2015	SPC extension pending in 2015
Bristol-Myers Squibb Pharma EEIG	Orencia	Abatacept	Bulgaria	Hungary
Otsuka Pharmaceutical Europe Ltd	Abilify	Aripiprazole		Netherlands Spain
Merck Sharp and Dohme	Cancidas	Caspofungin	Luxembourg	
Genzyme Europe BV	Cholestagel	Colesevelam		Netherlands
Pfizer Limited	Enbrel	Etanercept	Bulgaria Germany	
Merck Sharp & Dohme	Ezetrol and associated names	Ezetimibe	Denmark Italy Netherlands Sweden	Austria Czech Republic Finland France Germany Greece Ireland Slovakia Spain UK
Novartis Europharm Limited	Glivec	Imatinib	Austria Czech Republic Hungary Luxembourg Spain	
Novo Nordisk A	Levemir	Insulin detemir	Denmark Italy Slovenia	Austria Bulgaria Czech Republic Finland France Germany Greece Hungary Ireland Lithuania Luxembourg Romania Slovakia Sweden UK
Merck Sharp & Dohme	Maxalt	Rizatriptan	Czech Republic	

Company	Invented name(s)	INN	SPC extension granted in 2015	SPC extension pending in 2015
Boehringer Ingelheim	Spiriva	Tiotropium bromide	Czech Republic Romania	
Otsuka Pharmaceutical Europe Ltd.	Samsca	Tolvaptan		Denmark Germany
Pfizer Limited	Vfend	Voriconazole	Austria Czech Republic Germany Greece Hungary Ireland Luxembourg Romania Slovakia Spain	
J. Uriach y Compañía, S.A.	Rupafin	Rupatadine	Austria Spain	Czech Republic Germany Greece Luxembourg
Actelion Registration Ltd	TRACLEER	Bosentan	Denmark Finland France Germany Hungary Ireland Italy Netherlands Romania Spain Sweden	Austria Greece Luxembourg Slovakia
Roche Registration Limited	Valcyte	Valganciclovir	Finland Greece Ireland	Germany Hungary Poland
Bristol-Myers Squibb Pharma EEIG	Baraclude	Entecavir	Austria Greece Hungary Luxembourg Poland Romania Spain	
Alcon Laboratories (UK) Ltd	Travatan	Travoprost	Italy Netherlands Slovenia	Austria Denmark Germany Greece Ireland Luxembourg Spain

Company	Invented name(s)	INN	SPC extension granted in 2015	SPC extension pending in 2015
Sanofi Pasteur MSD	Gardasil	Vaccine against human papillomavirus	Austria Denmark France Greece Ireland Italy Luxembourg Spain Sweden	Germany Netherlands
Merck Sharp and Dohme (Europe), Inc.	Januvia	Sitagliptin		Hungary
Forest Laboratories UK Ltd	Colobreathe	Colistimethate		Germany
Janssen-Cilag International NV	PREZISTA	Darunavir	Denmark Finland France Greece Ireland Italy Luxembourg Spain Sweden	Austria Germany
Pfizer Limited	Tygacil	Tigecycline	Denmark Finland France Hungary Ireland Italy Netherlands Sweden UK	Austria Czech Republic Germany Greece Luxembourg Spain
Les Laboratoires Servier	Corlentor/ Procoralan	Ivabradine	Denmark France Italy Sweden UK	Austria Germany Greece Ireland Luxembourg Spain
AstraZeneca AB	Crestor and associated names	Rosuvastatin	Denmark France Germany Italy Luxembourg Netherlands Sweden	Austria Greece Hungary Spain UK

Company	Invented name(s)	INN	SPC extension granted in 2015	SPC extension pending in 2015
AbbVie Ltd	Humira	Adalimumab	Austria Denmark France Germany Hungary Ireland Italy Luxembourg Netherlands Poland Slovenia Sweden UK	Bulgaria Greece Romania Slovakia Spain
Celgene Europe Limited	Abraxane	Paclitaxel		Germany
Roche Registration Ltd	Avastin	Bevacizumab		Czech Republic Hungary Slovakia

3.4.2. Orphan market exclusivity extension

In 2015, one orphan medicinal product has benefited from a two-year extension of its market exclusivity: Soliris, indicated in adults and children for the treatment of paroxysmal nocturnal haemoglobinuria and treatment of atypical haemolytic uraemic syndrome (Alexion Europe SAS).

3.5. Marketing authorisation granted or varied with mention of a waiver or a deferral in the summary of product characteristics

In 2015, number of centrally-authorised medicinal products with added mention of a deferral or a waiver in the summary of product characteristics increased in comparison to 2014 (60 for new MA in 2015 compared to 55 in 2014), see Table 11 below.

Further information on these medicinal products can be found in the European public assessment reports with the product information available on the Agency's website.

Non-centralised products whose product information has been updated to reflect waivers and deferrals are listed in Table 12 below. Further information on these medicinal products can be found on the Head of Medicines Agency website (http://www.hma.eu/).

Table 11 - List of centrally-authorised products and companies for which a deferral/waiver statement has been included in SmPC (generics not included)

Invented name	INN	Company	Waiver stat. added	Deferral stat. added	Procedure (MA / variation/line extension)
Akynzeo	Netupitant / palonosetron	Helsinn Birex Pharmaceuticals Ltd	x		MA
Cerdelga	Eliglustat	Genzyme Europe BV	x	x	MA
Cosentyx	Secukinumab	Novartis Europharm Ltd	x	x	MA
EVOTAZ	Atazanavir / cobicistat	Bristol-Myers Squibb Pharma EEIG		x	MA
Exviera	Dasabuvir	AbbVie Ltd.	x	x	MA
FARYDAK	Panobinostat	Novartis Europharm Ltd	x		MA
Fexeric	Ferric citrate coordination complex	Keryx Biopharma UK Ltd.		x	MA
Hetlioz	Tasimelteon	Vanda Pharmaceuticals Ltd.		x	MA
Holoclar	Ex vivo expanded autologous human corneal epithelial cells containing stem cells	Chiesi Farmaceutici S.p.A.		x	MA
IKERVIS	Ciclosporin	Santen Oy	x		MA
Jinarc	Tolvaptan	Otsuka Pharmaceutical Europe Ltd		x	MA
Kanuma	Sebelipase alfa	Alexion Europe SAS		x	MA
Kengrexal	Cangrelor	The Medicines Company UK Ltd		x	MA
Keytruda	Pembrolizumab	Merck Sharp & Dohme Limited		x	MA
Lenvima	Lenvatinib	Eisai Europe Ltd.		x	MA
Lixiana	Edoxaban	Daiichi Sankyo Europe GmbH		x	MA
Mysimba	Naltrexone / bupropion	Orexigen Therapeutics Ireland Limited		x	MA
Nivolumab BMS	Nivolumab	Bristol-Myers Squibb Pharma EEIG		x	MA
Odomzo	Sonidegib	Novartis Europharm Ltd	x		MA
OFEV	Nintedanib	Boehringer Ingelheim Pharma GmbH & Co. KG	x		MA
Omidria	Phenylephrine / ketorolac	Omeros London Limited		x	MA
OPDIVO	Nivolumab	Bristol-Myers Squibb Pharma EEIG		x	MA
Orbactiv	Oritavancin	The Medicines Company UK Ltd		x	MA

Invented name	INN	Company	Waiver stat. added	Deferral stat. added	Procedure (MA / variation/line extension)
Praluent	Alirocumab	sanofi-aventis groupe	x	x	MA
Quinsair	Levofloxacin	Regintel Ltd		x	MA
Raplixa	Human fibrinogen / human thrombin	ProFibrix BV		x	MA
Repatha	Evolocumab	Amgen Europe B.V.	x	x	MA
Respreeza	Human alpha1-proteinase inhibitor	CSL Behring GmbH	x		MA
Senshio	Ospemifene	Shionogi Limited	x		MA
Sivextro	Tedizolid phosphatetrifenatate	CUBIST (UK) LTD		x	MA
Strensiq	Asfotase alfa	Alexion Europe SAS		x	MA
Synjardy	Empagliflozin / metformin	Boehringer Ingelheim GmbH	x		MA
Unituxin	Dinutuximab	United Therapeutics Europe Ltd		x	MA
Viekirax	Ombitasvir / paritaprevir / ritonavir	AbbVie Ltd.		x	MA
Xydalba	Dalbavancin	Durata Therapeutics International B.V.		x	MA
Zerbaxa	Ceftolozane / tazobactam	Merck Sharp & Dohme Limited		x	MA
Zontivity	Vorapaxar	Merck Sharp & Dohme Limited		x	MA
Zykadia	Ceritinib	Novartis Europharm Ltd	x		MA
BLINCYTO	Blinatumomab	Amgen Europe B.V.		x	MA
Cotellic	Cobimetinib	Roche Registration Ltd		x	MA
Cresemba	Isavuconazole	Basilea Medical Ltd		x	MA
ELOCTA	Efmoroctocog alfa	Biogen Idec Ltd		x	MA
Entresto	Sacubitril / valsartan	Novartis Europharm Ltd		x	MA
Genvoya	Elvitegravir / cobicistat / emtricitabine / tenofovir alafenamide	Gilead Sciences International Ltd		x	MA
IONSYS	Fentanyl	Incline Therapeutics Europe Ltd		x	MA

Invented name	INN	Company	Waiver stat. added	Deferral stat. added	Procedure (MA / variation/line extension)
Kyprolis	Carfilzomib	Amgen Europe B.V.	x		MA
Numient	Levodopa / carbidopa	Impax Laboratories Netherlands BV	x		MA
Obizur	Susoctocog alfa	Baxalta Innovations GmbH	x		MA
Orkambi	Lumacaftor / ivacaftor	Vertex Pharmaceuticals (Europe) Ltd.		x	MA
Praxbind	Idarucizumab	Boehringer Ingelheim International GmbH		x	MA
Stelara	Ustekinumab	Janssen-Cilag International N.V.		x	VA
Sycrest	Asenapine	N.V. Organon		x	VA
Imlygic	Talimogene laherparepvec	Amgen Europe B.V.		x	MA
Xadago	Safinamide	Zambon SpA		x	MA

For medicinal products authorised through national/decentralised/mutual recognition procedure, a statement on a deferral or a waiver was added in 25 cases (22 initial MAs and three MA variations, although, as seen in the table, there is a duplication because the same information is provided by several member states, see Table 12).

Table 12 - List of nationally authorised products and companies for which a deferral/waiver statement has been included in SmPC

MS	Invented name	INN	Company	Waiver stat. added	Deferral stat. added	Procedure (MA or variation)
Czech	IQYMUNE	Human normal immunoglobulin	Laboratoire Français du Fractionnement et des Biotechnologies	x		MA
Germany	Spiolto Respimat	tiotropium 2,5 µg + olodaterol 2,5 µg	Boehringer Ingelheim International GmbH	x		MA
Germany	Soolantra 10 mg/g Creme	Ivermectine	Galderma Laboratorium GmbH	x		MA
Germany	Mydrane	lidocaine hydrochloride 10mg + phenylephrine hydrochloride 3,1 mg + tropicamide 0,2 mg	Laboratoires Théa S.A.	x		MA

MS	Invented name	INN	Company	Waiver stat. added	Deferral stat. added	Procedure (MA or variation)
Germany	Triveram	atorvastatine + perindopril + amlodipine	Les Laboratoires Servier	x		MA
Germany	Somatuline	Lanreotide	IPSEN PHARMA GmbH	x		VA
Germany	ACARIZAX	allergen extract mixture 12 SQ-HDM	ALK-Abelló A/S		x	MA
Italy	Silketal	Human fibrinogen, Human thrombin, Aprotinin, Calcium chloride	Kedrion S.p.a.		x	MA
Hungary	IQYMUNE	human normal immunoglobulin	LFB Biomedicaments	x		MA
Italy	Keycute/ Naxiglo	Human Normal Immunoglobulin	Kedrion S.p.a.		x	MA
Slovenia	Spiolto Respimat	tiotropium bromide & olodaterol	Boehringer	x		MA
Slovenia	Rosmela	rosuvastatin & amlodipine	Krka, d.d.	x		MA
Slovenia	Implicor	metoprolol tartrate & ivabradine	Servier Pharma d.o.o.	x		MA
Slovenia	Atozet	Ezetimibe/Atorvastatin	Merck Sharp & Dohme Limited	x		MA
Slovenia	Crinone	Progesterone	Merck Sharp & Dohme Limited	x		MA
Sweden	Soolantra	Ivermectin	Galderma Nordic AB	x		MA
Sweden	Spiolto Respimat	Tiotropium olodaterol	Boehringer Ingelheim International GmbH	x		MA
Sweden	Yanimo Respimat	Tiotropium olodaterol	Boehringer Ingelheim International GmbH	x		MA
Sweden	Ramipril/Amlodipine Actavis	Ramipril, Amlodipine besilate	Actavis Group PTC ehf.	x		MA

MS	Invented name	INN	Company	Waiver stat. added	Deferral stat. added	Procedure (MA or variation)
Sweden	Seasonique	Levonorgestrel/ Ethynylestradiol and Ethinylestradiol	Teva BV	x		MA
Sweden	Acarizax	Standardised allergen extract from house dust mites (Dermatopltagoides pteronyssinus and Dermatophagoides farinae)	ALK-Abelló A/S	x		MA
Sweden	Somatuline Autogel	Lanreotide acetate	Institut Produits Synthése	x		VA
UK	Somatuline Autogel	LANREOTIDE	IPSEN LIMITED	x		VA
UK	Soolantra 10 mg/g cream	IVERMECTIN	GALDERMA (UK) LIMITED	x		MA
UK	PALEXIA 25 mg film-coated tablets	TAPENTADOL HYDROCHLORIDE	GRUNENTHAL LIMITED		x	MA

3.6. Research incentives

3.6.1. European Network of Paediatric Research at the European Medicines Agency

Based on the submitted Enpr-EMA[2] self-assessment reports, the Enpr-EMA paediatric clinical trials networks are classified in four categories[3].

In 2015, Enpr-EMA expanded with the addition of two new networks (one recognised as category 1 and one as category 3):

- Category 1: Duke Clinical Research Institute (DCRI);
- Category 3: Swiss Research Network of Clinical Pediatric Hubs (SwissPedNet)

At the end of the year, Enpr-EMA had 46 registered networks:

- 19 networks (41%) were recognised as Enpr-EMA Category 1 (full Enpr-EMA members);
- 3 networks (7%) were recognised as Category 2;
- 20 networks (43%) were recognised as Category 3;
- 4 networks (9%) were recognised as Category 4.

Information of each individual Enpr-EMA registered network that has submitted their data in a self-assessment report can be found in the fully searchable Enpr-EMA Network Database published on the Enpr-EMA website[2]. This is the central resource for researchers and study sponsors seeking to identify research networks for paediatric clinical trials in Europe. Centres can be identified through networks.

Highlights of Enpr-EMA activities in 2015 included:

- Seventh open workshop between networks, industry and patients organisations, followed by networks and Co-ordinating group meetings
- Establishment of an additional Enpr-EMA WG: a working group on educational training of the research staff in paediatric clinical trials.

3.6.2. Inventory of paediatric needs

The draft inventories of paediatric needs in endocrinology and gastroenterology were adopted in 2015.

The draft inventories of paediatric medicines in respiratory diseases and immunology will be finalised in 2016.

2 Enpr-EMA is the European network of existing national and European networks, investigators and centres with specific expertise in the performance of clinical trials in the paediatric population: http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000303.jsp

3 Category 1: networks fulfilling all minimum quality criteria for full membership of Enpr-EMA.
Category 2: networks potentially fulfilling all minimum criteria but in need of clarifying some issues before becoming a full member of Enpr-EMA.
Category 3: networks not currently fulfilling minimum criteria.
Category 4: networks who do not run paediatric clinical trials but have an expertise in clinical trial methodology.

3.7. Authorisation of paediatric clinical trials

The authorisation of clinical trials in the European Union is under the responsibility of the Member States.

The Agency (with its scientific committees) has been contributing to the EC guidance on the protocol-related information and results-related information concerning paediatric clinical trials to be entered into the European Clinical Trials Database (EudraCT), as well as the information to be made public in the European Clinical Trials Register.

The functionality to capture results-related data in the EudraCT database went live in October 2013, and the official "finalisation of the programming" date occurred on 21 July 2014. By the end of 2015 results-related information had been uploaded to the EudraCT database for more than one thousand paediatric trials.

The data presented in Table 13 and Table 14 were extracted from the protocol-related information in EudraCT. It is important to note that the compilation of most of the data fields in EudraCT is not mandatory, including some that are relevant for paediatric information, and that these data are provided by sponsors and entered by NCAs (for studies conducted in the EU). Any differences between the data reported for previous years in the following tables and this report may be due to continual data cleansing and improvement activities.

Table 13 - Paediatric clinical trials by year of authorisation (or, if not available, by year of protocol upload into EudraCT).

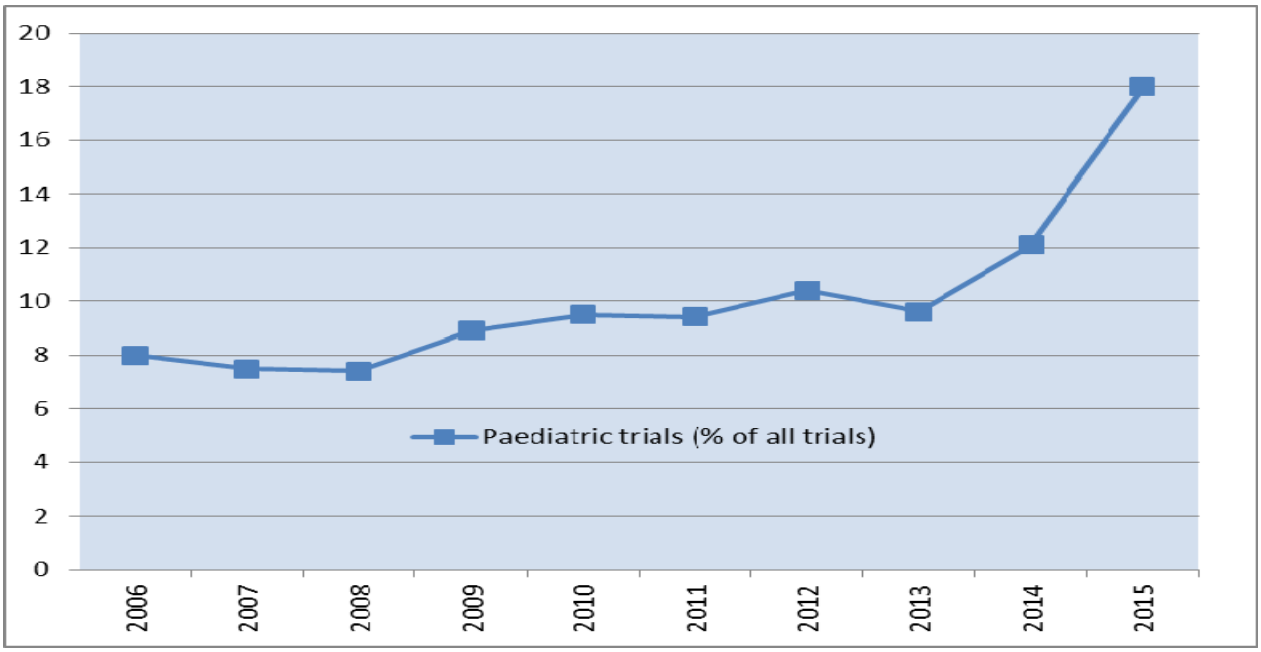
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Paediatric[1] trials	340	362	342	407	391	372	401	344	434	763
Total number of trials (adults and / or children)	4272	4855	4640	4555	4134	3971	3865	3576	3588	4242
Proportion of paediatric trials of all trials (%)	8.0	7.5	7.4	8.9	9.5	9.4	10.4	9.6	12.1	18
Exclusively[2] paediatric trials	196	188	185	241	230	218	257	211	284	473

Source: EudraCT Data.

[1] A paediatric trial is a trial that includes at least one participant < 18 years of age

[2] An exclusively paediatric trial is a trial that includes only participants < 18 years of age

Figure 7 - Proportion of paediatric clinical trials of all trials (by year of authorisation).



From the data shown above, the proportion of paediatric trials has increased to over 18% of all trials in 2015.

Table 14 - Number of children planned to be enrolled in clinical trials, by age by year of authorisation (or, if not available, by year of protocol upload into EudraCT).

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Preterm newborns	0	0	0	327	82	2,527	1,552	3,634	4,997	1,979
Newborns	0	98	5	184	169	1,353	2,283	1,488	2,168	1,749
Infants and toddlers	530	119	20	54,715	2,224	13,318	62,226	17,772	39,095	122,295
Children	2,683	706	270	5,783	2,771	21,665	30,831	27,994	65,824	48,358
Adolescents	435	36,458	285	5,801	4,869	20,206	22,680	17,628	45,177	36,921
Sum of above	3,648	37,381	580	66,810	10,115	59,069	119,572	68,516	157,261	211,302

Source: EudraCT Data. All clinical trials have been reported in this table, including clinical trials for immunological medicinal products.

Since the implementation of the Paediatric Regulation, the number of paediatric study participants in clinical trials has significantly increased to more than 210,000 in 2015. Compared to the first years after inception of the Paediatric Regulation significantly more children in all paediatric age groups are now included in clinical trials. However, beyond this general statement it is difficult to describe any further trends as the data are heavily influenced by a limited number of trials that include very high numbers of children (e.g. for vaccines); the initiation of these trials in a given year may significantly skew the data, as shown by the wide fluctuation in patient numbers.

3.8. Paediatric use marketing authorisation

No new PUMA was authorised in 2015.

3.9. Article 45/46 of the Paediatric Regulation

3.9.1. Article 45 submissions

In accordance with Article 45 of the Paediatric Regulation, existing paediatric studies were to be submitted by 26 January 2008. Information has been received for approximately one thousand active substances, with several documents for each of them (some may relate to the same study).

- For centrally-authorised products the project has been completed and no procedures were evaluated in 2015.
- For nationally authorised products, due to the large number of studies submitted, the assessment is ongoing and undertaken in work-sharing waves and between Member States. In 2015, 15 active substances (with/without combinations) were assessed. The list of substances and the resulting recommended amendments of the SmPCs are presented in Annex 4. Information can also be found on the CMD(h) website.

3.9.2. Article 46 submissions

In accordance with Article 46 of the Paediatric Regulation, a marketing authorisation holder has to submit to the NCA any MAH-sponsored studies involving the use of an authorised medicinal product in the paediatric population, whether or not they are part of a PIP, within 6 months of completion of the trial.

- For centrally authorised products, 85 procedures of evaluation were concluded in 2015. The CHMP recommended a change in the product information in 12 cases, corresponding to 11 medicinal products (for one product changes were recommended in two different procedures). There was no recommendation on change in a therapeutic indication.
- For nationally-authorised medicinal products, the assessment was finalised for 13 procedures with published public assessment reports which included 16 studies. 23% of the assessed procedures recommend change(s) to paediatric information in the summary of product characteristics one of which was a new paediatric indication for Leuprorelin.

The list of assessment reports products including amendments of the SmPCs is presented in Annex 5.

3.10. Register of placing on the market

In 2015, the Agency maintained the "Register of deadlines to put a medicinal product on the market" (Article 33 of the Paediatric Regulation), established in 2012. This lists the 2-year deadlines by which MAHs have to place their medicinal products on the market following completion of an agreed paediatric investigation plan and obtaining a paediatric indication (Annex 6).

4. Failure to comply with the obligations set out in the Paediatric Regulation

4.1. Submission of PIP and waiver applications to the PDCO

Article 16 of the Paediatric Regulation requires pharmaceutical companies to submit applications for a PIP and/or a waiver no later (except when duly justified) then upon completion of the human pharmacokinetic (PK) studies in adults specified in Section 5.2.3 of Part I of Annex I to Directive 2001/83/EC.

Late applications for PIPs or waivers may delay the submission or the validation of the applications for the marketing authorisation in adults if the applicant does not have the EMA decision at the time of submission.

Additionally, late submissions may put the PDCO in a difficult situation as the evaluation may conclude that inappropriate or unnecessary studies or trials have been performed (underpowered studies, invalid endpoints, inappropriate trial duration, etc.) but the PDCO is unable to request further data for ethical reasons, i.e. to avoid exposing children in further trials.

Late submissions of PIP/waiver are reported since 2010 (Table 15) for applications with a delay greater than six months. From 2014 only those considered not justified by the PDCO are reported.

Table 15 - Time lag between completion of adult PK studies and submission of PIP and waiver applications (procedures with EMA decision)

No. delayed** applications	2010	2011	2012	2013	2014	2015
PIPs (% of total)	65 (74%)	44 (59%)	34 (39%)	18 (20%)	12* (13%)	7* (10%)
Time lag (months) - median (range)	22	35 (9-159)	35 (9-241)	28 (9-66)	29 (7-52)	29 (15-65)
Full waivers (% of total)	26 (59%)	13 (42%)	11 (23%)	6 (11%)	4* (8%)	4* (8%)
Time lag (months) - median (range)	18	35 (9-137)	61 (19-179)	33 (14-60)	25.5 (10-41)	69.5 (10-123)

Source: EMA Paediatric database. *Delay considered not justified by the PDCO. ** Six months or later after deadline.

The list of unjustified late submissions of PIPs is presented in Annex 7.

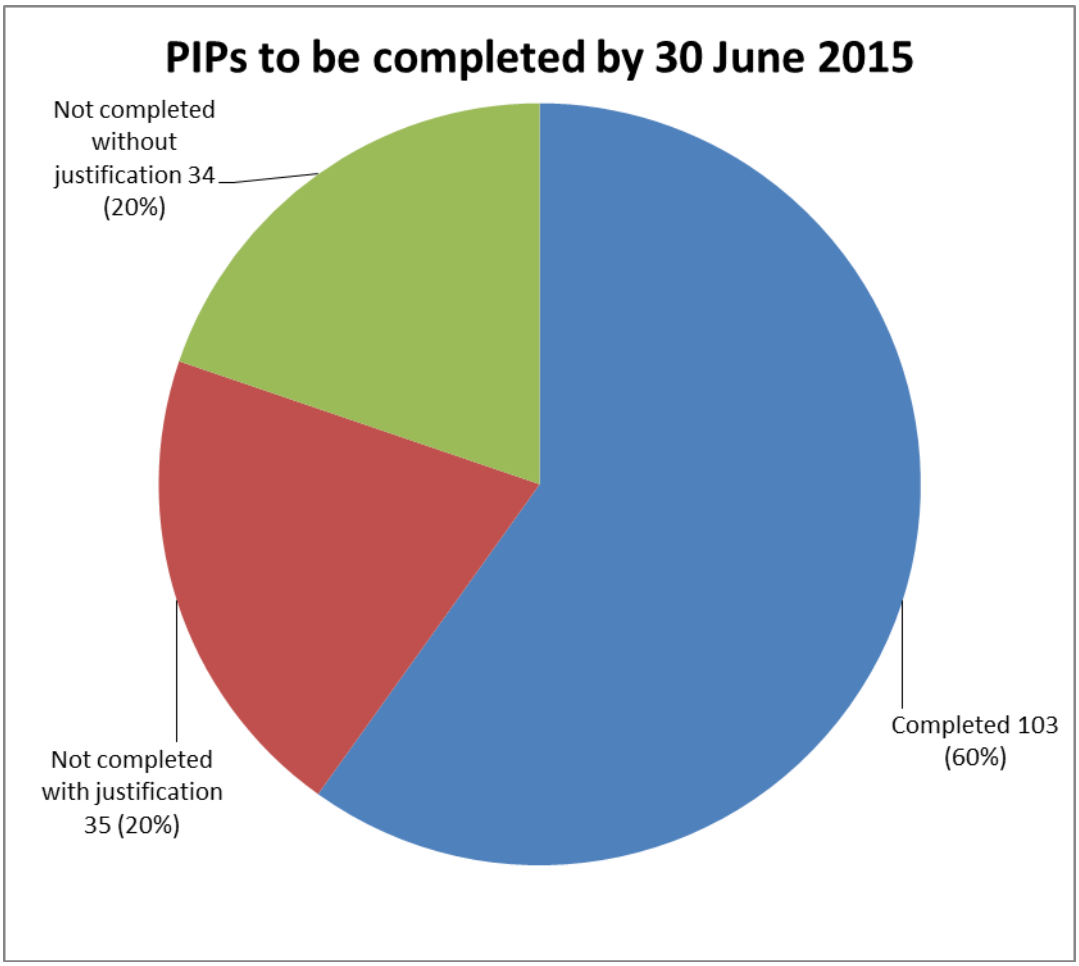
4.2. Completion of PIPs

The EMA decisions include dates of PIP completion.

The Agency made an analysis of the PIPs with a completion date scheduled before 30 June 2015. The cut-off date was chosen as end of June, as applicants must submit the complete study reports within six months of completion (Art. 46), and studies (and PIPs) completed after June 2015 may not have been subjected to compliance check.

In total, 172 PIPs were scheduled to be finished by 30 June 2015 (**Figure 8**). Of those, 103 PIPs have been completed. Of the remaining 69, 34 have not been completed and have not provided a justification, notified us of discontinuation of the development programme or submitted a modification to change the timelines.

Figure 8 - PIPs to be completed by 30 June 2015

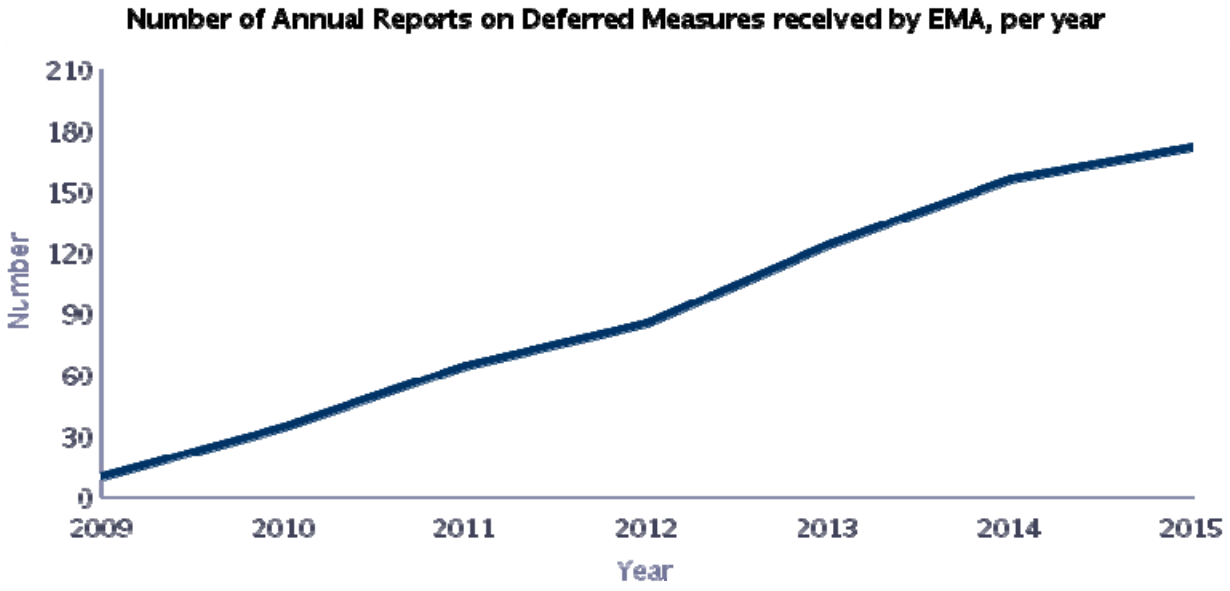


The detailed lists are in Annexes 8 and 9.

4.3. Annual reports on deferrals

The number of annual reports on deferred measures (for authorised medicinal products) submitted to the Agency is increasing linearly every year (**Figure 9**).

Figure 9 - Trend for Annual reports



The Agency received 172 annual reports on deferrals in 2015 (155 in 2014, 124 in 2013, 86 in 2012 and 65 in 2011). The total numbers of annual reports is presented in Table 16 and data are analysed according to the difficulties reported.

Over the years, more than half of the reports stated that the PIP was proceeding as planned. The types of issues are listed in Table 16. List of the companies that submitted annual report is available in Annex 10.

Table 16 - Annual reports on deferred measures

	2010	2011	2012	2013	2014	2015	Total	% of total
No problems reported	18	41	44	67	97	92	**365**	56%
Problems reported total	17	24	42	57	58	80	**282**	44%
Difficulties in developing age-related formulation(s)	*1*	*3*	*2*	*6*	*3*	*5*	***20***	*3%*
Economic problems				*1*	*0*	*3*	***4***	*0.6%*
Efficacy concerns	*4*	*1*	*2*	*1*	*2*		***12***	*1.85%*
Organizational issues (e.g. Acquisitions, mergers, applicant's internal restructuring, etc.)		*2*	*1*	*1*	*3*	*3*	***10***	*1.5%*
Other quality issues			*3*	*1*	*3*		***7***	*1.1%*
Other(s)	*9*	*10*	*17*	*26*	*29*	*37*	***128***	*20%%*
Recruitment difficulties	*10*	*15*	*29*	*35*	*31*	*45*	***167***	*25%*

	2010	2011	2012	2013	2014	2015	Total	% of total
Refusals/problems with National Competent Authority(ies)	*5*	*1*	*13*	*9*	*6*	*4*	***39***	*6%*
Refusals/problems with ethics committees	*6*	*3*	*9*	*6*	*3*	*1*	***28***	*4%*
Safety concerns	*5*	*3*	*2*	*5*	*7*	*5*	***27***	*4%*
Grand total	**35**	**65**	**86**	**124**	**155**	**172**	**647**	

In 2015, the number of MAHs not submitting the annual reports on deferred measures on time was significantly higher in comparison to 2014. The list of companies not submitting one or more annual reports is included in Table 17.

Table 17 - List of companies not submitting annual reports on deferred measures

Company	2010	2011	2012	2013	2014	2015
Merck Sharp & Dohme (Europe) Inc.	1	2	1	2		
Novartis (Europharm Limited, Vaccines and diagnostics)	1		2	1		
GlaxoSmithKline	2	1				
Pfizer Limited	1	2				
Roche Registration Limited	1	1	1	1		1
Novo Nordisk A/S		1	1	2		
Kowa Pharmaceutical Europe Company Ltd		1	1	4		
Bristol-Myers Squibb/AstraZeneca	1					
Eli Lilly and Company	1					
Janssen-Cilag International N.V.		1				1
Eisai Ltd.		1				
Genzyme Europe B.V.		1				
Sigma-Tau SpA			1	1		1
Takeda Global Research and Dev. Centre (Europe) Ltd			1			1
Theravance, Inc.			1	1		
Amgen Europe B.V.				1		
Omrix Biopharmaceuticals SA				1		1
Forest Laboratories Limited					1	1
Otsuka Pharmaceutical Europe Ltd.						
Savient Pharmaceuticals, Inc.						
AMAG Pharmaceuticals, Inc.						1
Pharmaxis Pharmaceuticals Limited						1
Clinuvel (UK) Limited						1
Sanofi-Aventis R&D						
Aastrom Biosciences DK Aps						1
Totals	**8**	**11**	**9**	**14**	**1**	**11**

The complete list of annual reports not submitted is to be found in Annex 11.

Following an amendment to the "Penalties Regulation" (EC) No 658/2007, which is applicable since July 2012, not submitting annual report is identified as one of the obligations under the Paediatric Regulation that could be subject to an infringement procedure and financial penalties. Regulation (EC) No 658/2007 applies to centrally authorised products.

Annex 1 - Guidance to Member States regarding collection of data

Annex

Preparation of the annual report to the European Commission

Guidance to Member states on compilation of data

- The information should cover the period from 1 January 2015 to 31 December 2015.
- All confidential information should be highlighted; such information will be removed prior to the publication of the report.
- You are kindly requested to complete the attached spread sheet and word document. Please try to answer all questions as accurately as possible.
- **No data is required on medicines authorised under the following legal basis: generic, biosimilar, hybrid, well-established use, homeopathic or traditional herbal medicines.**

Spread sheet

Part 1 – Marketing authorisations, variations, line extensions

According to the Article 23 of the Paediatric Regulation, the competent authority responsible for granting marketing authorisation shall verify whether an application for marketing authorisation or variation complies with the requirements laid down in Articles 7 and 8 and whether an application submitted pursuant to Article 30 complies with the agreed paediatric investigation plan.

In this sheet of the provided Excel table, we are looking for information on the statement on compliance with the paediatric investigation plan (PIP) included in a Marketing Authorisation (MA) for new medicinal products granted in 2014 either through national (N) or decentralised (DC) or mutual recognition procedure (MRP).

For each procedure (initial MA, line extension or variation with compliance statement) granted in 2014 please provide the following information:

- The international non-proprietary name (**INN**) in English or in your national language if INN not available in English;
- The **invented name** of the medicinal product;
- The name of the Marketing Authorisation Holder (**MAH**);
- Specify if the initial marketing authorisation (**MA**) was granted either through national (N),
- decentralised (DC) or mutual recognition procedure (MRP);
- The **date of the outcome** of the procedure (when the new MA, line extension or variation of the MA was granted);
- The **type of the reported procedure** (Initial MA, Line extension or variation of the MA);
- If a statement on compliance of the completed PIP has been issued;
- In which **sections of the SmPC** paediatric information was added or amended. In the columns related to section 4.1 please include wording of the new paediatric indication or the new wording relating to the extension of the paediatric indication. All other sections include drop down menus.
- If a **statement on full waiver** (meaning waiver in all paediatric subsets) or deferral has been included in the SmPC (section 5.1)

Part 2 - Scientific advice

In this specific sheet of the provided Excel table, we are looking for information on Scientific Advices given at national level only between 1 January 2015 and 31 December 2015. Please do not list any Scientific Advices given by the European Medicines Agency.

For each National Scientific Advice, please list or specify:

- The international non-proprietary name (**INN**) in English **or** in your national language only if the INN is not available in English;
- The **invented name** of the medicinal product;
- The name of the **pharmaceutical company** requesting this Scientific Advice;
- The **therapeutic area** of the concerned medicinal product;
- If this Scientific Advice was for a **paediatric development only** (paediatric only scientific advice) or **for adult and paediatric developments** (mixed scientific advice);

Word document

Part 3 – Benefits and infringements

Please complete the attached word document using the boxes provided

Annex 2 – List of National Competent Authorities and National Patent Offices that have replied to the request for information

Member State	National Competent Authorities	National Patent Office
Austria	x	x
Belgium	x	
Bulgaria	x	x
Croatia	x	
Cyprus	x	
Czech Republic	x	x
Denmark	x	x
Estonia	x	x
Finland	x	x
France	x	x
Germany	x	x
Greece		x
Hungary	x	x
Ireland	x	x
Italy	x	x
Latvia	x	x
Lithuania	x	x
Luxembourg		x
Malta	x	
The Netherlands		x
Poland	x	x
Portugal	x	
Romania	x	x
Slovakia		x
Slovenia	x	x
Spain	x	x
Sweden	x	x
United Kingdom	x	x
Iceland		
Norway		

Annex 3 - Compliance in Marketing Authorisation for products authorised nationally, under Mutual Recognition or decentralised procedures 2015

Member State	Marketing authorisation holder	Invented name(s)	International non-proprietary name	MA procedure	Type of procedure
Austria	Bayer	Gadovist	Gadobutrol	MRP	Variation
Czech Republic	Laboratoire Français du Fractionnement et des Biotechnologies	IQYMUNE	Human normal immunoglobulin	DC	Initial MA
Czech Republic	Eli Lilly	Strattera	Atomoxetine	DC	Line extension
Germany	ALK-Abelló A/S	ACARIZAX	allergen extract mixture 12 SQ-HDM	DC	Initial MA
Hungary	LFB Biomedicaments	IQYMUNE	human normal immunoglobulin	DC	Initial MA
Italy	J Uriach & Cia	Rupafin	Rupatadine	DC	Variation
Sweden	Bayer Pharma AG	Gadovist	Gadobutrol	DC	Variation
UK	IPSEN LIMITED	Somatuline Autogel	LANREOTIDE	MRP	Variation
UK	GALDERMA (UK) LIMITED	Soolantra 10 mg/g cream	IVERMECTIN	DC	Initial MA
UK	GRUNENTHAL LIMITED	PALEXIA	TAPENTADOL HYDROCHLORIDE	DC	Initial MA

Annex 4 - Article 45

Products authorised through national/mutual recognition/decentralised procedure

Further information – including the assessment report can be found on the webpage CMDh Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human- http://www.hma.eu/187.html.

[1] Section 4.1 Therapeutic indications

Section 4.2 Posology and method of administration

Section 4.3 Contraindications

Section 4.4 Special warnings and precaution for use

Section 4.6 Fertility, pregnancy and lactation

Section 4.8 Undesirable effects

Section 5.1 Pharmacodynamics properties

Section 5.2 Pharmacokinetic properties

Active substance	Assessment outcome: change in SmPC (Y/N)	SmPC sections [1] to be changed
Acebutolol	N	N/A
Amitriptyline	Y	Sections 4.1, 4.2 , 4.3, 4.4 and 4.5 (paediatric information clarified)
Doxazosin mesilate	Y	sections 4.2 (paediatric information clarified)
Epinephrine	Y	section 4.2 new paediatric posology, section 4.4
Famotidine	N	N/A
Famotidine in combinations	N	N/A
Indomethacin	N	N/A
Isoflurane	Y	section 4.2 (paediatric information clarified)

Active substance	Assessment outcome: change in SmPC (Y/N)	SmPC sections [1] to be changed
Phentolamine mesilate	N	N/A
Pravastatin*	N	N/A
Tinzaparin*	Y	Section 5.2 (new study data)
Zopiclone*	Y	sections 4.1, 4.2, 4.4 (paediatric information clarified)
Anti-human T-lymphocyte immunoglobulin from rabbits*	Y	sections 4.2, 4.8, 5.1 (paediatric information clarified)
Arginine hydrochloride*	N	N/A
Levocabastine*	Y	sections 4.1, 4.2, 4.8, 5.2 (paediatric information clarified)

*publication in 2015 (procedure finalised in a previous year)

Total:

- 15 active substances (with/without combinations) assessed
- 7 active substances (with/without combinations) for which no change to current SmPC is recommended
- 8 active substances for which a change to SmPC sections is recommended

Annex 5 – Article 46

Centrally authorised products

Further information on these medicinal products can be found under the European Public Assessment Report published on the Agency website.

Some products are repeated in the below table as there were several and different study submissions with the same products falling under the scope of Art.46, during the period 2015.

[1] Section 4.2 Posology and method of administration

Section 4.4 Special warnings and precaution for use

Section 4.8 Undesirable effects

Section 5.2 Pharmacokinetic properties

Active substance	Brand name	MAH	Assessment outcome: change in SmPC (Y/N)	SmPC sections [1] to be changed
Aripiprazole	Abilify	Otsuka Pharmaceutical Europe Ltd	N	N/A
Aripiprazole	Abilify	Otsuka Pharmaceutical Europe Ltd	N	N/A
Insuline glulisine	Apidra	Sanofi-aventis Deutschland GmbH	N	N/A
Meningococcal group b vaccine (rdna, component, adsorbed)	Bexsero	GSK Vaccines S.r.l	Y	4.8 and 5.1
Meningococcal group b vaccine (rdna, component, adsorbed)	Bexsero	GSK Vaccines S.r.l	N	N/A
Aztreonam	Cayston	Gilead Sciences International Ltd	N	N/A

Active substance	Brand name	MAH	Assessment outcome: change in SmPC (Y/N)	SmPC sections [1] to be changed
Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed)	Cervarix	GlaxoSmithKline Biologicals	N	N/A
Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed)	Cervarix	GlaxoSmithKline Biologicals	N	N/A
Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed)	Cervarix	GlaxoSmithKline Biologicals	N	N/A
Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed)	Cervarix	GlaxoSmithKline Biologicals	N	N/A
Daptomycin	Cubicin	Novartis Europharm Ltd	Y	sections 4.1 and 4.2 (new indication)
Daptomycin	Cubicin	Novartis Europharm Ltd	N	N/A
Dexmedetomidine	Dexdor	Orion Corporation	N	N/A
Sitagliptin / metformin hydrochloride	Efficib	Merck Sharp & Dohme Limited	N	N/A
Aprepitant	EMEND	Merck Sharp & Dohme Limited	N	N/A
Etanercept	Enbrel	Pfizer Limited	N	N/A
Deferasirox	Exjade	Novartis Europharm Ltd	Further information required	N/A
Agalsidase beta	Fabrazyme	Genzyme Europe BV	N	N/A
Perampanel	Fycompa	Eisai Europe Ltd.	Further information required	N/A
Perampanel	Fycompa	Eisai Europe Ltd.	Y	Section 4.8

Active substance	Brand name	MAH	Assessment outcome: change in SmPC (Y/N)	SmPC sections [1] to be changed
Imatinib	Glivec	Novartis Europharm Ltd	N	N/A
Human normal immunoglobulin	Hizentra	CSL Behring GmbH	N	N/A
Adalimumab	Humira	AbbVie Ltd.	N	N/A
Canakinumab	ILARIS	Novartis Europharm Ltd	N	N/A
Canakinumab	ILARIS	Novartis Europharm Ltd	N	N/A
Canakinumab	ILARIS	Novartis Europharm Ltd	N	N/A
Mecasermin	Increlex	Ipsen Pharma	N	N/A
Mecasermin	Increlex	Ipsen Pharma	N	N/A
Raltegravir	Isentress	Merck Sharp & Dohme Limited	N	N/A
Raltegravir	Isentress	Merck Sharp & Dohme Limited	N	N/A
Fosaprepitant	Ivemend	Merck Sharp & Dohme Limited	N	N/A
Sitagliptin / metformin hydrochloride	Janumet	Merck Sharp & Dohme Limited	N	N/A
Ivacaftor	Kalydeco	Vertex Pharmaceuticals (Europe) Ltd.	N	N/A
Ivacaftor	Kalydeco	Vertex Pharmaceuticals (Europe) Ltd.	N	N/A
Levetiracetam	Keppra	UCB Pharma SA	N	N/A
Levetiracetam	Keppra	UCB Pharma SA	N	N/A
Insulin glargine	Lantus	Sanofi-aventis Deutschland GmbH	N	N/A
Insulin detemir	Levemir	Novo Nordisk A/S	N	N/A
Lipegfilgrastim	Lonquex	Sicor Biotech UAB	Y	4.2, 4.8, 5.1, 5.2
Pregabalin	Lyrica	Pfizer Limited	N	N/A
Lixisenatide	Lyxumia	Sanofi-Aventis Groupe	N	N/A
Measles, mumps and rubella vaccine (live)	M-M-RVAXPRO	Sanofi Pasteur MSD SNC	N	N/A

Active substance	Brand name	MAH	Assessment outcome: change in SmPC (Y/N)	SmPC sections [1] to be changed
Meningococcal group a, c, w135 and y conjugate vaccine	Menveo	GSK Vaccines S.r.l	N	N/A
Meningococcal group a, c, w135 and y conjugate vaccine	Menveo	GSK Vaccines S.r.l	N	N/A
Cinacalcet	Mimpara	Amgen Europe B.V.	N	N/A
Alglucosidase alfa	Myozyme	Genzyme Europe BV	N	N/A
Alglucosidase alfa	Myozyme	Genzyme Europe BV	Further information required	N/A
Insulin aspart	NovoRapid	Novo Nordisk A/S	N	N/A
Insulin aspart	NovoRapid	Novo Nordisk A/S	N	N/A
Influenza vaccine (surface antigen, inactivated, prepared in cell cultures)	Optaflu	Novartis Influenza Vaccines Marburg GmbH	Y	5.1
Influenza vaccine (surface antigen, inactivated, prepared in cell cultures)	Optaflu	Novartis Influenza Vaccines Marburg GmbH	Y	5.1
Abatacept	Orencia	Bristol-Myers Squibb Pharma EEIG	N	N/A
Pregabalin	Pregabalin Pfizer	Pfizer Limited	N	N/A
Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)	Prevenar 13	Pfizer Limited	N	N/A
Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)	Prevenar 13	Pfizer Limited	N	N/A
Aliskiren	Rasilez	Novartis Europharm Ltd	Y	sections 4.2, 4.4, 4.8, 5.1

Active substance	Brand name	MAH	Assessment outcome: change in SmPC (Y/N)	SmPC sections [1] to be changed
Revatio	Sildenafil	Pfizer Limited	Further information required	N/A
Atazanavir / atazanavir sulfate	Reyataz	Bristol-Myers Squibb Pharma EEIG	N	N/A
Atazanavir / atazanavir sulfate	Reyataz	Bristol-Myers Squibb Pharma EEIG	N	N/A
Human rotavirus, live attenuated	Rotarix	GlaxoSmithKline Biologicals S.A.	N	N/A
Human rotavirus, live attenuated	Rotarix	GlaxoSmithKline Biologicals S.A.	N	N/A
Rotavirus vaccine (live, oral)	RotaTeq	Sanofi Pasteur MSD SNC	N	N/A
Rotavirus vaccine (live, oral)	RotaTeq	Sanofi Pasteur MSD SNC	N	N/A
Insulin degludec / insulin aspart	Ryzodeg	Novo Nordisk A/S	N	N/A
Basiliximab	Simulect	Novartis Europharm Ltd	N	N/A
Pneumococcal polysaccharide conjugate vaccine (adsorbed)	Synflorix	GlaxoSmithKline Biologicals	N	N/A
Tobramycin	TOBI Podhaler	Novartis Europharm Ltd	N	N/A
Insulin glargine	Toujeo	Sanofi-aventis Deutschland GmbH	N	N/A
Bosentan	Tracleer	Actelion Registration Ltd.	N	N/A
Bosentan	Tracleer	Actelion Registration Ltd.	N	N/A
Sitagliptin / metformin hydrochloride	Velmetia	Merck Sharp & Dohme Limited	N	N/A
Voriconazole	Vfend	Pfizer Limited	Y	sections 4.8, 5.1

Active substance	Brand name	MAH	Assessment outcome: change in SmPC (Y/N)	SmPC sections [1] to be changed
Liraglutide	Victoza	Novo Nordisk A/S	N	N/A
Elosulfase alfa	Vimizim	BioMarin Europe Ltd	N	N/A
Lacosamide	Vimpat	UCB Pharma SA	N	N/A
Lacosamide	Vimpat	UCB Pharma SA	N	N/A
Lacosamide	Vimpat	UCB Pharma SA	N	N/A
Human coagulation factor viii / human von willebrand factor	Voncento	CSL Behring GmbH	Y	section 4.2
Everolimus	Votubia	Novartis Europharm Ltd	Y	sections 4.2, 4.4
Everolimus	Votubia	Novartis Europharm Ltd	Y	sections 4.2, 4.4
Ipilimumab	Yervoy	Bristol-Myers Squibb Pharma EEIG	N	N/A
Eslicarbazepine acetate	Zebinix	Bial - Portela & Cª, S.A.	N	N/A
Ceftaroline fosamil	Zinforo	AstraZeneca AB	N	N/A
Ceftaroline fosamil	Zinforo	AstraZeneca AB	N	N/A
Zoledronic acid	Zometa	Novartis Europharm Ltd	N	N/A

Total:

- 85 assessment procedures
- 60 active substances
- 9 active substances for which a change in SmPC sections is recommended.
- New paediatric indication: Daptomycin (extension of indication to include paediatric patients from 1 to 17 years for the treatment of complicated skin and soft-tissue infections)

Products authorised through national/mutual recognition/decentralised procedure

Article 46 work-sharing 2015

Source: http://www.hma.eu/291.html

[1] Section 4.2 Posology and method of administration

Section 4.4 Special warnings and precaution for use

Section 4.8 Undesirable effects

Section 5.1 Pharmacodynamics properties

Section 5.2 Pharmacokinetic properties

Name of active substance	Brand name	MAH	Assessment outcome: change in SmPC (Y/N)	SmPC sections [1] to be changed
Pancreatin	Creon Micro	Abbott	Y	section 4.2 (paediatric information clarified)
Gadoxetic acid	Eovist/Primovist	Bayer Pharma AG	Y	sections 4.2, 5.1 (new study data included)
Leuprorelin acetate*	Daronda and associated names	Abbott	Y	section 4.2 (new indication); sections 4.3, 4.4, 4.8 (new safety information); sections 5.1, 5.2 (paediatric information clarified)
tapentadol hydrochloride*	Palexia and associated names	Grunenthal	N	N/A

Name of active substance	Brand name	MAH	Assessment outcome: change in SmPC (Y/N)	SmPC sections [1] to be changed
Haemophilus Type b Vaccine Conjugated to Tetanus protein and Diphteria, Tetanus, Acellular Pertussis and Poliomyelitis Vaccine Adsorbed, Inactivated Vaccine	Pentavac/Pentaxim	Sanofi Pasteur MSD	N	N/A
Pneumococcal polysaccharide vaccine*	Pneumovax and associated names	Sanofi Pasteur MSD	N	N/A
octreotide acetate	Sandostatin LAR	Novartis Europharm Limited	N	N/A
salmeterol xinafoate/fluticasone proprionate	Seretide Diskus/Seretide Eudraler and associated names	GlaxoSmithKline	N	N/A
montelukast	Singulair and associated names	Merck Sharp & Dohme B.V.	N	N/A
atomoxetine*	Strattera	Eli Lilly and Company	N	N/A
Diphtheria, tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine, adsorbed.	Tetravac and associated names	Sanofi Pasteur MSD Ltd	N	N/A

*publication in 2015 (procedure finalised in a previous year)

Total:

- 11 active substances
- 8 active substances for which no change to current SmPC is recommended
- 3 active substances for which a change to SmPC sections is recommended
- **New paediatric indication:**
- Leuprorelin acetate: Treatment of central precocious puberty (girls under 9 years of age, boys under 10 years of age).

Annex 6 - Register of deadlines to put a medicinal product on the market

Invented name	PIP procedure number	Active substance(s)	Authorised indication(s), including paediatric indication(s) (summarised if necessary)	Date of MA	Date of variation (to include the paediatric indication)	Deadline to put on the product on the market	On the market with paediatric indication*
PegIntron ViraferonPeg	EMEA-000071-PIP01-07	Peginterferon alfa-2b	PegIntron/ViraferonPeg is indicated in a combination regimen with ribavirin for the treatment of children 3 years of age and older and adolescents, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for HCV-RNA. When deciding not to defer treatment until adulthood, it is important to consider that the combination therapy induced a growth inhibition. The reversibility of growth inhibition is uncertain. The decision to treat should be made on a case by case basis (see section 4.4)."	25/05/2000	11/11/2009	11/11/2011	Yes
Rebetol	EMEA-000070-PIP01-07	Ribavirin	Rebetol is indicated, in a combination regimen with peginterferon alfa-2b or interferon alfa-2b, for the treatment of children 3 years of age and older and adolescents, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for HCV-RNA.	07/05/1999	11/11/2009	11/11/2011	yes

Invented name	PIP procedure number	Active substance(s)	Authorised indication(s), including paediatric indication(s) (summarised if necessary)	Date of MA	Date of variation (to include the paediatric indication)	Deadline to put on the product on the market	On the market with paediatric indication*
Orencia	EMEA-000118-PIP01-07-M01	Abatacept	Orencia in combination with methotrexate is indicated for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis (JIA) in paediatric patients 6 years of age and older who have had an insufficient response to other DMARDs including at least one TNF inhibitor.	21/05/2007	20/01/2010	20/01/2012	yes
Cozaar	EMEA-000008-PIP01-07	Losartan potassium	Treatment of essential hypertension in adults and children and adolescents 6-18 years of age.	23/02/2010	23/02/2010	23/02/2012	yes

Invented name	PIP procedure number	Active substance(s)	Authorised indication(s), including paediatric indication(s) (summarised if necessary)	Date of MA	Date of variation (to include the paediatric indication)	Deadline to put on the product on the market	On the market with paediatric indication*
Pediacel	EMEA-000278-PIP01-08-M01	Purified diphtheria toxoid, Purified tetanus toxoid, Five component acellular pertussis, Inactivated poliomyelitis vaccine, Purified polyribosylribitol phosphate capsular polysaccharide of Haemophilus influenzae type b covalently bound to Tetanus protein (PRP-T)	Pediacel is indicated for primary and booster vaccination against diphtheria, tetanus, pertussis, poliomyelitis and invasive Haemophilus influenzae type b disease in infants and children from the age of 6 weeks up to the fourth birthday.	03/12/2010	03/12/2010	03/12/2012	yes
Nexium and associated names	EMEA-000331-PIP01-08-M01	Esomeprazole sodium / Esomeprazole magnesium trihydrate	Treatment of children and adolescents with duodenal ulcers caused by H. Pylori infection.	09/12/2000	15/04/2011	15/04/2013	

Invented name	PIP procedure number	Active substance(s)	Authorised indication(s), including paediatric indication(s) (summarised if necessary)	Date of MA	Date of variation (to include the paediatric indication)	Deadline to put on the product on the market	On the market with paediatric indication*
Sortis and associated names, Lipitor, Tahor, Xarator, Zarator, Liprimar, Totalip, Torvast, Cardyl	EMEA-000073-PIP01-07	Atorvastatin calcium (trihydrate)	Atorvastatin is indicated as an adjunct to diet for reduction of elevated total cholesterol, apolipoprotein B, and triglycerides in patients with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (Corresponding to Types IIa and IIb of the Fredrickson classification) when response to diet and other nonpharmacological measures is inadequate. Atorvastatin is also indicated to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable.	03/08/2010	05/05/2011	05/05/2013	
Diovan	EMEA-000005-PIP01-07-M01	Valsartan	Treatment of hypertension in children and adolescents 6 - 18 years of age.	12/05/2010	11/05/2011	11/05/2013	yes

Invented name	PIP procedure number	Active substance(s)	Authorised indication(s), including paediatric indication(s) (summarised if necessary)	Date of MA	Date of variation (to include the paediatric indication)	Deadline to put on the product on the market	On the market with paediatric indication*
Buccolam	EMEA-000395-PIP01-08	midazolam	Treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents (from 3 months to < 18 years) BUCCOLAM must only be used by parents/carers where the patient has been diagnosed to have epilepsy For infants between 3-6 months of age treatment should be in a hospital setting where monitoring is possible and resuscitation equipment is available.	05/09/2011	05/09/2011	05/09/2013	
Viramune	EMEA-000391-PIP01-08-M01	Nevirapine	Tablets and oral suspension: Viramune is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1-infected adults, adolescents, and children of any age (see section 4.4). prolonged-release tablets: Viramune is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1-infected adolescents and children three years and above and able to swallow tablets (see section 4.2 and 4.4).	05/02/1998	05/09/2011	05/09/2013	yes

Invented name	PIP procedure number	Active substance(s)	Authorised indication(s), including paediatric indication(s) (summarised if necessary)	Date of MA	Date of variation (to include the paediatric indication)	Deadline to put on the product on the market	On the market with paediatric indication*
Gardasil	EMEA-000375-PIP01-08-M02	Human Papillomavirus type 6 L1 protein / Human Papillomavirus type 11 L1 protein / Human Papillomavirus type 16 L1 protein / Human Papillomavirus type 18 L1 protein	Gardasil is a vaccine for use from the age of 9 years for the prevention of: premalignant genital lesions (cervical, vulvar and vaginal) and cervical cancer causally related to certain oncogenic human papillomavirus (HPV) types; genital warts (condyloma acuminata) causally related to specific HPV types.	20/09/2006	16/11/2011	16/11/2013	yes
Remicade	EMEA-000549-PIP01-09-M01	Infliximab	Treatment of severely active ulcerative colitis, in paediatric patients aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies.	13/08/1999	21/02/2012	21/02/2014	yes

Invented name	PIP procedure number	Active substance(s)	Authorised indication(s), including paediatric indication(s) (summarised if necessary)	Date of MA	Date of variation (to include the paediatric indication)	Deadline to put on the product on the market	On the market with paediatric indication*
RotaTeq	EMEA-000967-PIP01-10-M01	Rotavirus type P1A[8]/rotavirus type G3/rotavirus type G1/rotavirus type G4/rotavirus type G2	To extend the upper limit of the administration of the third dose of vaccine from up to 26 weeks to up to 32 weeks of age.	27/06/2006	21/02/2012	21/02/2014	yes
Lantus	EMEA-000387-PIP01-08	Insulin glargine	Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.	09/06/2000	25/05/2012	25/05/2014	
Optisulin	EMEA-000396-PIP01-08	Insulin glargine	Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.	27/06/2000	25/05/2012	25/05/2014	

Invented name	PIP procedure number	Active substance(s)	Authorised indication(s), including paediatric indication(s) (summarised if necessary)	Date of MA	Date of variation (to include the paediatric indication)	Deadline to put on the product on the market	On the market with paediatric indication*
Enbrel	EMEA-000299-PIP01-08-M03	Etanercept	Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate. Treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate. Treatment of enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy. Treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.	03/02/2000	31/07/2012	31/07/2014	
Xalatan	EMEA-000011-PIP01-07-M03	Latanoprost	Reduction of elevated intraocular pressure in paediatric patients with elevated intraocular pressure and paediatric glaucoma	16/12/2010	15/10/2012	15/10/2014	

Invented name	PIP procedure number	Active substance(s)	Authorised indication(s), including paediatric indication(s) (summarised if necessary)	Date of MA	Date of variation (to include the paediatric indication)	Deadline to put on the product on the market	On the market with paediatric indication*
Spiriva	EMEA-000035-PIP01-07-M05	Tiotropium bromide (monohydrate)	Paediatric population COPD There is no relevant use of Spiriva Respimat in children and adolescents below 18 years Cystic fibrosis The efficacy and safety of Spiriva Respimat has not been established (see sections 4.4 and 5.1).	09/10/2001	21/05/2013	21/05/2015	
Glivec	EMEA-000463-PIP01-08-M03	Imatinib mesilate	Treatment of paediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ALL) integrated with chemotherapy.	07/11/2001	27/06/2013	27/06/2015	yes
Ezetrol, Ezetimibe MSD-SP and associated names, Viemm and associated names, Zient and associated names	EMEA-000007-PIP01-07-M02	Ezetimibe	Children and adolescents ≥ 10 years (pubertal status: boys Tanner Stage II and above and girls who are at least one year post-menarche): No dosage adjustment is required (see section 5.2). Ezetrol is not recommended for use in children below age 10 due to insufficient data on safety and efficacy.	17/10/2002	30/07/2013	30/07/2015	yes

Invented name	PIP procedure number	Active substance(s)	Authorised indication(s), including paediatric indication(s) (summarised if necessary)	Date of MA	Date of variation (to include the paediatric indication)	Deadline to put on the product on the market	On the market with paediatric indication*
Prezista	EMEA-000038-PIP01-07-M03	Darunavir (as ethanolate)	In combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adult and paediatric patients from the age of 3 years and at least 15 kg body weight.	12/02/2007	19/09/2013	19/09/2015	yes
Misodel	EMEA-001159-PIP02-12	Misoprostol	Mysodelle is indicated for induction of labour in women with an unfavourable cervix, from 36 weeks gestation, in whom induction is clinically indicated.	16/10/2013	21/11/2013	21/11/2015	
Vepacel	EMEA-000156-PIP01-07-M02	A/H5N1 pre-pandemic influenza vaccine (whole virion, Vero cell derived, inactivated)	Active immunisation against H5N1 subtype of influenza A virus. This indication is based on immunogenicity data from subjects from the age of 6 months onwards following administration of two doses of vaccine prepared with H5N1 subtype strains (see section 5.1).	17/02/2012	25/11/2013	25/11/2015	
Invega	EMEA-000014-PIP01-07-M06	paliperidone palmitate/paliperidone	Invega is indicated for the treatment of schizophrenia in adults and in adolescents 15 years and older.	25/06/2007	23/05/2014	23/05/2016	

Invented name	PIP procedure number	Active substance(s)	Authorised indication(s), including paediatric indication(s) (summarised if necessary)	Date of MA	Date of variation (to include the paediatric indication)	Deadline to put on the product on the market	On the market with paediatric indication*
Vfend	EMEA-000191-PIP01-08-M05	voriconazole	Voriconazole, is a broad spectrum, triazole antifungal agent and is indicated in adults and children aged 2 years and above as follows: treatment of invasive aspergillosis; treatment of in candidaemia non-neutropenic patients; treatment of fluconazole-resistant serious invasive Candida infections (including C. krusei); Treatment of serious fungal infections caused by Scedosporium spp. and Fusarium spp. Vfend should be administered primarily to patients with progressive, possibly life-threatening infections. Prophylaxis of invasive fungal infections in high risk allogeneic hematopoietic stem cell transplant (HSCT) recipients.	19/03/2002	23/06/2014	23/06/2016	
Baraclude	EMEA-000339-PIP02-09-M03	entecavir monohydrate	Baraclude is also indicated for the treatment of chronic HBV infection in nucleoside naive paediatric patients from 2 to < 18 years of age with compensated liver disease who have evidence of active viral replication and persistently elevated serum ALT levels, or histological evidence of moderate to severe inflammation and/or fibrosis.	26/06/2006	22/08/2014	22/08/2016	

Invented name	PIP procedure number	Active substance(s)	Authorised indication(s), including paediatric indication(s) (summarised if necessary)	Date of MA	Date of variation (to include the paediatric indication)	Deadline to put on the product on the market	On the market with paediatric indication*
Travatan	EMEA-001271-PIP01-12-M01	travoprost	Decrease of elevated intraocular pressure in paediatric patients aged 2 months to < 18 years with ocular hypertension or paediatric glaucoma (see section 5.1).	27/11/2001	19/12/2014	19/12/2016	
Cancidas	EMEA-000010-PIP01-07-M01	caspofungin	Treatment of invasive candidiasis in adult or paediatric patients. Treatment of invasive aspergillosis in adult or paediatric patients who are refractory to or intolerant of amphotericin B, lipid formulations of amphotericin B and / or itraconazole. Refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy. Empirical therapy for presumed fungal infections (such as Candida or Aspergillus) in febrile, neutropaenic adult or paediatric patients.	24/10/2001	26/11/2008	26/11/2010	Yes

*as declared by the Marketing Authorisation Holder

Annex 7 - List of non-justified late submissions of applications for PIPs or waivers

These lists only include 2015 applications for which a decision on a PIP or waiver has been adopted by the European Medicines Agency; applications that have been withdrawn or whose discussion is ongoing are not listed.

The number of months of delay is automatically calculated from the date of end of PK studies in adults as declared by the Applicant in the application for PIP or request for full waiver.

The below table presents the 2015 agreed PIPs or waivers for which **no justification** or an **unacceptable justification** has been provided with regards to the significant delay in submission of the PIP or waiver application.

Company	Substance	Opinion	Delay (in months)
Novo Nordisk A/S	Semaglutide	PIP	**65**
Menarini Ricerche S.p.A.	Ibodutant	PIP	**58**
Venus Pharma GmbH	Sulbactam (in the form of sodium salt) / Ceftriaxone (in the form of sodium salt)	PIP	**46**
Bristol-Myers Squibb International Corporation	(3-((4-Benzoyl-1-piperazinyl)(oxo)acetyl)-4-methoxy-7-(3-methyl-1H-1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-1-yl)methyl dihydrogen phosphate, 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1) (BMS-663068)	PIP	**29**
Tetraphase Pharmaceuticals, Inc.	eravacycline	PIP	**27**
DBV Technologies S.A.	Peanut allergen extract	PIP	**25**
Lexicon Celtic Limited	sotagliflozin	PIP	**15**
AB Science SA	masitinib (mesylate)	Waiver	**123**
Genexine, Inc.	recombinant human growth hormone fused to hybrid Fc composed of the hinge region and N-terminal of CH2 domain of IgD and C-terminal of CH2 and full CH3 domain of IgG4 (hGH-hyFc)	Waiver	**17**
Dompé farmaceutici SpA	Reparixin	Waiver	**122**
Xention Limited	(S)-1-{5-Phenyl-4-[(pyridin-2-ylmethyl)-amino]-thieno[2,3-d]pyrimidin-2-yl}-piperidine-3-carboxylic acid (2-hydroxy-ethyl)-amide	Waiver	**10**

Annex 8 - List of PIPs completed

By 30 June 2015

PIP number	Substance	Invented name	Company
EMEA-000024-PIP01-07	zoledronic acid	Zometa	Novartis Europharm Limited
EMEA-000010-PIP01-07-M01	caspofungin acetate	Cancidas	Merck Sharp & Dohme (Europe) Inc.
EMEA-000543-PIP01-09	Colesevelam	Cholestagel	Genzyme Europe B.V.
EMEA-000283-PIP01-08	anastrozole	ARIMIDEX and associated name R...	AstraZeneca AB
EMEA-000118-PIP01-07-M01	abatacept	ORENCIA	Bristol-Myers Squibb Pharma EEIG
EMEA-000070-PIP01-07	ribavirin	Rebetol	Merck Sharp & Dohme (Europe), Inc.
EMEA-000071-PIP01-07	Peginterferon alfa-2b	PegIntron, ViraferonPeg	Merck Sharp & Dohme (Europe), Inc.
EMEA-000384-PIP01-08	Peginterferon alfa-2b	ViraferonPeg	Merck Sharp & Dohme (Europe), Inc.
EMEA-000112-PIP01-07-M01	Soya-bean oil, refined, Ph. Eu...	Numeta	Baxter World Trade SPRL
EMEA-000008-PIP01-07	Losartan potassium	COZAAR	Merck Sharp & Dohme (Europe) Inc.
EMEA-000352-PIP01-08-M01	Motavizumab	not available at present	AbbVie Ltd
EMEA-000184-PIP01-08-M02	Tobramycin	TOBI Podhaler	Novartis Europharm Ltd.
EMEA-000278-PIP01-08-M01	Vaccinum haemophili type b con...	PEDIACEL	Sanofi Pasteur MSD SNC
EMEA-000005-PIP01-07-M01	Valsartan	Diovan 40/80/160/320 mg film-c...	Novartis Europharm Limited
EMEA-000012-PIP01-07-M01	Montelukast sodium	SINGULAIR	Merck Sharp & Dohme Inc.
EMEA-000073-PIP01-07	atorvastatin calcium	Sortis and associated names, A...	Pfizer Limited

PIP number	Substance	Invented name	Company
EMEA-000167-PIP01-07-M02	Human Normal Immunoglobulin	ClairYg	LBF Biotechnologies
EMEA-000120-PIP01-07-M05	Tigecycline	Tygacil	Pfizer Limited
EMEA-000375-PIP01-08-M02	Human Papillomavirus1 Type 18 ...	Gardasil	Sanofi Pasteur MSD SNC
EMEA-000391-PIP01-08-M01	Nevirapine	Viramune	Boehringer Ingelheim International GmbH
EMEA-000250-PIP01-08-M02	Estradiol / Nomegestrol	not available at present	N.V. Organon
EMEA-000395-PIP01-08	Midazolam (as the Hydrochlorid...	Not applicable	Auralis Limited
EMEA-000687-PIP01-09-M02	Split influenza virus, inactiv...	Arepanrix	GlaxoSmithKline Biologicals S.A.
EMEA-000032-PIP01-07-M04	Meningococcal group Y oligosac...	Menveo	Novartis Vaccines and Diagnostics S.r.L
EMEA-000084-PIP02-10	Rizatriptan benzoate	MAXALT and associated names	Merck Sharp & Dohme (Europe) Inc.
EMEA-000299-PIP01-08-M03	Etanercept	Enbrel	Pfizer Limited
EMEA-000463-PIP01-08-M03	Imatinib mesilate	Glivec	Novartis Europharm Limited
EMEA-000549-PIP01-09-M01	Infliximab	Remicade	Centocor B.V.
EMEA-001289-PIP01-12-M01	Autologous CD34+ cells transdu...	Strimvelis	GlaxoSmithKline Trading Services Limited
EMEA-000052-PIP01-07-M03	vandetanib	Caprelsa	AstraZeneca AB
EMEA-000038-PIP01-07-M03	Darunavir	PREZISTA	Janssen-Cilag International NV
EMEA-000725-PIP01-09-M03	Split Influenza virus, inactiv...	Pandemrix	GlaxoSmithKline Biologicals S.A.
EMEA-000387-PIP01-08	insulin glargine	LANTUS	Sanofi-Aventis Deutschland GmbH

PIP number	Substance	Invented name	Company
EMEA-000396-PIP01-08	insulin glargine	OPTISULIN	Sanofi-Aventis Deutschland GmbH
EMEA-000967-PIP01-10-M01	rotavirus vaccine	RotaTeq	Sanofi Pasteur MSD SNC
EMEA-000007-PIP01-07-M02	Ezetimibe	EZETROL	Merck Sharp & Dohme Limited
EMEA-000035-PIP01-07-M05	Tiotropium bromide	Spiriva	Boehringer Ingelheim International GmbH
EMEA-000191-PIP01-08-M05	voriconazole	Vfend	Pfizer Limited
EMEA-000511-PIP01-08-M04	Propranolol hydrochloride	Not available at present	PIERRE FABRE DERMATOLOGIE
EMEA-000025-PIP01-07-M01	Formoterol fumarate / Mometaso...	not available at present	Merck Sharp & Dogme (Europe) Inc.
EMEA-000014-PIP01-07-M06	paliperidone	INVEGA	Janssen-Cilag International NV
EMEA-001110-PIP01-10-M01	Human normal immunoglobulin	not available at present	Octapharma Pharmazeutika Produktionsges.m.b.H
EMEA-000013-PIP01-07-M03	Recombinant L-asparaginase	Spectrila	medac Gesellschaft für klinische Spezialpräparate mbH
EMEA-000156-PIP01-07-M02	Antigen of pre-pandemic strain	VEPACEL	Baxter Innovations GmbH
EMEA-001159-PIP02-12	Misoprostol	Misodel	Ferring pharmaceuticals A/S
EMEA-000459-PIP01-08-M02	Prucalopride succinate	Resolor	Shire-Movetis NV
EMEA-000720-PIP01-09-M02	anagrelide hydrochloride	Xagrid 0.5mg hard capsules	Shire Pharmaceutical Contracts Limited
EMEA-001005-PIP01-10-M01	ritonavir / lopinavir	Kaletra	AbbVie Ltd
EMEA-001051-PIP01-10-M03	Influenza vaccine	Fluenz Tetra	MedImmune Limited
EMEA-000339-PIP02-09-M03	entecaventecavir (monohydrate)	Baraclude	Bristol-Myers Squibb Pharma EEIG

PIP number	Substance	Invented name	Company
EMEA-001442-PIP01-13	raltegravir / lamivudine	Not available at present	Merck Sharp & Dohme (Europe), Inc.
EMEA-000726-PIP01-09-M02	Valganciclovir hydrochloride	Valcyte	Roche Registration Limited
EMEA-000784-PIP02-11-M01	nitisinone	Orfadin	Swedish Orphan Biovitrum Internatio nal AB
EMEA-000147-PIP01-07	Dienogest		Bayer Schering Pharma AG
EMEA-000558-PIP01-09-M02	Human Normal Immunoglobulin	Not available at present	LFB Biotechnologies
EMEA-000582-PIP01-09-M03	rupatadine fumarate	rupafin and associated names	J. Uriach y Compañía, S.A.
EMEA-000412-PIP01-08-M01	Insulin detemir	Levemir	Novo Nordisk A/S
EMEA-001476-PIP01-13	Sapropterin Dihydrochloride	Kuvan	Merck KGaA
EMEA-000456-PIP01-08-M02	insulin degludec	Tresiba	Novo Nordisk A/S
EMEA-000745-PIP01-09-M03	Guanfacine Hydrochloride	not available at present	Shire Pharmaceuticals Contracts Ltd.
EMEA-000463-PIP02-10	Imatinib mesilate	Glivec	Novartis Europharm Limited
EMEA-000305-PIP01-08-M02	ulipristal acetate	ellaOne	Laboratoire HRA Pharma
EMEA-000425-PIP02-10-M04	Bosentan monohydrate	Tracleer	Actelion Registration Ltd
EMEA-000654-PIP01-09-M02	Human Papillomavirus vaccine	not available at present	Sanofi Pasteur MSD SNC
EMEA-001167-PIP02-11-M01	Atomoxetine (hydrochloride)	Strattera	Eli Lilly & Company
EMEA-001212-PIP01-11	Anakinra	Kineret	Swedish Orphan Biovitrum AB (publ)
EMEA-001271-PIP01-12-M01	Travoprost	Travatan	Alcon Laboratories (UK) Ltd.

PIP number	Substance	Invented name	Company
EMEA-001398-PIP02-13	Sodium benzylpenilloate / Benzylpenicilloyl octa L-lysine	DAP Penicillin	Diater Laboratorio de Diagnóstico y Aplicaciones Terapéuticas, S.A.
EMEA-000265-PIP01-08-M04	golimumab	Simponi	Janssen Biologics BV
EMEA-000627-PIP01-09-M04	Ivabradine hydrochloride	CORLENTOR	Les Laboratoires Servier
EMEA-000628-PIP01-09-M04	Ivabradine hydrochloride	PROCORALAN	Les Laboratoires Servier
EMEA-000022-PIP01-07-M04	Rosuvastatin calcium	CRESTOR and associated names	AstraZeneca AB
EMEA-000994-PIP01-10-M01	gadobutrol	Gadovist	Bayer Pharma AG
EMEA-000366-PIP01-08-M06	Adalimumab	Humira	AbbVie Limited
EMEA-000049-PIP01-07-M03	Clopidogrel	Plavix	Sanofi Pharma Bristol-Myers Squibb SNC
EMEA-000050-PIP01-07-M01	clopidogrel	Iscover	Bristol-Myers Squibb Pharma EEIG
EMEA-000331-PIP01-08-M01	Esomeprazole	Nexium and associated names	AstraZeneca AB
EMEA-000394-PIP01-08-M01	Hepatitis B Surface Antigen	not available at present	Sanofi Pasteur MSD SNC
EMEA-000617-PIP01-09	Clopidogrel	Clopidogrel Winthrop	Sanofi Pharma Bristol-Myers Squibb SNC
EMEA-000618-PIP01-09	Clopidogrel	Clopidogrel BMS	Bristol-Myers Squibb Pharma EEIG
EMEA-000648-PIP01-09	taliglucerase alfa	Uplyso	Pfizer Ltd.
EMEA-000312-PIP01-08-M07	Human coagulation Factor VIII	Voncento	CSL Behring
EMEA-000347-PIP01-08-M06	Bilastine	Bilaxten and associated names	Faes Farma, S.A.
EMEA-000876-PIP01-10-M01	Eculizumab	SOLIRIS	ALEXION EUROPE SAS

PIP number	Substance	Invented name	Company
EMEA-000830-PIP02-10-M02	Human normal immunoglobulin	Gammaplex	Bio Products Laboratory Limited
EMEA-001637-PIP01-13	Human normal immunoglobulin	not available at present	Baxter Innovations GmbH
EMEA-000144-PIP01-07-M05	aprepitant	EMEND	Merck Sharp & Dohme Ltd.
EMEA-000406-PIP01-08-M04	fosaprepitant	IVEMEND	Merck Sharp & Dohme Ltd.
EMEA-001366-PIP01-12-M02	Glycopyrronium bromide	Sialanar	Proveca Limited
EMEA-000479-PIP01-08-M03	insulin aspart / insulin degludec	Ryzodeg	Novo Nordisk A/S
EMEA-000036-PIP01-07-M06	Pneumococcal polysaccharide se...	Prevenar 13	Pfizer Limited
EMEA-000060-PIP01-07-M03	canakinumab	Ilaris	Novartis Europharm Limited
EMEA-000127-PIP01-07-M03	Formoterol fumarate / Fluticasone	Flutiform	Mundipharma Research Limited
EMEA-000170-PIP01-07-M03	eltrombopag	Revolade	Novartis Pharmaceuticals UKLtd
EMEA-000573-PIP01-09-M05	Solifenacin succinate	Vesicare	Astellas Pharma Europe B.V.
EMEA-000777-PIP01-09-M05	artemether (20 mg) and lumefantrine	Riamet	Novartis Europharm Limited
EMEA-000117-PIP01-07-M07	Ipilimumab	Yervoy	Bristol-Myers Squibb Pharma EEIG
EMEA-000019-PIP06-09-M05	everolimus	Certican and associated names	Novartis Europharm Limited
EMEA-000020-PIP01-07-M05	Maraviroc	Celsentri	ViiV Healthcare UK Ltd
EMEA-000060-PIP02-08-M06	Canakinumab	ILARIS	Novartis Europharm Limited
EMEA-000981-PIP01-10-M04	Ozenoxacin	Not available at present	Ferrer Internacional S.A.
EMEA-001684-PIP01-14	Adenovirus associated viral vector	Not available at present	Spark Therapeutics Inc.

PIP number	Substance	Invented name	Company
	serotype 2 containing the human RPE65 gene		

Annex 9 - List of PIPs not completed by the agreed date

By 30 June 2015

It should be noted that this list does not specify if the development of the medicinal product has been discontinued or not, as the EMA may not necessarily have the information. For the purpose of this analysis, a PIP is considered completed if there has been a positive compliance check by the EMA/PDCO, or reported by a National Competent Authority.

Substance(s)	Invented name	Company	Latest PIP number	Obligation to complete PIP
Mercaptopurine monohydrate		Nova Laboratories Limited	EMEA-000350-PIP01-08	Yes
Sodium bituminosulphonate / Clindamycin phosphate	Ichthoseptal N	Ichthyol -GesellschafT Cordes, Hermanni & Co. (GmbH & Co.) KG	EMEA-000532-PIP01-09	Yes
Skimmed cow's milk powder	Diallertest	DBV Technologies	EMEA-000201-PIP01-08-M01	Yes
Split influenza virus, inactivated containing antigen equivalent to A/California/7/2009 (H1N1)-like strain (A/California/7/2009 (NYMC X-179A)), adjuvanted	Humenza (INN: Pandemic Influenza vaccine (H1N1) (split virion, inactivated, adjuvanted))	Sanofi Pasteur SA	EMEA-000669-PIP01-09-M01	Yes
Paracetamol, Eur. Ph.		Baxter World Trade SA/NV	EMEA-000130-PIP01-07	No
Glucose (monohydrate)		Cblaya & Mhuguet S.L.	EMEA-000221-PIP01-08	No
Thrombin alfa		Bayer HealthCare AG	EMEA-000163-PIP01-07	No
Cholic acid		FGK Representative Service GmbH	EMEA-000651-PIP01-09-M02	Yes
Furosemide		PonsPharma Inc.	EMEA-000982-PIP01-10	No
Bromocriptine mesilate	Cycloset	VeroScience EU Ltd	EMEA-000487-PIP01-08	Yes
Rabeprazole (sodium)	Pariet and associated names	Eisai Limited	EMEA-000055-PIP01-07-M05	Yes
Levonorgestrel		Bayer Schering Pharma AG	EMEA-000606-PIP01-09	No

Substance(s)	Invented name	Company	Latest PIP number	Obligation to complete PIP
Grass Pollen Preparation		Allergopharma J. Ganzer KG	EMEA-000337-PIP01-08	Yes
Methoxyflurane	Penthrox	ORION Clinical Services	EMEA-000334-PIP01-08-M02	Yes
Pagibaximab		Biosynexus, Incorporated	EMEA-000608-PIP01-09	Yes
Chimeric monoclonal antibody to GD2		United Therapeutics Europe Limited	EMEA-001285-PIP01-12-M01	Yes
Secretin	Safinea	Repligen Europe Limited	EMEA-001069-PIP01-10	Yes
Cyclophosphamide		KEOCYT SAS	EMEA-000530-PIP02-11	No
Human normal immunoglobulin		LFB Biotechnologies	EMEA-001290-PIP01-12	Yes
misoprostol	Angusta dispersible tablet	Azanta Danmark A/S	EMEA-001601-PIP01-13	Yes
Risperidone	Risperidone	Wockhardt UK Ltd	EMEA-001034-PIP01-10	No
fentanyl citrate		EPMC PHARMA SPRL	EMEA-000712-PIP01-09	No

Annex 10 - List of companies that have submitted annual report(s) on deferred measures

Company name	Total	2009	2010	2011	2012	2013	2014	2015
Alexion Europe SAS	**4**			1	1	1	1	
AMAG Pharmaceuticals, Inc.	**2**					1	1	
ARIAD Pharma, Ltd.	**1**						1	1
AbbVie Limited	**8**			2	2	2	2	3
Actelion Registration Ltd	**1**						1	1
Alexion Europe SAS	**2**					1	1	
Alexza UK Limited	**1**						1	2
Almirall S.A.	**2**					1	1	1
Amgen Europe B.V.	**12**		1	2	3	3	3	3
Astellas Pharma Europe B.V.	**4**				1	1	2	5
AstraZeneca AB	**11**		1	2	2	3	3	3
BIAL - Portela & Ca, SA	**3**				1	1	1	
Basilea Pharmaceutica International Ltd.	**2**						2	
Baxter Innovations GmbH	**1**						1	1
Bayer Pharma AG	**1**						1	1
Bayer Schering Pharma AG	**17**		5	4	3	3	2	2
Bio Products Laboratory	**1**						1	
BioAlliance Pharma	**1**						1	1
Biogen Idec Limited	**2**					1	1	3
Boehringer Ingelheim International GmbH	**13**	3	2		2	3	3	4
Bristol-Myers Squibb / Pfizer EEIG	**3**					2	1	1
Bristol-Myers Squibb International Corporation	**13**				4	5	4	5
Bristol-Myers Squibb Pharma EEIG	**11**		1	2	3	3	2	2
Bristol-Myers Squibb/AstraZeneca EEIG	**6**			1	1	2	2	1
CSL Behring	**1**						1	

Company name	Total	2009	2010	2011	2012	2013	2014	2015
CTI Life Sciences, Ltd.	**2**					1	1	1
Celgene Europe Limited	**2**						2	5
Centocor B.V.	**5**		1	1	1	1	1	
Chiesi Farmaceutici S.p.A.	**2**					1	1	1
Clinigen Healthcare Ltd	**1**						1	1
Eisai Ltd.	**6**				2	2	2	3
Eli Lilly and Company Limited	**9**			1	2	4	2	3
Estetra S.A.	**1**						1	1
Exelixis Inc.								1
F. Hoffmann La Roche	**2**					1	1	1
Faes Farma, S.A.	**4**			1	1	1	1	
Forest Laboratories Limited	**1**					1		
GW Pharma Ltd	**1**			1				1
Genzyme Europe B.V.	**7**		1		1	1	4	2
Gilead Sciences International Limited	**14**			2	3	3	6	9
Glaxo Group Limited	**12**			2	2	4	4	4
GlaxoSmithKline Biologicals S.A.	**19**		1	3	4	5	6	7
GlaxoSmithKline Trading Services Limited	**9**				2	2	5	6
Grünenthal GmbH	**18**			6		6	6	4
H. Lundbeck A/S	**2**						2	1
Ipsen Pharma	**1**						1	2
Janssen Biologics B.V.	**3**				1	1	1	1
Janssen-Cilag International NV	**25**	2	2	4	6	5	6	7
Janssen Infectious Diseases BVBA								1
Jerini AG	**1**						1	1
Johnson & Johnson PRD	**6**		3	1	1	1		
Kowa Pharmaceutical Europe Company Ltd	**3**						3	
Laboratoire HRA Pharma	**3**		1	1	1			

Company name	Total	2009	2010	2011	2012	2013	2014	2015
Les Laboratoires Servier	**9**			2	2	4	1	1
Merck Sharp and Dohme (Europe), Inc.	**19**	3	5	3	3	3	2	6
Merz Pharmaceuticals GmbH								1
Mitsubishi Pharma Europe Ltd	**1**					1		1
N.V. Organon	**8**			2	2	2	2	2
Novartis Europharm Limited	**41**	1	5	7	8	10	10	10
Novartis Vaccines and Diagnostics S.r.l.	**5**			1		2	2	1
Novo Nordisk A/S	**12**		1	1	1	4	5	4
Nycomed Danmark ApS	**2**					1	1	1
Octapharma								1
Omrix Biopharmaceuticals SA	**2**						2	
Otsuka Frankfurt Research Institute GmbH								1
Otsuka Pharmaceutical Europe Ltd.	**3**				1	1	1	2
PTC Therapeutics Inc.								1
Pfizer Limited	**13**		1	1	3	4	4	5
Pharmaxis Pharmaceuticals Limited	**1**						1	
Pharming Group N.V.	**4**			1	1	1	1	1
Rapidscan Pharma Solutions (RPS) EU Ltd	**4**			1	1	1	1	
Roche Products Ltd	**2**					1	1	1
Roche Registration Ltd	**16**	1	1	3	3	3	5	3
SP Europe	**3**				1	1	1	1
Sanofi Pasteur SA	**3**			2			1	1
Sanofi Pharma Bristol-Myers Squibb SNC	**1**		1					
Shire Pharmaceutical Contracts Ltd	**4**				1	1	2	2
Shire Pharmaceuticals Ireland Limited	**4**			1	1	1	1	1
Shire-Movetis NV	**1**				1			
Sigma-Tau SpA	**1**						1	
Takeda Global Research and Development Centre (Europe) Ltd	**6**				1	2	3	3

Company name	Total	2009	2010	2011	2012	2013	2014	2015
Teva Pharma B.V.	**1**						1	1
The Medicines Company	**3**				1	1	1	1
Tibotec BVBA	**3**				1	1	1	2
UCB Pharma SA	**3**					1	2	2
Valeant Pharmaceuticals Ltd.	**3**				1	1	1	1
Vertex Pharmaceuticals Incorporated	**2**					1	1	1
ViiV Healthcare UK Ltd	**2**					1	1	2
ViroPharma SPRL	**2**				1	1		
Wyeth Europa Limited	**2**			1	1			
Wyeth Lederle Vaccines S.A.	**6**		2	2	1	1		
sanofi-aventis R&D	**2**						2	1
Number of annual reports submitted	**476**	**10**	**35**	**65**	**86**	**124**	**156**	**172**

Annex 11 - List of due annual reports on deferred measures that have not been submitted in 2015

PIP number	Product name	Substances	Company name	Original MA Date	Annual report due date
EMEA-000176-PIP01-07	Colobreathe	Colistimethate	Forest Laboratories UK Limited	13/02/2012	13/02/2015
EMEA-000153-PIP01-07	Eurartesim	Piperaquine phosphate anhydride / Dihydroartemisinin	Sigma-Tau SpA	27/10/2011	27/10/2015
EMEA-000309-PIP01-08	RoActemra	Tocilizumab	Roche Registration Limited	16/01/2009	16/01/2015
EMEA-000373-PIP02-09	Rienso	Ferumoxytol	AMAG Pharmaceuticals, Inc.	15/06/2012	15/06/2015
EMEA-000436-PIP01-08	Bronchitol	Mannitol	Pharmaxis Pharmaceuticals Limited	13/04/2012	13/04/2015
EMEA-000645-PIP01-09	Entyvio	vedolizumab	Takeda Global Research & Development Centre (Europe) Ltd	22/05/2014	22/05/2015
EMEA-000737-PIP02-11	SCENESSE	Afamelanotide	Clinuvel (UK) Limited	22/12/2014	22/12/2015
EMEA-000979-PIP01-10	MACI	autologous cartilage derived cultured chondrocytes	Aastrom Biosciences DK ApS	27/06/2013	27/06/2015
EMEA-001030-PIP01-10	Invokana	Canagliflozin	Janssen-Cilag International N.V.	15/11/2013	15/11/2015
EMEA-001149-PIP01-11	EVARREST	Human Fibrinogen / Human Thrombin	Omrix Biopharmaceuticals SA	06/10/2008	06/10/2015