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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 2014

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

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Acronyms, abbreviations

AEPC	Association for European Paediatric Cardiology
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
HMA	Heads of Medicines Agencies
ICAN Research	International Children's Advisory Network
IMI	Innovative Medicines Initiative
MA	marketing authorisation
MAH	marketing authorisation holder(s)
MCRN	Medicines for Children Research Network
NCA	National Competent Authorities
NHS	National Health Service
NIHR	National Institute for Health Research
PDCO	Paediatric Committee
PEDDCReN	Paediatric European Digestive Disease Clinical Research Network
PIP	paediatric investigation plan(s)
PPRS	Pharmaceutical Price Regulation Scheme
PSP	Pediatric Study Plan
PUMA	paediatric use marketing authorisation
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 8th year following the implementation of the Paediatric Regulation (EC) No 1901/2006. It includes an analysis on annual reports on deferrals, completion of paediatric investigation plans (PIP) and registration of deadlines to put a medicinal product on the market; these analyses started in the 2012 report.

A summary of the trends observed in 2014 is provided below:

- In 2014, the PDCO adopted the highest number of positive opinions on final compliance checks so far - almost double compared to 2013, continuing delivery on the key outcomes of the Paediatric Regulation. This will eventually lead to more marketing authorisations and more information on paediatric medicines.
- The number of CHMP scientific advices including paediatric questions has increased steadily from the start of the Paediatric Regulation and Paediatric Committee (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 scientific advices and paediatric investigation plans (PIP).
- The number of scientific advices provided by National Competent Authorities (NCA) on paediatric matters has increased significantly in 2014.
- The number of positive opinions on PIPs has stabilised in recent years.
- In 2014, the second paediatric use marketing authorisation (PUMA) was adopted.
- The proportion of paediatric trials of all trials (source EudraCT) continues to increase despite the decrease in the number of clinical trials overall.
- European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA): more networks were enrolled bringing the number to 44 at the end of 2014. The ever increasing engagement of scientific networks has a positive impact on the development of paediatric medicines.
- Three inventories of paediatric needs were adopted in 2014. This provides information for applicants on identification of unmet needs by the PDCO.
- Annual reports on deferrals indicated that many PIPs progressed without major difficulties. In 2014, the number of applicants' not submitting annual reports on deferred measures has significantly decreased, possibly as their awareness of the requirements of the paediatric regulation increased.
- Applicants seem to be more aware of the required timing of the submission of the PIP as generally the trend has been of less unjustified late submissions over the previous two years.
- Submissions under Articles 45 and 46 continued to generate a large body of new and relevant results, with amendments of the product information where appropriate. The assessment reports are published and are available on the EMA and HMA websites.
- More active substances benefited from the 6-month extension of the supplementary protection certificate (an increase of approximately 40% in 2014 compared to 2013).
- The first two orphan medicines have benefited from the additional specific reward in 2014 (the additional 2 years of market exclusivity).

Issues identified in this report include:

- Even though the number of marketing authorisation holders (MAH) not submitting annual reports on deferred measures within the required timelines has decreased, there are still few not complying with this requirement. The tracking of this activity is fully operational and is monitored by the Agency.
- Altogether 130 PIPs were scheduled to be finished by 30 June 2014. Of those, 79 PIPs were completed, 27 have not been completed and have not provided a justification or submitted a request for modification to change the timelines.

Major projects completed or significantly progressed in 2014 include:

- Publication of a draft strategic collaborative approach document by EMA and FDA to facilitate agreement of the PIP (EMA) and Pediatric Study Plan (PSP) (FDA) for products intended for the treatment of Gaucher disease. The aim is not only to assist drug development with the regulatory process but also to address the feasibility of developing globally multiple medicines for a rare disease within a reduced timeframe and with a limited number of patients.
- Systematic collection of data for the 10 year report to the EC (Art. 50.3 of the Paediatric Regulation) has started in 2014. All PIPs and waivers from the start of the Paediatric Regulation have been reviewed and data on various indicators to be reported have been collected.
- Publication of a document agreed with the European Centre for Disease Prevention and Control (ECDC) outlining the PIP key elements and requirements for a new diphtheria-tetanus-polio vaccine in order to avoid unnecessary clinical trials in children.
- Organisation of workshops relating to paediatric medicines in the areas of: hepatitis C, osteoporosis and pharmacovigilance.

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 2014 and follows a similar structure as the previous reports prepared by the Agency for the EC. The data are presented as a follow-up of the European Medicines Agency's five-year report to the EC, to allow continuity and analysis of the evolution over the years. In addition, the data collected annually will form part of the body of the European Medicines Agency's ten-year report to the EC, for which work has started.

2.2. Data collection and methodology

In September 2014, the Agency sent a letter to all Member States requiring their contributions to the preparation of this report. The data spreadsheet was simplified taking into account the comments received from Member States during the 2013 data collection. The data spreadsheet used for the compilation of data is attached in Annex 1.

The Agency also contacted the National Patent Offices of each Member State with regards to the medicinal products that had obtained in 2014 a 6-month extension of the supplementary protection certificate (SPC). Information was also requested on medicinal products for which the extension of the SPC was pending as well as those which do not have any SPC or patent that qualifies for an SPC.

The Agency received contributions from 26 out of 28 (93%) Member States and from 23 out of 28 (82%) National Patent Offices (hereinafter "NPO"), see Annex 2. Participation was higher compared to 2013 when contribution was 23 out of 28 (82%) Member States and 22 out of 28 (78%) NPOs.

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 the previous years (up to 2012) may be marginally different from those in the previous annual reports. These differences are minor and do not affect the conclusions.

In March 2015, companies identified as potentially infringing the Paediatric Regulation in 2014 were contacted in order to provide comments on the identified infringement before publication. In cases were listing of the infringement was incorrect, 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 request containing questions on paediatric development. The advice is provided by the Scientific Advice Working Party (SAWP) and is adopted by the Committee for Medicinal Products for Human Use (CHMP). For the requests on paediatric development, members of the PDCO routinely contribute to the provision of scientific advice through the scientific advice procedures (Table 1,Figure 1).

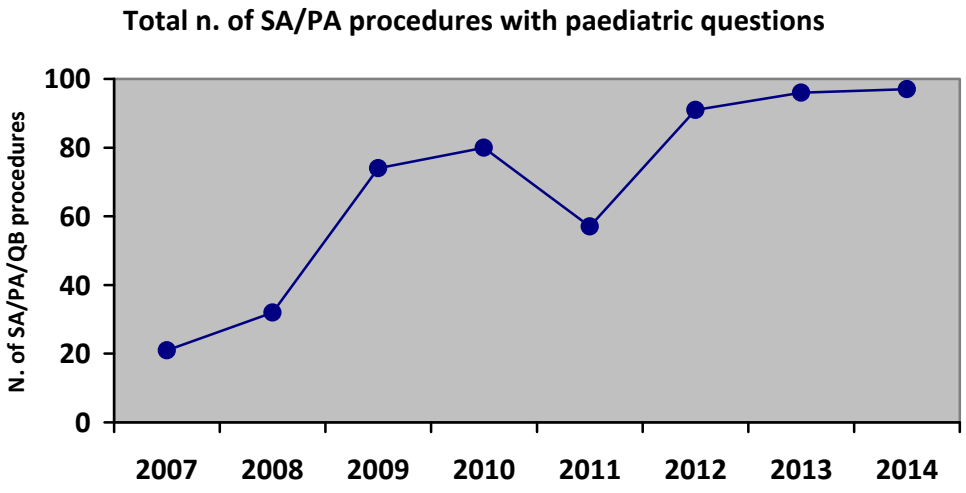
The number of scientific advice procedures including paediatric questions has increased steadily from the start of the implementation of the paediatric regulation. In 2014, 551 requests for scientific advice were submitted, of which 97 included paediatric development questions. The majority of scientific advice procedures in paediatric development (91%) involved a PDCO member as expert.

Table 1 - Scientific advice and protocol assistance, including follow-ups (provided by the EMA, SAWP and CHMP, per year in the last 5 years)

	2009	2010	2011	2012	2013	2014
Total number of advice (Scientific Advice and Protocol Assistance)	388	400	433	420	473	551
N. of SA/PA/qualification of biomarker procedures including questions on paediatric development	74	80	57	91	96	97*
Paediatric-only or mixed advice that involved a PDCO member(s) as expert(s)	68	80	67	94	93	88

Source: EMA databases. * biomarker procedures with paediatric relevance n=7

Figure 1 - Scientific advice and protocol assistance in paediatrics



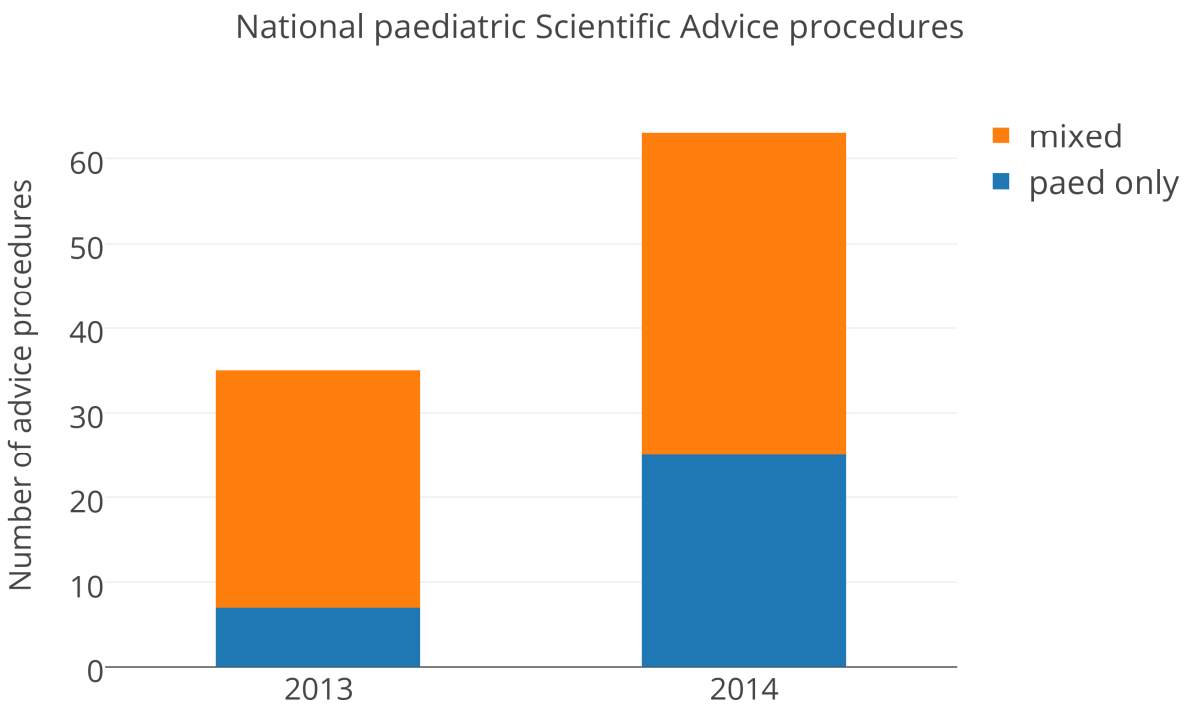
3.1.2. Advice from the National Competent Authorities

In 2014, a total of 63 either mixed adult-paediatric or paediatric only scientific advices were provided by Member States (Table 2). Compared to 2013, 28 additional paediatric advice procedures were given nationally, an increase by 80% (Table 2, Figure 2).

Table 2 - Number of national scientific advice provided by Member States in 2013 and 2014

	2013			**2014**		
Member state	Paed.only	Mixed	**Total**	Paed.only	Mixed	**Total**
Austria	0	0	**0**	0	2	**2**
Belgium				3	4	**7**
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	0	1	**1**	2	0	**2**
Estonia	0	0	**0**	0	0	**0**
Finland	0	1	**1**	1	0	**1**
France	2	2	**4**	1	2	**3**
Germany	2	9	**11**	12	16	**28**
Hungary	0	0	**0**	0	0	**0**
Ireland						
Italy	1	1	**2**	1	1	**2**
Latvia						
Lithuania				0	0	**0**
Luxembourg	0	0	**0**			
Malta	0	0	**0**	0	0	**0**
Poland	0	0	**0**	0	0	**0**
Portugal	0	0	**0**	1	0	**1**
Romania	0	0	**0**	0	0	**0**
Slovakia	0	0	**0**			
Slovenia	0	0	**0**	0	0	**0**
Spain	0	1	**1**	2	0	**2**
Sweden	0	3	**3**	0	0	**0**
The Netherlands				0	0	**0**
United Kingdom	2	10	**12**	2	13	**15**
Total of advices	**7**	**28**	**35**	**25**	**38**	**63**

Figure 2 - National scientific advice procedures in 2013 and 2014



3.2. Paediatric investigation plans and waivers

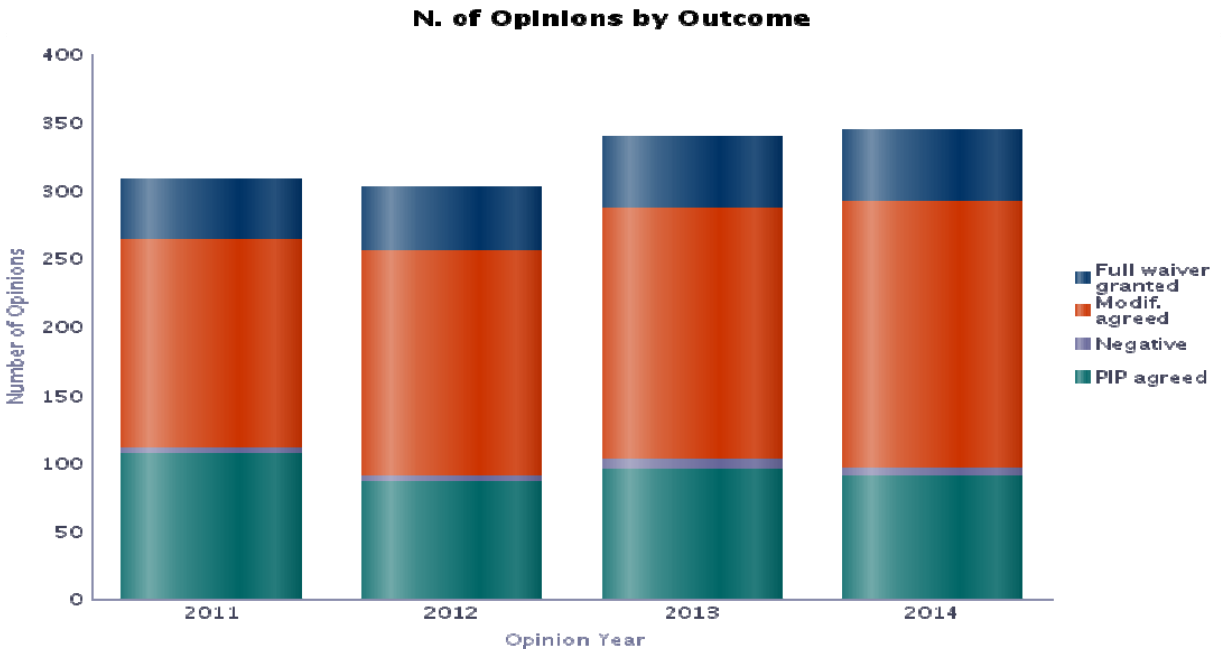
The table below (Table 3) is a compilation of PDCO opinions per year since 2011. It includes opinions on first PIP, product specific waivers, modifications of agreed PIPs and waivers granted on PDCO's own motion when the original application was for a PIP.

Table 3 - Opinions on paediatric investigations plans and waivers

	2011	2012	2013	2014
Number of positive opinions on first PIP applications	107	87	96	91
Number of positive opinions on product-specific ("full") waivers	44	47	51	46
Number of positive opinions on a modification of an agreed PIP	151	165	184	195
Number of product-specific waivers granted on PDCO's own motion when original application was for PIP	1	0	1	5
Negative opinions on first PIP	1	1	2	1
Negative opinions on product-specific waivers	2	2	2	1
Negative opinions on modifications of an agreed PIP	2	0	3	3
Grand total of opinions	**308**	**302**	**339**	**342**

A summary of the data is provided in Figure 3.

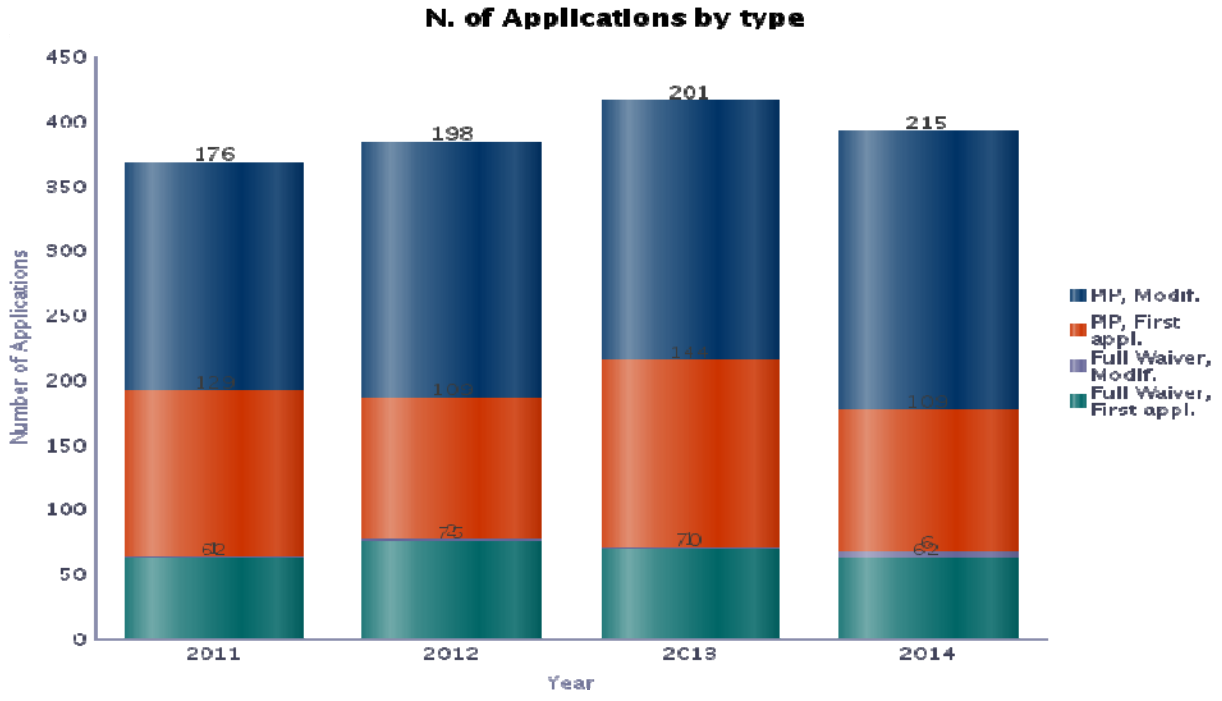
Figure 3 - Number of opinions by outcome



3.2.1. Applications

The total number of applications for first PIPs, waivers, and modifications of agreed PIPs in 2014 (392) marginally decreased compared to 2013 (416) but increased compared to 2012 (384) (see Figure 4). The relatively low increase in number of initial applications, compared to previous forecasts, could be explained by later submissions of PIPs/waivers in the life cycle, i.e. after most of the attrition of development has occurred.

Figure 4 - Applications for PIPs, waivers and modifications of agreed PIPs



3.2.2. Publication of PDCO opinions and EMA decisions

The decisions issued by the Agency include the PDCO opinion and are published in a summarised form. They can be found on the EMA website, in a dedicated webpage. In 2014, 312 decisions were published.

3.2.3. Class waivers

The latest EMA decision on class waivers, dated 19 December 2011, can be found on the EMA website: (Class waiver decision CW/1/2011).

No additional EMA decision on class waivers has been published in 2014. A revision of the list is under consideration.

In 2014, 41 requests for class waivers applicability were assessed and their outcomes were adopted during monthly PDCO plenary meetings (table 4):

- 88% 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.
- 12% of the requests were given a negative outcome, on the following conditions: diagnosis of prostate cancer (2x), treatment of psychosis complications of Alzheimer's disease, prophylactic treatment of oesophageal cancer, treatment of squamous cell cancer of head and neck. For each of these requests, the proposed indication did not fall under the scope of the Agency's decision on class waivers since the indication was assessed as not being covered by the condition which is class waived in children. The applicants were advised to submit a product-specific waiver application should they wish.
- 56% of the requests involved products used in oncology.
- The PDCO recommended that for 68% of the requests, the products may be developed for another condition for which a therapeutic need in children has been identified.

Table 4 - Requests of confirmation of applicability of a class waiver - 2014

	Confirmed	Not confirmed	Total
All requests	36	5	41
Of which in the therapeutic area of oncology:	*20*	*3*	*23*
Potential use in children identified by PDCO in another condition	27	1	28 (68%)

3.2.4. Modifications of agreed PIPs

In 2014, there were 185 EMA decisions on modifications of agreed PIPs compared to 179 in 2013.

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 increasing and has not reached a "steady state" yet. It was always expected that an agreed PIP would be subjected to modification procedures as the progress in development of the product requires changes to the development plan.

The number and type of changes in modification of an agreed PIP procedures is varies considerably, since a full modification procedure is required to change any key element such as 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 5).

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

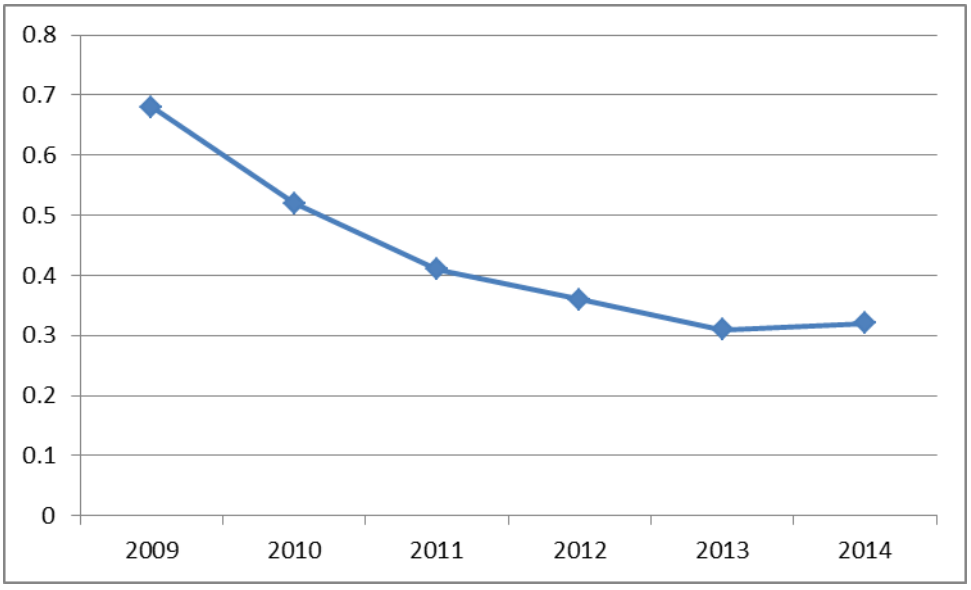


Table 5 - PIPs agreed and modifications requested - ratio of PIP modification requests to cumulative number of first PIPs

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

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.

3.3. Compliance statement included in a marketing authorisation

A compliance check can be done at the EMA or by NCAs, either as part of: 1) validation of applications for marketing authorisation (MA); 2) validation of applications for variations/extensions of the MA; or 3) 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).

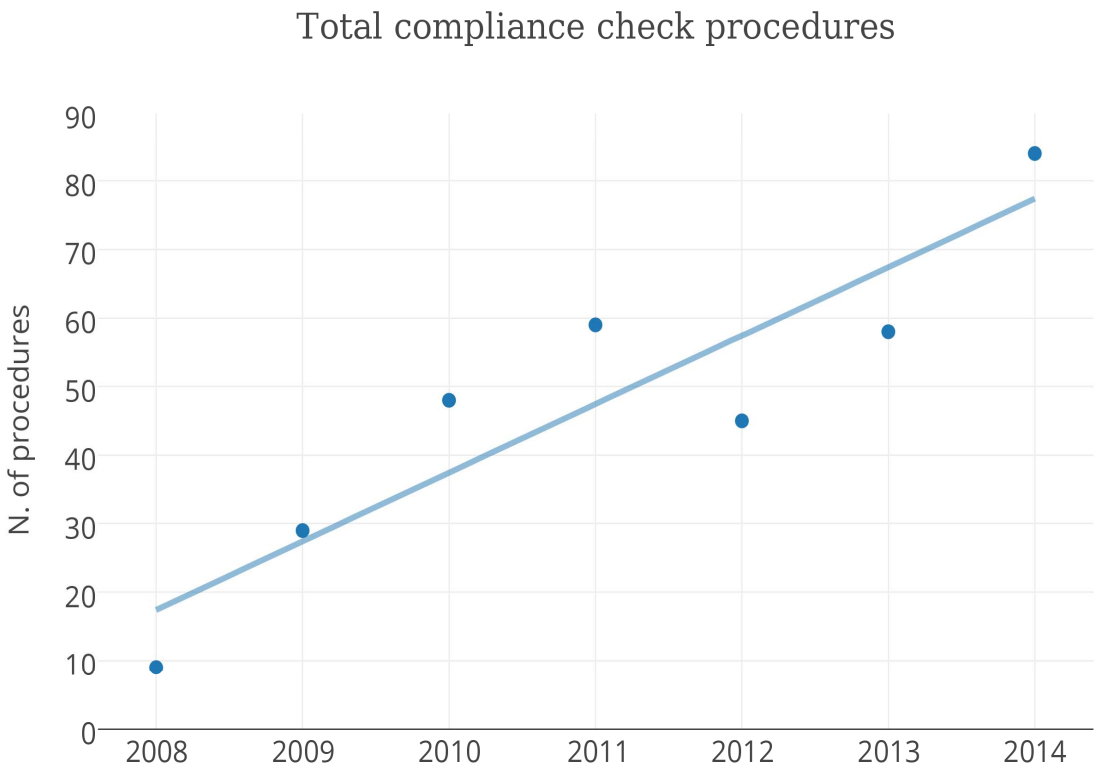
No NCA reported having checked compliance of a PIP in 2014. This may be because the NCAs have delegated it to the EMA / PDCO, or because MAHs have obtained a PDCO opinion in advance of the regulatory procedure at the NCA.

In 2014, the PDCO adopted the highest number (31) of positive opinions on final compliance check so far- almost double compared to 2013 (see Table 6 and Figure 6).

Table 6 - PDCO Opinions on compliance and letters on interim compliance check

	2008	2009	2010	2011	2012	2013	2014	**Total**
PDCO negative letters on interim compliance	0	2	0	3	1	1	1	**8**
PDCO positive letters on interim compliance	4	18	39	47	40	40	52	**240**
PDCO negative opinions on full/final compliance check	0	1	0	0	0	1	0	**2**
PDCO positive opinions on full/final compliance check	5	8	9	9	4	16	31	**82**
Totals	**9**	**29**	**48**	**59**	**45**	**58**	**84**	**332**

Figure 6 - Total compliance check procedures



3.3.1. Compliance statement for centrally-authorised medicinal products

In 2014, the EMA issued seven compliance statements, related to regulatory submissions for authorised products in accordance with Article 7 and 8 (Table 7). This represents an increase compared to 2013 (3 issued in 2013)

Table 7 - List of companies and products with a compliance statement (centrally-authorised)

Companies	invented name	INN	Type of procedure
Bristol-Myers Squibb Pharma EEIG	Baraclude	Entecavir	Type II variation
Alcon Laboratories (UK) Ltd	Travatan	Travoprost	Type II variation
Pierre Fabre Dermatologie	Hemangiol	Propranolol	Initial MA
Janssen-Cilag International NV	Invega	Paliperodone	Type II variation
Janssen-Cilag International NV	Prezista	Darunavir	Type II variation
AbbVie Ltd	Synagis	Palivizumab	Line extension
Shire Pharmaceutical Contracts Limited	Xagrid	Anagrelide	Type II variation

3.3.2. Compliance statement for medicinal products authorised through national/decentralised/mutual recognition procedure, including those subject to Article 29 of the Paediatric Regulation

The access to the reward for both centralised and nationally-authorised products was higher in 2014 compared to 2013 (16 products in 2014 compared to 8 products in 2013). There was no reward granted following use of Article 29 paediatric referral in 2014.

Table 8 - List of companies and products with a compliance statement (authorised through national/decentralised/mutual recognition procedure)

Companies	international non-proprietary name (INN)	invented name
Roche	Valganciclovir	Valcyte, RoValcyte
J Uriach & Cia	Rupatadine	Rupatall, Rupafin, Tamalis
AstraZeneca	Rosuvastatin	Crestor
Ferring	Misoprostol	Misodel, Mysodelle
LEO Pharmaceutical products DK	Betamethasone/Calcipotriol	Xamiol
Eli Lilly	Atomoxetine	Strattera
MEDA Pharma GmbH & Co. KG	Clindamycin phosphate / Tretinoin	Acnex / Zaria
Boehringer Ingelheim International GmbH	Tiotropium	Spiriva Respimat
Merck Sharp & Dohme	Ezetimibe	Ezetrol

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 9).

In 2014, more active substances benefited from the 6-month extension compared to 2013 (13 in 2014 compared to 9 in 2013). 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 9 - List of companies/products which have benefited from 6-months extension of the SPC granted by National Patent Offices in 2014

MAH	**Invented name(s)**	**International non-proprietary name**	**SPC extension granted in 2014**	**SPC extension pending in 2014**
Bristol-Myers Squibb Pharma EEIG	Orencia	Abatacept	Romania	Czech Republic Hungary
Otsuka Pharmaceutical Europe Ltd	Abilify	Aripiprazole	Italy	Netherlands Romania UK
Merck Sharp and Dohme	Cancidas	Caspofungin	Bulgaria Czech Republic	
Genzyme Europe BV	Cholestagel	Colesevelam		Netherlands
Pfizer Limited	Enbrel	Etanercept	Belgium	Bulgaria
Novartis Europharm Limited	Glivec	Imatinib	Sweden Denmark Finland France Germany Italy Netherlands UK	Czech Republic Hungary Spain
Janssen Biologics B.V.	Remicade	Infliximab	Belgium	Austria
Sanofi-Aventis Deutschland GmbH	Lantus Optisulin	Insulin – glargine	Belgium	
Merck Sharp & Dohme	Maxalt	Rizatriptan		Czech Republic
Boehringer Ingelheim	Spiriva	Tiotropium bromide	Bulgaria France Netherlands Poland Spain Austria	Czech Republic Romania

MAH	**Invented name(s)**	**International non-proprietary name**	**SPC extension granted in 2014**	**SPC extension pending in 2014**
Otsuka Pharmaceutical Europe Ltd.	Samsca	Tolvaptan		France Netherlands Spain UK
Pfizer Limited	Vfend	Voriconazole	Denmark Finland France Italy Netherlands UK	Belgium Czech Republic Hungary Ireland Latvia Romania Slovakia Spain Sweden
J. Uriach y Compañía, S.A.	Rupafin	Rupatadine	Italy Netherlands	Belgium Czech Republic France Ireland Slovakia UK
Actelion Registration Ltd	TRACLEER	Bosentan		Belgium Finland Hungary Netherlands Slovakia UK
Roche Registration Limited	Valcyte	Valganciclovir	Italy Austria	Belgium Czech Republic Denmark Finland France Hungary Ireland Netherlands Poland Spain Sweden UK
Bristol-Myers Squibb Pharma EEIG	Baraclude	Entecavir	Denmark Finland Ireland Italy	Belgium France Germany Hungary Netherlands Poland Spain Sweden UK

MAH	Invented name(s)	International non-proprietary name	SPC extension granted in 2014	SPC extension pending in 2014
Alcon Laboratories (UK) Ltd	Travatan	Travoprost		Belgium Denmark Ireland Italy Lithuania Slovenia Sweden UK Austria
Sanofi Pasteur MSD	Gardasil	Vaccine against human papillomavirus	France Italy UK	Belgium Denmark Germany Ireland Netherlands Spain Sweden Austria
Merck Sharp and Dohme (Europe), Inc.	Januvia	Sitagliptin		Czech Republic Hungary
Merck Sharp & Dohme	Bridion	Sugammadex		Czech Republic
Forest Laboratories UK Ltd	Colobreathe	Colistimethate		Germany
Janssen-Cilag International NV	PREZISTA	Darunavir		Ireland UK Austria

3.4.2. Orphan market exclusivity extension

For the first time since the Paediatric Regulation came into force, two orphan medicinal products have benefited from a two year extension of their Market Exclusivity in 2014. These were Xagrid which is indicated for the reduction of elevated platelet counts in at risk essential thrombocythaemia patients (Shire Pharmaceutical Contracts Limited) and Tobi Podhaler for the suppressive therapy of chronic pulmonary infection due to *Pseudomonas aeruginosa* in adults and children aged 6 years and older with cystic fibrosis (Novartis Europharm Ltd.).

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

In 2014, there was a similar number of centrally-authorised medicinal products with added mention on deferral or waiver in the summary of product characteristics as in 2013 (55 for new MA in 2014 compared to 52 in 2013) (see Table 10 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 11 below. Further information on these medicinal products can be found on the Head of Medicines Agency website (http://www.hma.eu/).

Table 10 - List of centrally-authorised products and companies for which a deferral/waiver statement has been included in SmPC (generics not included)

Invented name	International non-proprietary name	Marketing authorisation holder	Waiver stat. added	Deferral stat. added	Procedure (MA / variation/line extension)
Anoro	Umeclidinium bromide/vilanterol	Glaxo Group Ltd	x		MA
Aubagio	Teriflunomide	Sanofi-Aventis Groupe	x		MA
Adempas	Riociguat	Bayer Pharma AG		x	MA
Brimica Genuair	Aclidinium bromide / formoterol fumarate dihydrate	Almirall S.A	x		MA
Clopidogrel/Acetylsalicylic acid Teva	Clopidogrel / acetylsalicylic acid	Teva Pharma B.V.	x		MA
Cometriq	Cabozantinib s-malate	TMC Pharma Services Ltd		x	MA
CYRAMZA	Ramucirumab	Eli Lilly Nederland B.V.	x		MA
Daklinza	Daclatasvir	Bristol-Myers Squibb Pharma EEIG		x	MA
Deltyba	Delamanid	Otsuka Novel Products GmbH		x	MA
Ebilfumin	Oseltamivir	Actavis Group PTC ehf		x	MA
Entyvio	Vedolizumab	Takeda Pharma A/S		x	MA
Eperzan	Albiglutide	GlaxoSmithKline Trading Services	x		MA
Gazyvaro	Obinutuzumab	Roche Registration Ltd	x		MA
Harvoni	Sofosbuvir / ledipasvir	Gilead Sciences International Ltd		x	MA
Imbruvica	Ibrutinib	Janssen-Cilag International NV	x		MA
Incruse	Umeclidinium bromide	Glaxo Group Ltd	x		MA
Isentress	Raltegravir	Merck Sharp & Dohme Limited		x	LE
Latuda	Lurasidone	Takeda Pharma A/S		x	MA
Laventair	Umeclidinium bromide / vilanterol	Glaxo Group Ltd	x		MA
Lymphoseek	Tilmanocept	Navidea Biopharmaceuticals Limited		x	MA
Lynparza	Olaparib	AstraZeneca AB	x		MA
Mekinist	Trametinib	Glaxo Group Ltd		x	MA
Moventig	Naloxegol	AstraZeneca AB		x	MA

Invented name	International non-proprietary name	Marketing authorisation holder	Waiver stat. added	Deferral stat. added	Procedure (MA / variation/line extension)
Neuraceq	Florbetaben (18f)	Piramal Imaging Limited	x		MA
Nuwiq	Simoctocog alfa	Octapharma AB		x	MA
OLYSIO	Simeprevir	Janssen-Cilag International N.V.		x	MA
Orencia	Abatacept	Bristol-Myers Squibb Pharma EEIG	x	x	VA
Paliperidone Janssen	Paliperidone	Janssen-Cilag International NV	x		MA
Plegridy	Peginterferon beta-1a	Biogen Idec Ltd		x	MA
REVINTY ELLIPTA	Fluticasone furoate / vilanterol trifenatate	Glaxo Group Ltd	x	x	MA
Revatio	Sildenafil	Pfizer Limited		x	VA
Rezolsta	Darunavir / cobicistat	Janssen-Cilag International N.V.		x	MA
SIMBRINZA	Brinzolamide / brimonidine tartrate	Alcon Laboratories (UK) Ltd	x		MA
SIRTURO	Bedaquiline	Janssen-Cilag International N.V.		x	MA
SYLVANT	Siltuximab	Janssen-Cilag International NV	x		MA
Serelaxin	Serelaxin	Novartis Europharm Ltd		x	MA
Sovaldi	Sofosbuvir	Gilead Sciences International Ltd		x	MA
Stivarga	Regorafenib	Bayer Pharma AG		x	VA
Synflorix	Pneumococcal polysaccharide conjugate vaccine (adsorbed)	GlaxoSmithKline Biologicals		x	VA
TECFIDERA	Dimethyl fumarate	Biogen Idec Ltd		x	MA
Tivicay	Dolutegravir	ViiV Healthcare		x	MA
Translarna	Ataluren	PTC Therapeutics International Limited	x	x	MA
Trulicity	Dulaglutide	Eli Lilly Nederland B.V.		x	MA
Ulunar Breezhaler	Indacaterol / glycopyrronium bromide	Novartis Europharm Ltd	x		MA
VIZAMYL	Flutemetamol (18f)	GE Healthcare Ltd	x		MA

Invented name	International non-proprietary name	Marketing authorisation holder	Waiver stat. added	Deferral stat. added	Procedure (MA / variation/line extension)
Vargatef	Nintedanib	Boehringer Ingelheim International GmbH	x		MA
Velphoro	Mixture of polynuclear iron(iii)-oxyhydroxide, sucrose and starches	Vifor Fresenius Medical Care Renal Pharma France		x	MA
Vimizim	Elosulfase alfa	BioMarin Europe Ltd		x	MA
Vokanamet	Canagliflozin / metformin	Janssen-Cilag International N.V.	x		MA
Xigduo	Dapagliflozin / metformin	AstraZeneca AB	x		MA
Xultophy	Insulin degludec / liraglutide	Novo Nordisk A/S	x		MA
Zydelig	Idelalisib	Gilead Sciences International Ltd		x	MA

For medicinal products authorised through national/decentralised/mutual recognition procedure, statement on deferral or waiver was added in 41 procedures (17 initial MAs and 24 variations of MA, although as seen in the table there is duplication as the same information is provided from several member states, see Table 11).

Table 11 - List of nationally authorised products and companies for which a deferral/waiver statement has been included in SmPC

Member State	Invented name	International non-proprietary name	Marketing authorisation holder	Waiver stat. added	Deferral stat. added	Procedure (MA or variation)
Croatia	Crestor	Rosuvastatin	Astra Zeneca	x		VA
Cyprus	Crestor	Rosuvastatin	Astra Zeneca	x		VA
Cyprus	Rupafin	Rupatadine	J. Uriach & CIA	x		VA
Cyprus	Valcyte	Valganciclovir	GA Stamatis & CO LTD	x		VA
Czech	Valcyte	Valganciclovir	Roche s.r.o.	x		VA
Czech	Misodel	Misoprostol	Ferring Pharmaceuticals	x		MA
Czech	Tamalis 1 mg/ml	Rupatadine	J. Uriach & CIA	x		VA
Denmark	Crestor	Rosuvastatin	Astra Zeneca	x		VA
Estonia	Valcyte	Valganciclovir	Roche	x		VA

Member State	Invented name	International non-proprietary name	Marketing authorisation holder	Waiver stat. added	Deferral stat. added	Procedure (MA or variation)
Estonia	Crestor	Rosuvastatin	Astra Zeneca	x		VA
Estonia	Rupafin	Rupatadine	J. Uriach & CIA	x		VA
Finland	Valcyte	Valganciclovir	Roche	x		VA
Finland	Rupafin	Rupatadine	J. Uriach & CIA	x		VA
Finland	Misodel	Misoprostol	Ferring	x		MA
Finland	Zevtera	Ceftobiprolum	Basilea		x	MA
Finland	Viazet	Rosuvastatin/ezetimibe	Egis Pharmaceuticals	x		MA
Finland	Xenacine	Tetrabenazine	PharmaSwiss Ceská republica s.r.o.	x		MA
Italy	Valcyte	Valganciclovir	Roche	x		VA
Lithuania	Crestor	Rosuvastatin	Astra Zeneca	x		VA
Lithuania	Valcyte	Valganciclovir	Roche	x		VA
Lithuania	Rupafin	Rupatadine	J. Uriach & CIA	x		VA
Poland	Misodel	Misoprostol	Ferring	x		MA
Portugal	RoValcyte	Valganciclovir	Roche	x		VA
Portugal	Crestor	Rosuvastatin	Astra Zeneca	x		VA
Romania	Crestor	Rosuvastatin	Astra Zeneca	x		VA
Slovenia	Valcyte	Valganciclovir	Roche	x		VA
Slovenia	Mysodelle	Misoprostol	Ferring	x		VA
Slovenia	Stiverdi Respimat	Olodaterol	Boehringer Ingelheim International GmbH	x		MA
Slovenia	Vesomni	Solifenacin/tamsulosin	Astellas	x		MA
Slovenia	Diklofenak/omeprazol Pharmaswiss	Diclofenac/omeprazole	PharmaSwiss	x		MA
Slovenia	Triplixam	Perindopril/indapamide/amlpodipine	Servier Pharma	x		MA

Member State	Invented name	International non-proprietary name	Marketing authorisation holder	Waiver stat. added	Deferral stat. added	Procedure (MA or variation)
Slovenia	Ramelso	Ramipril/amlodipine	Adamed Sp.	x		MA
Slovenia	Ramipril/Amlodipine PharmaSwiss	Ramipril/amlodipine	Astra Zeneca	x		MA
Slovenia	Crestor	Rosuvastatin	Astra Zeneca	x		VA
Slovenia	Rupafin	Rupatadine	J. Uriach & CIA	x		VA
Sweden	Trimonia	Ramipril/atorvastatin/acetylsalicylic acid	Ferrer	x		MA
Sweden	Taptiqom	Tafluprost/timolol	Santen Oy	x		MA
Sweden	Atozet	Atorvastatin/ezetimibe	Merck Sharp & Dohme	x		MA
Sweden	Rupafin	Rupatadine	J. Uriach & CIA	x		VA
Sweden	Iluvien	Fluocinolone	Alimera sciences Limited	x		MA
UK	Diclopram	Diclofenac	PharmaSwiss	x		MA

3.6. Price/reimbursement benefits

The Agency has received information on price and reimbursement benefits for paediatric medicines in the Member States, which is listed under national initiatives (3.7.3.).

3.7. Research incentives

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

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

In 2014, Enpr-EMA expanded with the addition of three new networks that joined as Enpr-EMA registered category 3 networks:

- EPLTN (European Paediatric Liver Transplantation Network);
- PEDDCReN (Paediatric European Digestive Disease Clinical Research Network);
- ESPNIC (European Society of Paediatric Neonatal Intensive Care) Medicine Research Network.

At the end of the year, Enpr-EMA had 44 registered networks:

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

There is still an identified need for the creation and establishment of a European paediatric clinical trial network specialised in cardiology as well as a network of European Paediatric Pharmacists. The former is currently under establishment.

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.

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.

Table 12 – Enpr-EMA networks

Type of network	Category 1	Category 2	Category 3	Category 4
National and multispecialty	NIHR-MCRN FinPedMed MCRN-NL MICYRN ScotCRN CICPed	RED SAMID	IPCRN NCCHD BLF RIPPS Futurenest CR BPDN SwissPedNet Hospital Sant Joan De Deu	
Oncology (solid / haematologic malignancies)	Newcastle-CLLG ITCC IBFMSG EPOC	CLG of EORTC		
Diabetes / Endocrinology / metabolic disorders / Gynaecology			AMIKI	
Gastroenterology / Hepatology			ESPGHAN PEDDCReN EPLTN	
Allergology / Immunology/ Rheumatology	PRINTO		JSWG of PRES	
Stem Cell and Organ Transplantation / Haematology (non-malignant) / Haemostaseo-logy	EBMT		IPTA	
Respiratory diseases / Cystic Fibrosis	ECFS-CTN			
Cardiovascular diseases / Nephrology				
Psychiatry / Neurology	EUNETHYDIS			
Infectious diseases / Vaccinology	PENTA-ID UKPVG			
Pharmacology			ESDPPP	
Intensive Care / Pain / Anaesthesiology / Surgery		Network of Excellence for research in paediatric clinical care-NL	ESPNIC Research Network	
Neonatology	GNN		EuroNeoNet Neo-circulation INN	
European Paediatric Pharmacists				

Type of network	Category 1	Category 2	Category 3	Category 4
Special Activities (pharmaco-vigilance, long-term follow up, community paediatricians)	FIMP-MCRN			
Expertise in Clinical Trial Methodology				TEDDY* PRIOMEDCHILD* ECRIN* GRIP*

* Criteria not applicable to these networks

Enpr-EMA activities throughout 2014 included:

- The report on the 1 year deliverables[4] of the Enpr-EMA working groups since their creation at the Enpr-EMA June 2013 workshop.
- Development of a Global Paediatric Clinical Trial Network with 50 large paediatric clinical research centres having the capacity to conduct paediatric drug trials (Phases I –IV), starting in the US and Canada and later to phase out to Europe (large centres and existing Enpr-EMA national/specialty networks will be considered). A business case will be created in 2015.
- The current activities and status of Enpr-EMA were advertised to the clinicians who attended the EAPS 2014 in Barcelona, where a poster on "*Enpr-EMA: a platform for disseminating good practices about paediatric medicines research across Europe and with international partners*" was displayed during the EAPS poster session.
- An abstract on the results of a 2012 survey on the involvement of young people and families in the Enpr-EMA networks was presented to the clinicians who attended the EAPS 2014 in Barcelona. *B. Pelle, P. Helms, J. Drabdwell, J. Preston, M.Turner and I. Eichler. Young people and family involvement in paediatric research networks: outcomes of a survey among Enpr-EMA networks. 5th congress of the European Academy of Paediatric Societies. Primary and General Paediatrics. Child Protection. 19 October 2014.*
- A summary of lessons learnt from the EU programme to fund research into off-patent medicines was published by several Enpr-EMA members (*L. Ruggieri, V. Giannuzzi, P. Baiardi, F. Bonifazi, E. H. Davies, C. Giaquinto, D. Bonifazi, M. Felisi, C. Chiron, R. Pressler, H. Rabe, M. J. Whitaker, A. Neubert, E. Jacqz-Aigrain, I. Eichler and M. A. Turner & A. Ceci. Successful private–public funding of paediatric medicines research: lessons from the EU programme to fund research into off-patent medicines. Eur J Pediatr 2014; DOI 10.1007/s00431-014-2398-z)*
- A plenary discussion, on future approaches to funding of paediatric clinical trials, with representatives from the EC and EFPIA/IMI as well as the Enpr-EMA chair/co-chair and representatives from Enpr-EMA networks was held during the November 2014 PDCO plenary. Future activities are to be planned on this topic in 2015.
- A framework was established to allow industry representative as observer within coordinating group for ad-hoc topics in order to improve communication and collaboration with industry, a main stakeholder.

3.7.2. Inventory of paediatric needs

As announced in the previous annual report, the draft inventories of paediatric needs in infectious

[4] Minutes of Enpr-EMA Coordinating Group Minutes, 24/10/2014: http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/document_listing/document_listing_000346.jsp&mid=WC0b01ac058050027a#section4

diseases, nephro-urology and ophthalmology were adopted in 2014 (http://bit.ly/1PtYmzq).

The draft inventories of paediatric medicines in neurology and oncology were published for public consultation in 2014 and will be finalised in 2015.

The PDCO is currently working on the inventory of paediatric medicines in gastroenterology and endocrinology.

3.7.3. National initiatives on paediatric medicines

New activities mentioned by Member States in respect of paediatric medicines:

Austria

OKids http://www.okids-net.at/ is a consortium to implement a platform for paediatric research for both academia and industry.

United Kingdom

Financial incentives to encourage use of authorised paediatric medicines including PUMA:

The Pharmaceutical Price Regulation Scheme (PPRS) is the mechanism that the UK Department of Health uses to control the prices of branded prescription medicines supplied to the National Health Service (NHS) by regulating the profits that companies can make on their NHS sales. It provides support for research and development (R&D) through an allowance for R&D in its assessment of a company's profitability of its business with the NHS.

Medicines for Children Research Network:

The UK Government provides support for the NIHR Medicines for Children Research Network (MCRN), which provides infrastructure across all of England to support the delivery of paediatric medicines studies although not direct funding.

From its establishment in 2006 to the end of 2014, the MCRN/CRN Children has supported a total of 336 industry studies, 56 of which were taken on in 2014. 222 public (academic/health service) studies have been taken on by the network since 2006, 13 in 2014, with grants awarded under a number of European, UK and other research programmes. Further information is available on: (http://www.crn.nihr.ac.uk/children/).

Of the 13 publicly-sponsored studies taken on in 2014, funding was provided by:

- UK government (NIHR, Public Health England etc.; 5 studies)
- Charities (5 studies, 1 of which has been included in above set as well, for 2 studies this is also in collaboration with companies)
- European Commission (2 studies)
- National Institute of Health, United States (1 study)
- Companies (1 study).

3.8. 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. Therefore, according to Commission Guideline 2012/C 302/03, pharmaceutical companies were not yet obliged to post results of paediatric trials in EudraCT. The first deadlines for posting of trial results will occur in 2015.

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). Differences between the data reported for previous years in the following tables and in the report to the EC for the year 2014 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).

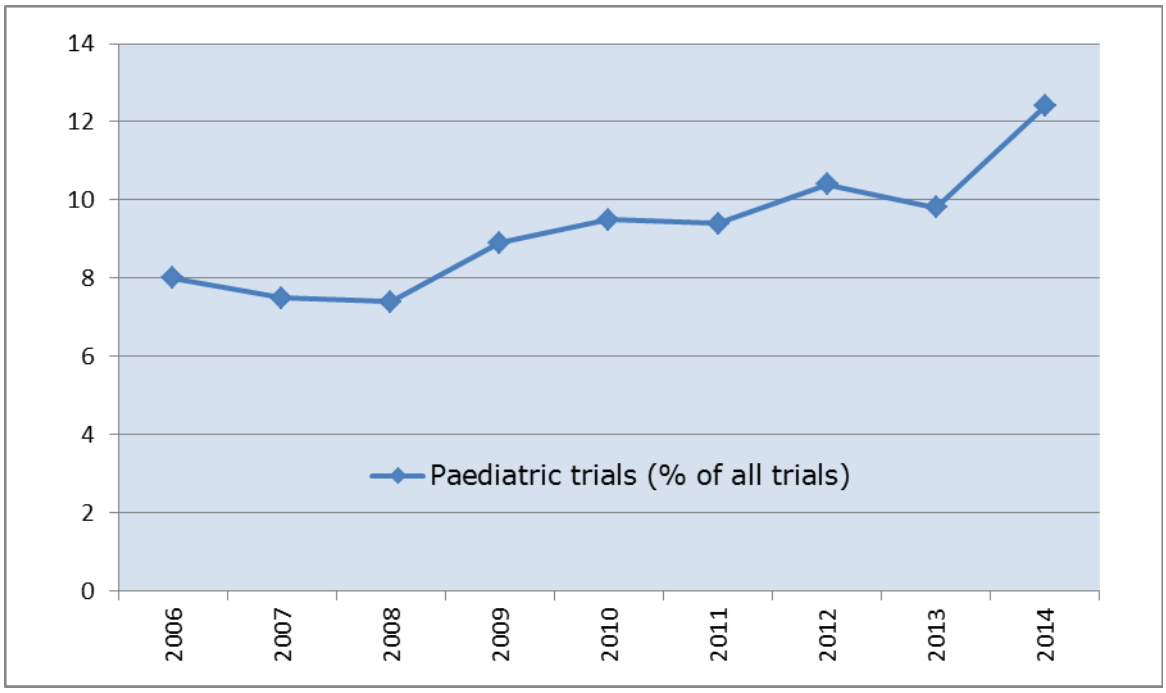
	2006	2007	2008	2009	2010	2011	2012	2013	2014
Paediatric[1] trials (number)	340	362	342	406	392	372	401	337	432
Total number of trials (adults and / or children)	4274	4854	4641	4553	4138	3969	3866	3442	3484
Proportion of paediatric trials of all trials (%)	*8.0*	*7.5*	*7.4*	*8.9*	*9.5*	*9.4*	*10.4*	*9.8*	*12.4*
Exclusively[2] paediatric trials (number)	196	188	185	241	231	217	257	211	278

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 12 % of all trials in 2014, whereas there is a general decrease in overall numbers of clinical trials included in EudraCT (adults and children).

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).

Number of subjects	2006	2007	2008	2009	2010	2011	2012	2013	2014
Preterm newborns	0	0	0	327	82	2,522	1,552	3,724	4,331
Newborns	0	98	5	184	169	1,348	2,283	1,496	1,948
Infants and toddlers	530	119	20	54,715	2,212	13,313	62,224	13,414	39,615
Children	2,683	706	270	5,783	2,721	21,654	30,826	23,230	62,979
Adolescents	435	36,458	285	5,801	4,831	20,206	22,680	17,300	42,353
Sum of above	3,648	37,381	580	66,810	10,015	59,043	119,565	59,164	151,226

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 150,000 in 2014, without significant increase in number of trials. 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.

Moreover, it should be mentioned that in recent years the PDCO has increasingly implemented modelling and simulation as well as extrapolation strategies in PIPs, in order to not subject children to unnecessary trials.

3.9. Paediatric use marketing authorisation

In the past year, the CHMP granted a paediatric use marketing authorisation (PUMA) for Hemangiol for the treatment of proliferating infantile haemangioma, which are benign tumours of blood vessels. PUMAs can be granted for medicines which are already authorised but no longer under patent or supplementary certificate protection, and that have been developed specifically for children. As an incentive to stimulate the development of existing medicines for the treatment of children, PUMA medicines are granted ten years of market protection.

This is the second PUMA authorised since the beginning of the Paediatric Regulation.

3.10. Article 45/46 of the Paediatric Regulation

3.10.1. 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 1,000 active substances, with several documents for each of them (some may relate to the same study).
- For centrally-authorised products, 2 procedures of evaluation concluded for 2 medicinal products in 2014, with no recommended change of current SmPCs. Information can be found in Annex 4.
- 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 2014, 3

additional waves have been agreed, corresponding to 20 active substances (with/without combinations). The assessment of the data has been finalised for 25 active substances (with/without combinations). The list of substances and the resulting recommended amendments of the SmPCs with a public assessment report are presented in Annex 4. Information can also be found on the CMD(h) website (http://www.hma.eu/99.html).

3.10.2. 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 in the paediatric population of an authorised medicinal product, whether or not they are part of a PIP, within 6 months of completion of the trial.
- For centrally authorised products, 95 procedures of evaluation were concluded in 2014. The CHMP recommended a change in the product information in 7 cases, corresponding to 7 medicinal products. The list of products and the resulting amendments of the summary of product characteristics is presented in Annex 5. There was no recommendation on change in a therapeutic indication. The proportion of changes in 2014 is lower than in 2013, 7% versus 26%.
- For nationally-authorised medicinal products, 51 studies were submitted in 2014, and the assessment was finalised for 15 procedures with published public assessment reports. 27% of the assessed procedures recommend change(s) to paediatric information in the summary of product characteristics. The list of assessment reports products and amendments of the SmPCs is reported in Annex 5.

3.11. Register of placing on the market

In 2012, the Agency established the "Register of deadlines to put a medicinal product on the market" (Article 33 of the Paediatric Regulation). 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). The EMA maintains this register, updating it at least once a year.

3.12. Transfer of marketing authorisation or access to data after discontinuation of marketing

The use of the possibility for a MAH to transfer the marketing authorisation or provide access, or for an applicant to require access to data (Article 35) at centralised or national level has not been made yet.

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 Agency 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 6 months. In 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)

Delayed applications (submissions 6 months or later than deadline)	**2010**	**2011**	**2012**	**2013**	**2014**
PIPs: number of delayed applications (and percent of total)	65 (74%)	44 (59%)	34 (39%)	18 (20%)	12* (13%)
Time lag (months): median (range)	22	35 (9-159)	35 (9-241)	28 (9-66)	29 (7-52)
Full (product-specific) waivers: number of **unjustified** delayed applications (and percent of total)	26 (59%)	13 (42%)	11(23%)	6 (11%)	4* (8%)
Time lag (months): median (range)	18	35 (9-137)	61 (19-179)	33 (14-60)	25.5 (10-41)

Source: EMA Paediatric database. *Delay considered not justified by the PDCO.

In 2014, overall fewer applications for PIPs and waivers were submitted late compared to 2013, however, from 2014, data are only reported when the late submission was not considered justified by the PDCO. Nevertheless, the positive trend observed in the previous years continued in 2014.

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

The reasons given for late submissions include a concern for the resources needed to prepare paediatric plan for products whose development may be discontinued and uncertainties and fear of potential multiple modifications of agreed PIP.

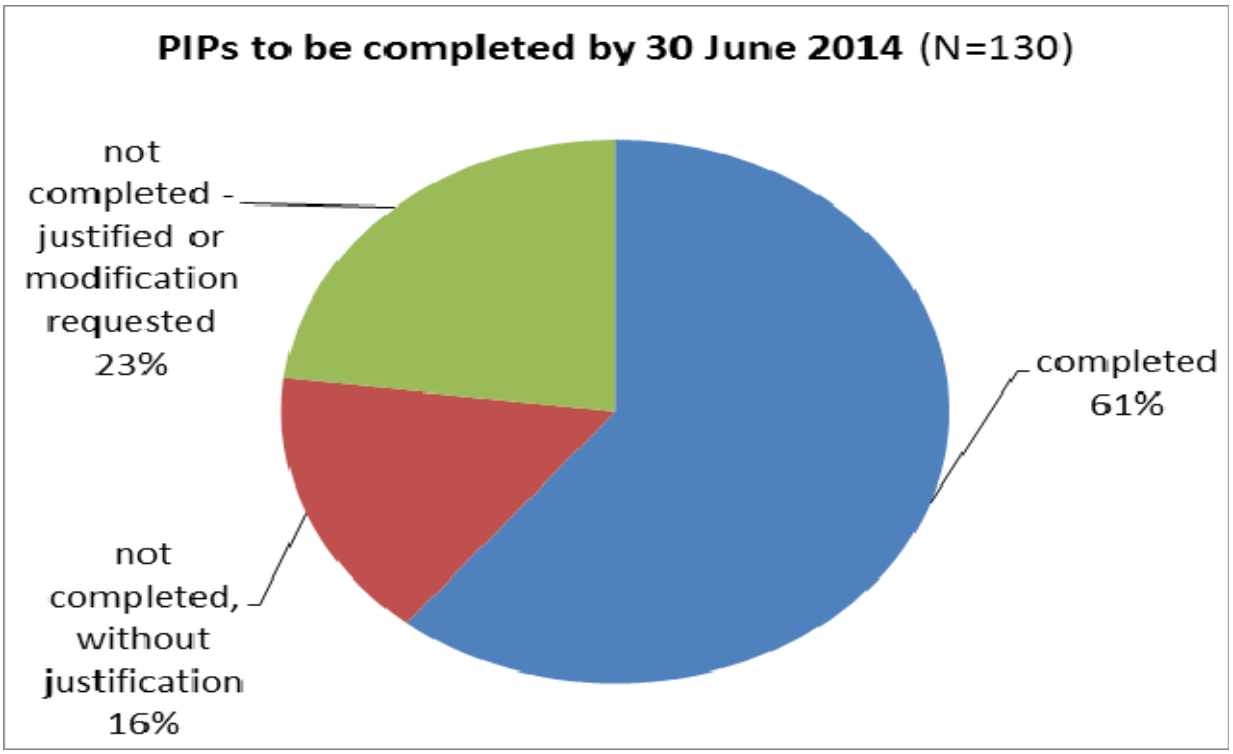
4.2. Completion of PIPs

The EMA decisions include dates of PIP completion.

The Agency made an analysis of the PIPs with a completion date scheduled before 30 June 2014. The cut-off date was chosen as end of June, as applicants must submit the complete study reports within 6 months of completion (Art. 46), and studies (and PIPs) completed after June 2014 may not have been subjected to compliance check.

In total, 130 PIPs were scheduled to be finished by 30 June 2014 (Figure 9). Of those, 79 PIPs have been completed. Of the remaining 51, 21 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 9 - PIPs to be completed by 30 June 2014



The detailed lists are in Annexes 8 and 9.

4.3. Compliance with agreed PIP

When a regulatory application (such as a marketing authorisation, variation or line extension) falling under the scope of Articles 7, 8, or 30 of the Paediatric Regulation is submitted to a competent authority, compliance with the agreed PIP is checked as part of the validation. If the outcome of the compliance check is negative, the marketing authorisation application or the variation/extension application cannot be validated.

In 2014, the EMA performed 85 compliance checks (Table 6, Figure 10, Figure 11), of which 54 were interim (i.e. partial) and 31 were full (i.e. final). This represents a significant increase compared to 2013 when 41 interim and 17 full compliance checks were conducted. Two interim compliance check procedures had negative outcome in 2014 (amikacin, mepolizumab); no full compliance check procedure had a negative outcome.

So far, no NCA has reported the finalisation of a compliance check procedure for a nationally approved product.

Figure 10 - EMA compliance check procedures

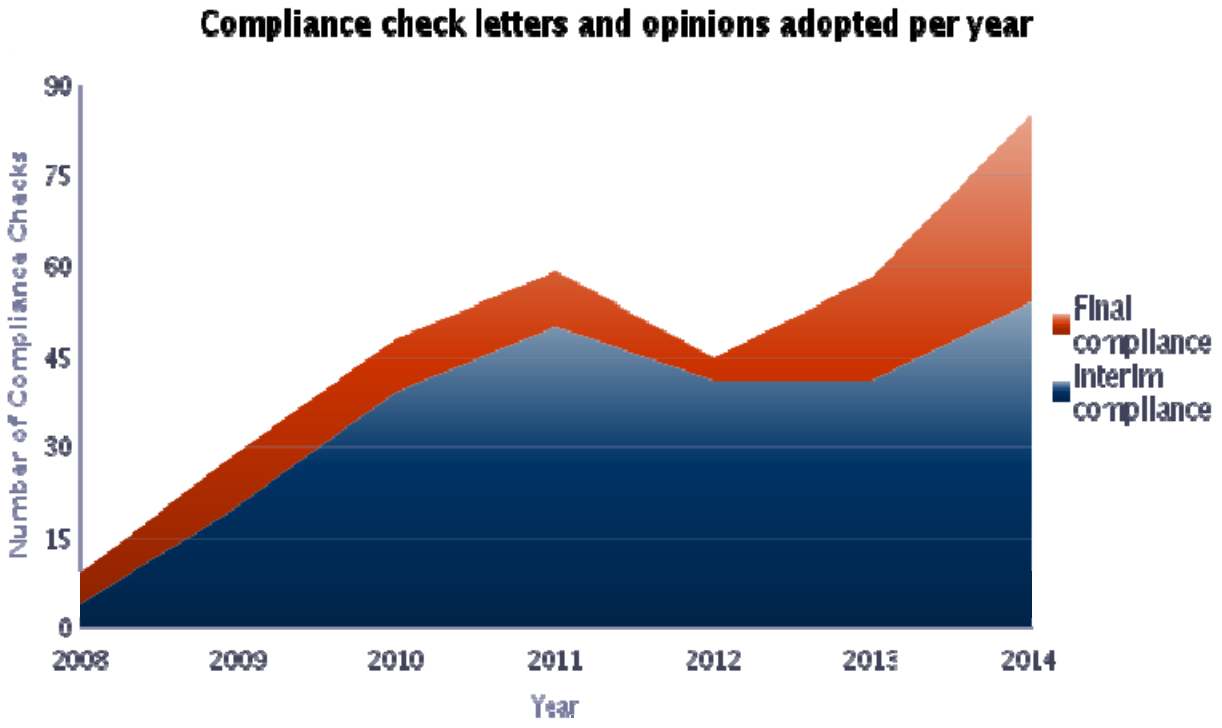
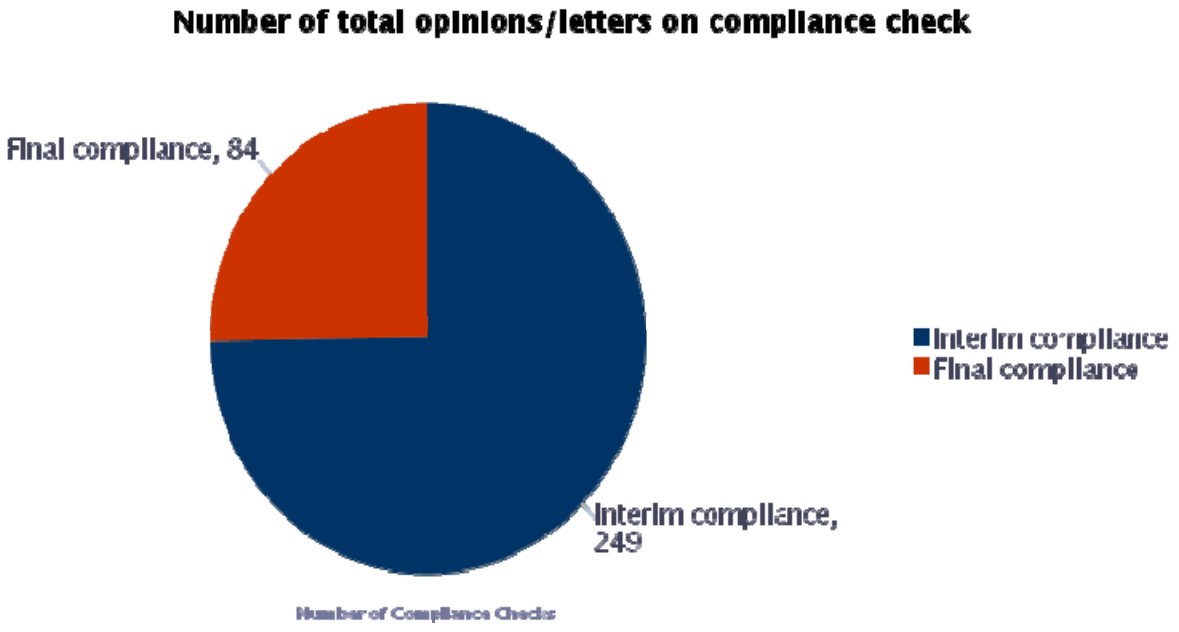


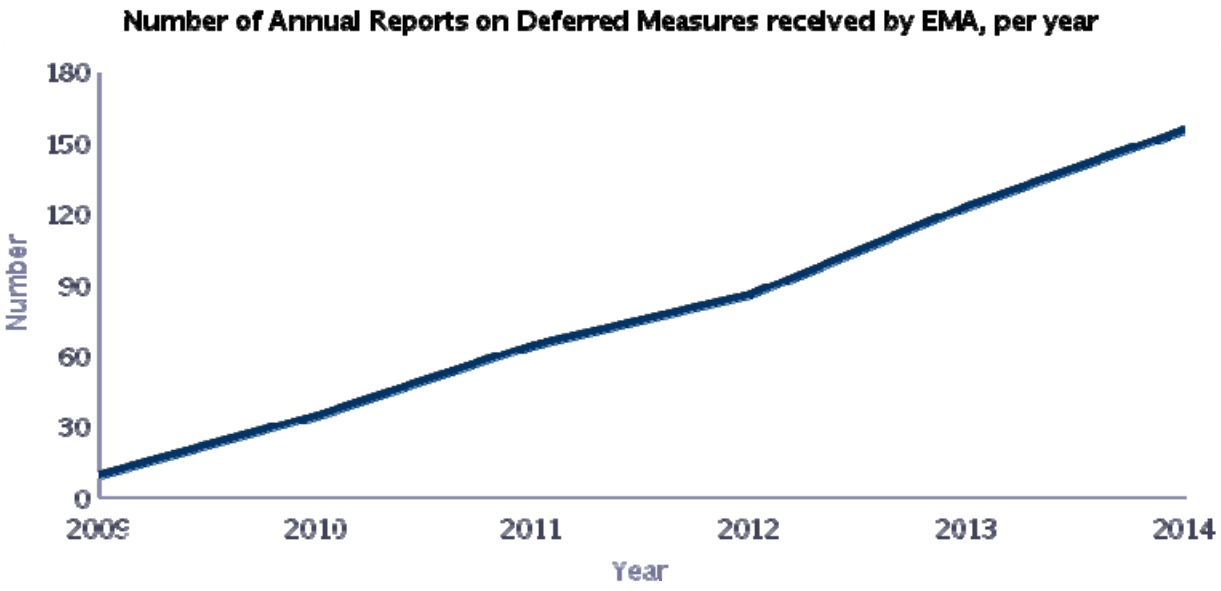
Figure 11 - Number of interim/full compliance check procedures 2008-2014



4.4. 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 12).

Figure 12 - Trend for Annual reports



The Agency received 155 annual reports on deferrals 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.

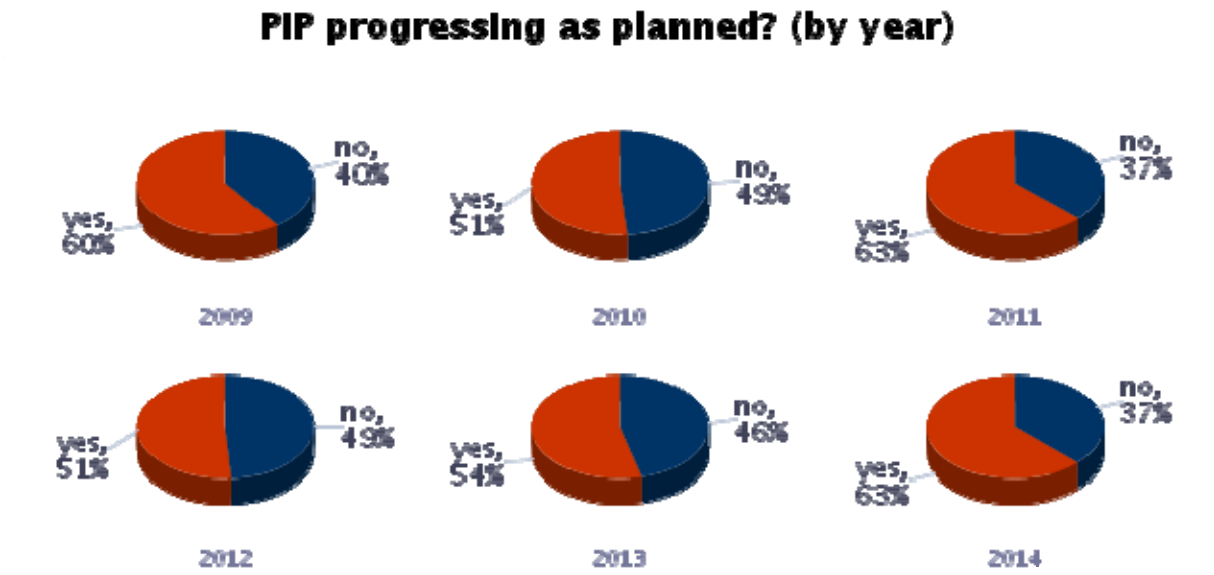
Over the years, more than half of the reports stated that the PIP was proceeding as planned; in 2014, the number of PIPs proceeding as planned is substantially higher than the number of PIPs were problems are reported (Figure **13**). The types of issues are listed in Table 16. List of the companies that submitted annual report is available in Annex 10.

Table 16 - Annual reports on deferred measures

	2010	2011	2012	2013	2014	Total	% of total
No problems reported	18	41	44	67	97	**273**	57%
Problems reported total	17	24	42	57	58	**202**	43%
Difficulties in developing age-related formulation(s)	*1*	*3*	*2*	*6*	*3*	***15***	*4.4%*
Economic problems				*1*	*0*	***1***	*0.3%*
Efficacy concerns	*4*	*1*	*2*	*1*	*2*	***12***	*3.5%*
Organizational issues (e.g. Acquisitions, mergers, applicant's internal restructuring, etc.)		*2*	*1*	*1*	*3*	***7***	*2.1%*
Other quality issues			*3*	*1*	*3*	***7***	*2.1%*
Other(s)	*9*	*10*	*17*	*26*	*29*	***91***	*26.8%*

	2010	2011	2012	2013	2014	Total	% of total
Recruitment difficulties	*10*	*15*	*29*	*35*	*31*	***122***	*36%*
Refusals/problems with National Competent Authority(ies)	*5*	*1*	*13*	*9*	*6*	***35***	*10.3%*
Refusals/problems with ethics committees	*6*	*3*	*9*	*6*	*3*	***27***	*8%*
Safety concerns	*5*	*3*	*2*	*5*	*7*	***22***	*6.5%*
Grand total	**35**	**65**	**86**	**124**	**339**	**320**	**100%**

Figure 13 - Percentage of annual reports stating whether the PIP is progressing as planned



The number of MAHs not submitting the annual reports on deferred measures on time was much smaller in 2014. The list of companies not submitting one or more annual reports is Table 17.

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

Applicant	2010	2011	2012	2013	2014
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	
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			
Eisai Ltd.		1			
Genzyme Europe B.V.		1			

Applicant	2010	2011	2012	2013	2014
Sigma-Tau SpA			1	1	
Takeda Global Research and Dev. Centre (Europe) Ltd			1		
Theravance, Inc.			1	1	
Amgen Europe B.V.				1	
Omrix Biopharmaceuticals SA				1	
Forest Laboratories Limited					1
Otsuka Pharmaceutical Europe Ltd.					
Totals	**8**	**11**	**9**	**14**	**1**

The complete list of annual reports not submitted is to be found in Annex 11. Overall, non-compliance with this obligation is very limited.

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 2014 to 31 December 2014.
- 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 beenincluded 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 2014 and 31 December 2014. 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 which have replied to the request for information

Member State	National Competent Authorities	National Patent Office
Austria	x	x
Belgium	x	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
Lithuania	x	x
Luxembourg		
Malta	x	x
The Netherlands	x	x
Poland	x	x
Portugal	x	
Romania	x	x
Slovakia	x	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 or under Mutual Recognition 2014

Member State	Marketing authorisation holder	Invented name(s)	International non-proprietary name	MA procedure	Type of procedure
Belgium	Roche SA	Valcyte	Valganciclovir	Mutual recognition(MRP)	Variation
Belgium	J Uriach & Cia	Rupatall	Rupatadine	MRP	Variation
Belgium	AstraZeneca	Crestor	Rosuvastatin	MRP	Variation
Bulgaria	Roche Bulgaria	Valcyte	Valganciclovir	MRP	Variation
Bulgaria	J Uriach & Cia	Rupafin	Rupatadine	MRP	Variation
Bulgaria	AstraZeneca	Crestor	Rosuvastatin	National	Variation
Croatia	J Uriach & Cia	Rupafin	Rupatadine	MRP	Variation
Croatia	Roche	Valcyte	Valganciclovir	MRP	Variation
Croatia	AstraZeneca	Crestor	Rosuvastatin	National	Variation
Cyprus	AstraZeneca	Crestor	Rosuvastatin	National	Variation
Cyprus	J Uriach & Cia	Rupafin	Rupatadine	MRP	Variation
Cyprus	GA STAMATIS & CO LTD	Valcyte	Valganciclovir	Decentralised (DC)	Variation
Cyprus	LEO Pharmaceutical products DK	Xamiol	Betamethasone dipropionate/calcipotriol monohydrate	MRP	Variation
Czech Republic	Roche	Valcyte	Valganciclovir	DC	Variation
Czech Republic	AstraZeneca	Crestor	Rosuvastatin	National	Variation
Czech Republic	Ferring	Misodel	Misoprostol	DC	Initial MA
Czech Republic	J Uriach & Cia	Tamalis	Rupatadine	DC	Variation
Denmark	Eli Lilly Danmark	STRATTERA	Atomoxetine	DC	Line extension

Member State	Marketing authorisation holder	Invented name(s)	International non-proprietary name	MA procedure	Type of procedure
Denmark	AstraZeneca	Crestor	Rosuvastatin	MRP	Variation
Estonia	Roche	Valcyte	Valganciclovir	DC	Variation
Estonia	AstraZeneca	Crestor	Rosuvastatin	National	Variation
Estonia	J Uriach & Cia	Rupafin	Rupatadine	DC	Variation
Finland	AstraZeneca	Crestor	Rosuvastatin	MRP	Variation
Finland	Ferring	Misodel	Misoprostol	DC	Initial MA
Finland	Roche	Valcyte	Valganciclovir	DC	Variation
Finland	J Uriach & Cia	Rupafin	Rupatadine	MRP	Variation
France	MEDA Pharma GmbH & Co. KG	Acnex / Zaria	Clindamycin phosphate / tretinoin, 10 mg/g + 0.25 mg/g, gel	DC (Decentralised)	Not provided
Italy	Roche	Valcyte	Valganciclovir	DC	Variation
Italy	AstraZeneca	Crestor	Rosuvastatin	MRP	Variation
Lithuania	AstraZeneca	Crestor	Rosuvastatin	National	Variation
Lithuania	Roche	Valcyte	Valganciclovir	DC	Variation
Lithuania	J Uriach & Cia	Rupafin	Rupatadine	DC	Variation
Poland	Ferring	Misodel	Misoprostol	DC	Initial MA
Poland	AstraZeneca	Crestor	Rosuvastatin	MRP	Variation
Poland	J Uriach & Cia	Rupafin	Rupatadine	DC	Variation
Poland	Boehringer Ingelheim International GmbH	Spiriva Respimat	Tiotropium	DC	Variation
Poland	Roche	Valcyte	Valganciclovir	MRP	Variation
Portugal	AstraZeneca	Crestor	Rosuvastatin	MRP	Variation
Portugal	Roche	RoValcyte	Valganciclovir	MRP	Variation
Romania	AstraZeneca	Crestor	Rosuvastatin	National	Variation
Romania	Roche	Valcyte	Valganciclovir	DC	Variation
Romania	J Uriach & Cia	Tamalis	Rupatadine	DC	Variation
Romania	Merck Sharp & Dohme	Ezetrol	Ezetimibe	National	Variation

Member State	Marketing authorisation holder	Invented name(s)	International non-proprietary name	MA procedure	Type of procedure
Slovenia	Roche	Valcyte	Valganciclovir	MRP	Variation
Slovenia	Ferring	Mysodelle	Misoprostol	DC	Initial MA
Slovenia	AstraZeneca	Crestor	Rosuvastatin	National	Variation
Slovenia	J Uriach & Cia	Rupafin	Rupatadine	DC	Variation
Spain	Biohorm, S.A.	ALERGOLIBER 1 mg/ml SOLUCIÓN ORAL	Rupatadine	DC	Variation
Spain	Roche	Valcyte	Valganciclovir	MRP	Variation
Sweden	J Uriach & Cia	Rupatall	Rupatadine	MRP	Variation
Sweden	Eli Lilly Sweden	Strattera	Atomoxetine	DC	Initial MA
UK	J Uriach & Cia	Rupafin	Rupatadine	MRP	Variation

Annex 4 - List of medicinal products assessed in 2014 further to submission of data through Article 45 and resulting amendment of the SmPC

Centrally authorised products

Active substance	Brand Name	MAH	Assessment outcome: change in SmPC (Y/N)	SmPC sections [1] to be changed
Octocog alfa	Helixate NexGen	Bayer Pharma AG	N	N/A
Octocog alfa	Kogenate	Bayer Pharma AG	N	N/A

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
Amisulpride	N	N/A
Gadoteric acid	Y	Sections 4.1, 4.2 (new indication)
Idarubicin	Y	Sections 4.1, 4.2 (paediatric information clarified)
Gadodiamide	N	N/A
Ibuprofen	Y	sections 4.2 and 4.4 (paediatric information clarified)

Active substance	Assessment outcome: change in SmPC (Y/N)	SmPC sections [1] to be changed
Metoprolol succinate	Y	sections 4.1 (new indication) and sections 4.2, 5.1 and 5.2 (paediatric information clarified)
Protirelin	Y	section 4.2 (paediatric information clarified)
Calcium carbonate	N	N/A
Budesonide	Y	section 4.1 (new indication) and sections 4.2, 4.4, 4.8, 5.1 and 5.2 (paediatric information clarified)
Glatiramer acetate	N	N/A
Theophylline	Y	sections 4.1, 4.2, 4.3, 4.4 and 5.2 (paediatric information clarified)
Gadopentetate	Y	section 5.2 (new paediatric information)
Bisoprolol	N	N/A
Colecalciferol	Y	sections 4.1, 4.3, 4.4 (paediatric information clarified)
Ibuprofen	Y	sections 4.2, 4.4 (paediatric information clarified)
Vigabatrin	Y	sections 4.2, 4.6, 4.8 and 5.2 (paediatric information clarified)
Atorvastatin calcium	N	N/A
Calcium (in combinations)	N	N/A
Estradiol/Estradiol & Norethisterone	N	N/A
Zolpidem	Y	sections 4.1, 4.2, 5.1 (paediatric information clarified)
Bisoprolol / hydrochlorothiazide	N	N/A
Fluarix	N	N/A
Nimodipine	Y	section 4.2 (paediatric information clarified)
Desmopressin	N	N/A
Phenylephrine	Y	sections 4.2, 4.4, 4.6, 4.9 (paediatric information clarified)

Total:

- 25 active substances (with/without combinations) assessed
- 11 active substances (with/without combinations) for which no change in current SmPC is recommended
- 14 active substances for which a change in SmPC sections is recommended
- 3 active substance assessment lead to 3 new paediatric indications

New paediatric indications:

- Gadoteric acid as contrast agent in the paediatric population (0-18 years) for Magnetic resonance imaging (MRI) for cerebral and spinal disease and whole-body MRI
- Metoprolol succinate: Treatment of hypertension in children and adolescents 6-18 years of age
- Budenoside (Pulmicort Respules): treatment of very serious pseudocroup (laryngitis subglottica) in which hospitalisation is indicated

Annex 5 – List of medicinal products assessed in 2014 further to submission of data through Article 46 and resulting amendment of the SmPC

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 2014.

[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
Adalimumab	Humira	AbbVie Ltd.	N	N/A
Alogliptin	Vipidia	Takeda Pharma A/S	N	N/A
Aprepitant	Emend	Merck Sharp & Dohme Limited	Further data is required	N/A within this procedure
Aprepitant	Emend	Merck Sharp & Dohme Limited	Further data is required	N/A within this procedure
Aprepitant	Emend	Merck Sharp & Dohme Limited	Further data is required	N/A within this procedure
Aripiprazole	Abilify	Otsuka Pharmaceutical Europe Ltd	Further data is required	N/A within this procedure
Asenapine	Sycrest	N.V. Organon	N	N/A
Azilsartan medoxomil	Edarbi	Takeda Pharma A/S	N	N/A
Azilsartan medoxomil	Ipreziv	Takeda Pharma A/S	N	N/A
Bivalirudin	Angiox	The Medicines Company UK Ltd.	Further data is required	Section 5.2
Boceprevir	Victrelis	Merck Sharp & Dohme Limited	N	N/A
Caspofungin	Cancidas	Merck Sharp & Dohme Limited	Further data is required	See subsequent procedure
Caspofungin	Cancidas	Merck Sharp & Dohme Limited	Y	Section 4.4
Clofarabine	Evoltra	Genzyme Europe BV	N	N/A

Active substance	Brand name	MAH	Assessment outcome: change in SmPC (Y/N)	SmPC sections [1] to be changed
Deferasirox	Exjade	Novartis Europharm Ltd	N	N/A
Deferasirox	Exjade	Novartis Europharm Ltd	N	N/A
Desloratadine	Aerius	Merck Sharp & Dohme Limited	N	N/A
Desloratadine	Aerius	Merck Sharp & Dohme Limited	N	N/A
Desloratadine	Azomyr	Merck Sharp & Dohme Limited	N	N/A
Desloratadine	Azomyr	Merck Sharp & Dohme Limited	N	N/A
Desloratadine	Neoclarityn	Merck Sharp & Dohme Limited	N	N/A
Desloratadine	Neoclarityn	Merck Sharp & Dohme Limited	N	N/A
Dexmedetomidine	Dexdor	Orion Corporation	Further data is required	N/A within this procedure
DTP-HepB-Polio-Hib conjugate vaccine (adsorbed)	Hexaxim	Sanofi Pasteur	N	N/A
DTP-HepB-Polio-Hib conjugate vaccine (adsorbed)	Hexaxim	Sanofi Pasteur	N	N/A
DTP-HepB-Polio-Hib conjugate vaccine (adsorbed)	Hexyon	Sanofi Pasteur MSD SNC	N	N/A
DTP-HepB-Polio-Hib conjugate vaccine (adsorbed)	Infanrix hexa	GlaxoSmithKline Biologicals	N	N/A
DTP-HepB-Polio-Hib conjugate vaccine (adsorbed)	Infanrix hexa	GlaxoSmithKline Biologicals	N	N/A
Doripenem	Doribax	Janssen-Cilag International N.V.	N	N/A
Doripenem	Doribax	Janssen-Cilag International N.V.	N	N/A
Doripenem	Doribax	Janssen-Cilag International N.V.	N	N/A

Active substance	Brand name	MAH	Assessment outcome: change in SmPC (Y/N)	SmPC sections [1] to be changed
Eculizumab	Soliris	Alexion Europe SAS		
Eltrombopag	REVOLADE	GlaxoSmithKline Trading Services	N	N/A
Eslicarbazepine acetate	Zebinix	Bial - Portela & Cª, S.A.	Y	Section 4.2
Everolimus	Votubia	Novartis Europharm Ltd	N	N/A
Fidaxomicin	Dificlir	Astellas Pharma Europe B.V.	N	N/A
Fluticasone furoate / vilanterol	Relvar Ellipta	Glaxo Group Ltd	Further data is required	N/A within this procedure
Fluticasone furoate / vilanterol	Relvar Ellipta	Glaxo Group Ltd	N	N/A
Fluticasone furoate / vilanterol	Relvar Ellipta	Glaxo Group Ltd	Further data is required	N/A within this procedure
Fluticasone furoate / vilanterol	Relvar Ellipta	Glaxo Group Ltd	N	N/A
Fluticasone furoate / vilanterol	Relvar Ellipta	Glaxo Group Ltd	Further data is required	N/A within this procedure
Fluticasone furoate / vilanterol	Relvar Ellipta	Glaxo Group Ltd	N	N/A
Fluticasone furoate / vilanterol	Relvar Ellipta	Glaxo Group Ltd	Further data is required	N/A within this procedure
Fluticasone furoate / vilanterol	Relvar Ellipta	Glaxo Group Ltd	N	N/A
Fosamprenavir	Telzir	ViiV Healthcare Uk Limited	N	N/A
Fosaprepitant dimeglumine	Ivemend	Merck Sharp & Dohme Limited	Further clarification is required	N/A within this procedure
Human coagulation factor viii / human von willebrand factor	Voncento	CSL Behring GmbH	Y	Section 4.4
Human normal immunoglobulin	HyQvia	Baxter Innovations GmbH	N	N/A

Active substance	Brand name	MAH	Assessment outcome: change in SmPC (Y/N)	SmPC sections [1] to be changed
Human normal immunoglobulin	HyQvia	Baxter Innovations GmbH	N	N/A
Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed)	Cervarix	GlaxoSmithKline Biologicals	N	N/A
Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)	Gardasil	Sanofi Pasteur MSD SNC	N	N/A
Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)	Gardasil	Sanofi Pasteur MSD SNC	N	N/A
Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)	Silgard	Merck Sharp & Dohme Limited	N	N/A
Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)	Silgard	Merck Sharp & Dohme Limited	N	N/A
Human rotavirus, live attenuated	Rotarix	GlaxoSmithKline Biologicals S.A.	N	N/A
Human thrombin / human fibrinogen	TachoSil	Takeda Austria GmbH	N	N/A
Human thrombin / human fibrinogen	TachoSil	Takeda Austria GmbH	N	N/A

Active substance	Brand name	MAH	Assessment outcome: change in SmPC (Y/N)	SmPC sections [1] to be changed
Insulin degludec	Tresiba	Novo Nordisk A/S	Further data is required	N/A within this procedure
Insulin detemir	Levemir	Novo Nordisk A/S	Further data is required	N/A within this procedure
Lacosamide	Vimpat	UCB Pharma SA	Not available	Not available
Lacosamide	Vimpat	UCB Pharma SA	N	N/A
Laronidase	Aldurazyme	Genzyme Europe BV	N	N/A
Laronidase	Aldurazyme	Genzyme Europe BV	N	N/A
Levetiracetam	Keppra	UCB Pharma SA	N	N/A
Levetiracetam	Keppra	UCB Pharma SA	N	N/A
Levetiracetam	Keppra	UCB Pharma SA	N	N/A
Lixisenatide	Lyxumia	Sanofi-Aventis Groupe	Further data is required	N/A within this procedure
Lurasidone	Latuda	Takeda Pharma A/S	Further data is required	See subsequent procedure
Lurasidone	Latuda	Takeda Pharma A/S	Y	Sections 4.2 and 5.2
Measles, mumps, rubella and varicella vaccine (live)	Proquad	Sanofi Pasteur MSD SNC	N	N/A
Mecasermin	Increlex	Ipsen Pharma	N	N/A
Melatonin	Circadin	RAD Neurim Pharmaceuticals EEC Ltd.	N	N/A
Meningococcal group a, c, w135 and y conjugate vaccine	Menveo	Novartis Vaccines and Diagnostics S.r.l.	Y	Section 4.8
Meningococcal group a, c, w135 and y conjugate vaccine	Nimenrix	GlaxoSmithKline Biologicals S.A.	N	N/A
Meningococcal group b vaccine (rdna, component, adsorbed)	Bexsero	Novartis Vaccines and Diagnostics S.r.l.	N	N/A

Active substance	Brand name	MAH	Assessment outcome: change in SmPC (Y/N)	SmPC sections [1] to be changed
Meningococcal group b vaccine (rdna, component, adsorbed)	Bexsero	Novartis Vaccines and Diagnostics S.r.l.	N	N/A
Octocog alfa	Helixate NexGen	Bayer Pharma AG	N	N/A
Octocog alfa	Helixate NexGen	Bayer Pharma AG	N	N/A
Octocog alfa	Kogenate	Bayer Pharma AG	N	N/A
Omalizumab	Xolair	Novartis Europharm Ltd	N	N/A
Pandemic influenza vaccine (h5n1) (split virion, inactivated, adjuvanted)	Pumarix	GlaxoSmithKline Biologicals	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
Pneumococcal polysaccharide conjugate vaccine (adsorbed)	Synflorix	GlaxoSmithKline Biologicals	N	N/A
Pneumococcal polysaccharide conjugate vaccine (adsorbed)	Synflorix	GlaxoSmithKline Biologicals	N	N/A
Pregabalin	Lyrica	Pfizer Limited	Further data is required	N/A within this procedure

Active substance	Brand name	MAH	Assessment outcome: change in SmPC (Y/N)	SmPC sections [1] to be changed
Rotavirus vaccine, live, oral	RotaTeq	Sanofi Pasteur MSD SNC	N	N/A
Rufinamide	Inovelon	Eisai Ltd	Further data is required	See subsequent procedure
Rufinamide	Inovelon	Eisai Ltd	N	N/A
Sildenafil	Revatio	Pfizer Limited	N	N/A
Sirolimus	Rapamune	Pfizer Limited	N	N/A
Tobramycin	TOBI Podhaler	Novartis Europharm Ltd	N	N/A
Voriconazole	Vfend	Pfizer Limited	Further clarification is required	Section 4.8

Total:

- 95 assessment procedures concluded in 2014
- 61 active substances assessed in 2014
- 7 active substances for which a change in SmPC sections is recommended.

Products authorised through national/mutual recognition/decentralised procedure

Article 46 work-sharing finalised in 2014 and published

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
Haemophilus type b vaccine conjugated to Tetanus protein and Diphteria, Tetanus, Acellular Pertussis and Poliomyelitis Vaccine Adsorbed	Pentavac/Pentaxim	Sanofi Pasteur MSD	N	N/A
Gadopentetate	Magnevist	Bayer PLC	Y	section 5.2 (new paediatric information)
Diphtheria, Tetanus, Pertussis (acellular, component) Vaccine	Covaxis (Triaxis/Adacel)	Sanofi Pasteur MSD	N	N/A
Crisantaspase	Erwinase	EUSA Pharma SAS	Y	section 5.2 (paediatric information clarified)
Live attenuated measles virus (Schwarz strain), Live attenuated mumps virus (RIT 4385 strain, derived from Jeryl Lynn strain)), Live attenuated rubella virus (Wistar RA 27/3 strain)	Priorix	GlaxoSmithKline GmbH & Co. KG	N	N/A
Atomoxetine	Strattera	Eli Lilly	N	N/A

Name of active substance	Brand name	MAH	Assessment outcome: change in SmPC (Y/N)	SmPC sections [1] to be changed
Calcipotriol / Betamethasone Dipropionate	Daivobet, Dovobet, Xamiol	Leo Pharma A/S	Y	sections 4.2, 4.8 and 5.1 (paediatric information clarified)
Hepatitis A vaccine	Vaqta	Sanofi Pasteur MSD GmbH	N	N/A
A/California/7/2009 (H1N1), A/Victoria/361/2011 (H3N2), B/Wisconsin/1/2010	Fluarix	GlaxoSmithKline GmbH & Co. KG	N	N/A
Haemophilus influenzae type b conjugate, Neisseria meningitidis capsular polysaccharide C, Tetanus toxoid conjugates	Menitorix	GlaxoSmithKline Biologicals S.A.	N	N/A
Mometasone furoate	Zenhale	Merck Sharp & Dohme	N	N/A
Haemophilus influenzae type b conjugate, Neisseria meningitidis capsular polysaccharide C, Tetanus toxoid conjugates	Menitorix	GlaxoSmithKline Biologicals S.A.	N	N/A
Tapentadol hydrochloride	Palexia, Yantil, Tapentadol Grünenthal	Grünenthal GmbH	N	N/A
Mometasone furoate	Nasonex	Merck Sharp & Dohme	Y	sections 4.4 (paediatric information clarified)
Aciclovir / Hydrocortisone	Xerclear	Medivir AB	N	N/A

Total:

- 15 active substances assessed in 2014
- 11 active substances for which no change in current SmPC is recommended
- 4 active substances for which a change in SmPC sections is recommended

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

Invented name	PIP procedure number	Active substance(s) (abbreviated if necessary)	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*
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.	24/10/2001	26/11/2008	26/11/2010	
PegIntron	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.	29/05/2000	11/11/2009	11/11/2011	
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	

Invented name	PIP procedure number	Active substance(s) (abbreviated if necessary)	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*
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.	25/05/2000	11/11/2009	11/11/2011	
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	
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	
Pediacel®	EMEA-000278-PIP01-08-M01	Purified diphtheria toxoid, Purified tetanus toxoid, Five component acellular pertussis,	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	03/12/2010	03/12/2010	03/12/2012	

Invented name	PIP procedure number	Active substance(s) (abbreviated if necessary)	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*
		Inactivated poliomyelitis vaccine, Purified polyribosylribitol phosphate capsular polysaccharide of Haemophilus influenzae type b covalently bound to Tetanus protein (PRP-T)	birthday.				
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	
Sortis and associated names, Lipitor, Tahor, Xarator, Zarator,	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)	03/08/2010	05/05/2011	05/05/2013	

Invented name	PIP procedure number	Active substance(s) (abbreviated if necessary)	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*
Liprimar, Totalip, Torvast, Cardyl			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.				
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	
Buccolam	EMEA-000395-PIP01-08	Midazolam	Treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents (from 3 months to < 18 years)	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	05/02/1998	05/09/2011	05/09/2013	

Invented name	PIP procedure number	Active substance(s) (abbreviated if necessary)	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*
			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).				
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	
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	13/08/1999	21/02/2012	21/02/2014	11/06/2012

Invented name	PIP procedure number	Active substance(s) (abbreviated if necessary)	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*
			AZA, or who are intolerant to or have medical contraindications for such therapies.				
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	
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	
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	03/02/2000	31/07/2012	31/07/2014	

Invented name	PIP procedure number	Active substance(s) (abbreviated if necessary)	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*
			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.				
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	
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-	Imatinib mesilate	Treatment of paediatric patients with	07/11/2001	27/06/2013	27/06/2015	

Invented name	PIP procedure number	Active substance(s) (abbreviated if necessary)	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*
	PIP01-08-M03		newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ALL) integrated with chemotherapy.				
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	
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	
Misodel	EMEA-001159-	Misoprostol	Mysodelle is indicated for induction of	16/10/2013	21/11/2013	21/11/2015	

Invented name	PIP procedure number	Active substance(s) (abbreviated if necessary)	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*
	PIP02-12		labour in women with an unfavourable cervix, from 36 weeks gestation, in whom induction is clinically indicated.				
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	

*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 2014 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 on-going 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 2014 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 name	Substance(s)	Opinion	Delay (in months)
FORUM Pharmaceuticals, Inc.	(R)-7-Chloro-benzo[b]thiophene-2-carboxylic acid (1-aza-bicyclo[2.2.2]oct-3-yl)-amide hydrochloride hydrate	PIP agreed	**51**
Acceleron Pharma, Inc.	Recombinant soluble fusion protein with a modified form of the extracellular domain of human activin receptor IIB linked to the human IgG1 Fc domain	PIP agreed	**12**
Amgen Europe B.V.	D-Argininamide, N-acetyl-D-cysteinyl-D-alanyl-D-arginyl-D-arginyl-D-arginyl-D-alanyl-, disulfide with L-cysteine (AMG 416)	PIP agreed	**27**
Merck Sharp and Dohme (Europe), Inc.	Ertugliflozin	PIP agreed	**32**
Vanda Pharmaceuticals Ltd.	Tasimelteon	PIP agreed	**14**
Sunesis Europe Ltd	Vosaroxin	PIP agreed	**47**
Pfizer Ltd.	Inotuzumab	PIP agreed	**7**
Zymenex	Recombinant human alpha-mannosidase	PIP agreed	**10**
ALFA WASSERMANN S.p.A.	Potassium chloride / Sodium chloride / Simeticone / Citric acid, anhydrous / Sodium citrate / Sodium sulphate, anhydrous / Macrogol 4000	PIP agreed	**52**
Bristol-Myers Squibb International Corporation	Clazakizumab	PIP agreed	**31**
Roche Products Limited	Etrolizumab	PIP agreed	**18**

Company name	Substance(s)	Opinion	Delay (in months)
Janssen Cilag International NV	4-{[(1R,2s,3S,5s,7s)-5-Hydroxy-2-adamantyl]amino}-1H-pyrrolo[2,3-b]pyridine-5-carboxamide monohydrobromide	PIP agreed	**32**
AstraZeneca AB	Dapagliflozin / Saxagliptin	Full waiver granted	**20**
Triskel EU Services, Ltd	Abaloparatide	Full waiver granted	**31**
CTI Life Sciences, Ltd	Pacritinib	Full waiver granted	**41**
Versartis, Inc.	Recombinant human growth hormone modified by fusion with two hydrophilic polypeptide chains (VRS-317)	Full waiver granted	**10**

Annex 8 - List of PIPs completed (by 30 June 2014)

Substance(s) (abbreviated)	Company	Latest PIP number
Valsartan	Novartis Europharm Limited	EMEA-000005-PIP01-07-M01
Ezetimibe	Merck Sharp & Dohme Limited	EMEA-000007-PIP01-07-M02
Losartan potassium	Merck Sharp & Dohme (Europe) Inc.	EMEA-000008-PIP01-07
Caspofungin acetate	Merck Sharp & Dohme (Europe) Inc.	EMEA-000010-PIP01-07
Montelukast sodium	Merck Sharp & Dohme Inc.	EMEA-000012-PIP01-07-M01
r-L-Asparaginase	medac Gesellschaft für klinische Spezialpräparate	EMEA-000013-PIP01-07-M01
Zoledronic acid	Novartis Europharm Limited	EMEA-000024-PIP01-07
Darunavir	Janssen-Cilag International NV	EMEA-000038-PIP01-07-M03
Ribavirin	Schering-Plough Europe	EMEA-000070-PIP01-07
Peginterferon alfa-2b	Schering-Plough Europe	EMEA-000071-PIP01-07
Atorvastatin calcium	Pfizer Limited	EMEA-000073-PIP01-07
Rizatriptan benzoate	Merck Sharp & Dohme (Europe) Inc.	EMEA-000084-PIP02-10
Soya-bean oil, refined, Ph. Eur. / Olive oil, refined, Ph. Eur.	Baxter World Trade SPRL	EMEA-000112-PIP01-07-M01
Abatacept	Bristol-Myers Squibb Pharma EEIG	EMEA-000118-PIP01-07-M01
Antigen of pre-pandemic strain* A/Vietnam/1203/2004	Baxter Innovations GmbH	EMEA-000156-PIP01-07-M02
Human Normal Immunoglobulin	LBF Biotechnologies	EMEA-000167-PIP01-07-M02
Estradiol / Nomegestrol	N.V. Organon	EMEA-000250-PIP01-08-M02
Vaccinum poliomyelitidis / pertussis / haemophili / poliomyelitidis inactivatum stirpe 2 / poliomyelitidis inactivatum stirpe 1 /pertussis sine cellulis (PRN) / pertussis sine cellulis (FHA) / pertussis sine cellulis (PT) / tetani / diphtheriae	Sanofi Pasteur MSD SNC	EMEA-000278-PIP01-08-M01
Anastrozole	AstraZeneca AB	EMEA-000283-PIP01-08
Etanercept	Pfizer Limited	EMEA-000299-PIP01-08-M03

Substance(s) (abbreviated)	Company	Latest PIP number
Human Papillomavirus1 Type 18 L1 protein / Type 16 L1 protein / Type 11 L1 protein / Type 6 L1 protein	Sanofi Pasteur MSD SNC	EMEA-000375-PIP01-08-M02
Peginterferon alfa-2b	Schering-Plough Europe	EMEA-000384-PIP01-08
Insulin glargine	Sanofi-Aventis Deutschland GmbH	EMEA-000387-PIP01-08
Midazolam (as the Hydrochloride salt)	Auralis Limited	EMEA-000395-PIP01-08
Insulin glargine	Sanofi-Aventis Deutschland GmbH	EMEA-000396-PIP01-08
Imatinib mesilate	Novartis Europharm Limited	EMEA-000463-PIP01-08-M03
Propranolol hydrochloride	Pierre Fabre Dermatologie	EMEA-000511-PIP01-08-M03
Colesevelam	Genzyme Europe B.V.	EMEA-000543-PIP01-09
Infliximab	Centocor B.V.	EMEA-000549-PIP01-09-M01
Clindamycin Phosphate / Tretinoin	MEDA Pharma GmbH & Co. KG	EMEA-000892-PIP01-10
Rotavirus type P1A[8] / rotavirus type G4 / rotavirus type G3 / rotavirus type G2 / rotavirus type G1	Sanofi Pasteur MSD SNC	EMEA-000967-PIP01-10-M01
Misoprostol	Ferring pharmaceuticals A/S	EMEA-001159-PIP02-12
Paliperidone	Janssen-Cilag International NV	EMEA-000014-PIP01-07-M06
Human normal immunoglobulin	Octapharma Pharmazeutika Produktionsges.m.b.H	EMEA-001110-PIP01-10-M01
Prucalopride succinate	Shire-Movetis NV	EMEA-000459-PIP01-08-M02
Influenza Virus Type B, Victoria lineage/ Influenza Virus Type A, H1N1/ Influenza virus Type B, Yamagata lineage/ Influenza Virus Type A, H3N2	MedImmune Limited	EMEA-001051-PIP01-10-M03
Raltegravir / lamivudine	Merck Sharp & Dohme (Europe), Inc.	EMEA-001442-PIP01-13
Valganciclovir hydrochloride	Roche Registration Limited	EMEA-000726-PIP01-09-M02
Nitisinone	Swedish Orphan Biovitrum International AB	EMEA-000784-PIP02-11-M01
rupatadine fumarate	J. Uriach y Compañía, S.A.	EMEA-000582-PIP01-09-M03
Motavizumab	AbbVie Ltd	EMEA-000352-PIP01-08-M01
Tobramycin	Novartis Europharm Ltd.	EMEA-000184-PIP01-08-M02
Tigecycline	Pfizer Limited	EMEA-000120-PIP01-07-M05

Substance(s) (abbreviated)	Company	Latest PIP number
Nevirapine	Boehringer Ingelheim International GmbH	EMEA-000391-PIP01-08-M01
Pandemic influenza vaccine (H1N1) (split virion, inactivated, adjuvanted), containing antigen equivalent to Influenza A/California/7/2009 (Produced at Quebec manufacturing site)	GlaxoSmithKline Biologicals S.A.	EMEA-000687-PIP01-09-M02
Meningococcal group A oligosaccharide Conjugated to Corynebacterium diphteriae CRM197 protein (MenA-CRM)/Meningococcal group C oligosaccharide Conjugated to Corynebacterium diphteriae CRM197 protein (MenC-CRM)/Meningococcal group W-135 oligosaccharide Conjugated to Corynebacterium diphteriae CRM197 protein (MenW-CRM)/Meningococcal group Y oligosaccharide Conjugated to Corynebacterium diphteriae CRM197 protein (MenY-CRM)	Novartis Vaccines and Diagnostics S.r.L	EMEA-000032-PIP01-07-M04
Autologous CD34+ Cells Transduced ex-vivo with Retroviral Vector (GIADAI) Containing Human Adenosine Deaminase Gene from cDNA	GlaxoSmithKline Trading Services Limited	EMEA-001289-PIP01-12-M01
Split influenza virus, inactivated containing antigen equivalent to A/California/7/2009 (H1N1)-like strain (A/California/7/2009 (NYMC X-179A)), non-adjuvanted	Sanofi Pasteur SA	EMEA-000670-PIP01-09-M02
Vandetanib	AstraZeneca AB	EMEA-000052-PIP01-07-M03
Split Influenza virus, inactivated, containing antigen: A/California/7/2009 (H1N1)v like strain (X-179A)	GlaxoSmithKline Biologicals S.A.	EMEA-000725-PIP01-09-M03
Tiotropium bromide	Boehringer Ingelheim International GmbH	EMEA-000035-PIP01-07-M05
Voriconazole	Pfizer Limited	EMEA-000191-PIP01-08-M05
Formoterol / Mometasone	Merck Sharp & Dogme (Europe) Inc.	EMEA-000025-PIP01-07-M01

Substance(s) (abbreviated)	Company	Latest PIP number
Misoprostol	Ferring pharmaceuticals A/S	EMEA-001159-PIP02-12
Anagrelide hydrochloride	Shire Pharmaceutical Contracts Limited	EMEA-000720-PIP01-09-M02
Ritonavir / lopinavir	AbbVie Ltd	EMEA-001005-PIP01-10-M01
Entecavir	Bristol-Myers Squibb Pharma EEIG	EMEA-000339-PIP02-09-M03
Human Normal Immunoglobulin	LFB Biotechnologies	EMEA-000558-PIP01-09-M02
Insulin detemir	Novo Nordisk A/S	EMEA-000412-PIP01-08-M01
Sapropterin Dihydrochloride	Merck KGaA	EMEA-001476-PIP01-13
Insulin degludec	Novo Nordisk A/S	EMEA-000456-PIP01-08-M02
Guanfacine Hydrochloride	Shire Pharmaceuticals Contracts Ltd.	EMEA-000745-PIP01-09-M03
Imatinib mesilate	Novartis Europharm Limited	EMEA-000463-PIP02-10
Ulipristal acetate	Laboratoire HRA Pharma	EMEA-000305-PIP01-08-M02
Bosentan monohydrate	Actelion Registration Ltd	EMEA-000425-PIP02-10-M04
Human Papillomavirus Type 6 L1 protein / Human Papillomavirus Type 11 L1 protein / Human Papillomavirus Type 16 L1 protein / Human Papillomavirus Type 18 L1 protein / Human Papillomavirus Type 31 L1 protein / Human Papillomavirus Type 33 L1 protein / Human Papillomavirus Type 45 L1 protein / Human Papillomavirus Type 52 L1 protein / Human Papillomavirus Type 58 L1 protein	Sanofi Pasteur MSD SNC	EMEA-000654-PIP01-09-M02
Atomoxetine	Eli Lilly & Company	EMEA-001167-PIP02-11-M01
Anakinra	Swedish Orphan Biovitrum AB (publ)	EMEA-001212-PIP01-11
Travoprost	Alcon Laboratories (UK) Ltd.	EMEA-001271-PIP01-12-M01
Sodium benzylpenilloate / benzylpenicilloyl octa- L-lysine	Diater Laboratorio de Diagnóstico y Aplicaciones Terapéuticas, S.A.	EMEA-001398-PIP02-13
Golimumab	Janssen Biologics BV	EMEA-000265-PIP01-08-M04
Ivabradine hydrochloride	Les Laboratoires Servier	EMEA-000627-PIP01-09-M04
Rosuvastatin	AstraZeneca AB	EMEA-000022-PIP01-07-M04

Substance(s) (abbreviated)	Company	Latest PIP number
Gadobutrol	Bayer Pharma AG	EMEA-000994-PIP01-10-M01
Adalimumab	AbbVie Limited	EMEA-000366-PIP01-08-M06
Clopidogrel	Sanofi Pharma Bristol-Myers Squibb SNC	EMEA-000049-PIP01-07-M03
Esomeprazole sodium Esomeprazole magnesium trihydrate	AstraZeneca AB	EMEA-000331-PIP01-08-M01
Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), inactivated poliovirus and Haemophilus type b (meningococcal protein conjugate) vaccine (adsorbed)	Sanofi Pasteur MSD SNC	EMEA-000394-PIP01-08-M01
Taliglucerase alfa	Pfizer Ltd.	EMEA-000648-PIP01-09

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

(Scheduled by 30 June 2014)

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
Docetaxel	Taxotere	AVENTIS PHARMA SA	EMEA-000029-PIP01-07	Yes
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	Undetermined
Glucose (monohydrate)		Cblaya & Mhuguet S.L.	EMEA-000221-PIP01-08	Undetermined
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	Undetermined
Bromocriptine mesilate	Cycloset	VeroScience EU Ltd	EMEA-000487-PIP01-08	Yes
Rabeprazole (sodium)	Pariet and associated names	Eisai Limited	EMEA-000055-PIP01-07-M05	Undetermined

Substance(s)	Invented name	Company	Latest PIP number	Obligation to complete PIP
Levonorgestrel		Bayer Schering Pharma AG	EMEA-000606-PIP01-09	No (off-patent authorised product, intending to apply in the future for PUMA)
2,6-Bis-{(1-napthalenyl-3,6-disulfonic acid)-oxyacetamido}-2,6-bis-2,6-bis-2,6-bis-(2,6-diamino-hexanoylamino)-2,6-diamino-hexanoic acid (diphenylmethyl)-amide, polysodium salt	Vivagel	Starpharma Pty Ltd	EMEA-001354-PIP01-12	Yes
Dienogest		Bayer Schering Pharma AG	EMEA-000147-PIP01-07	Yes
Grass Pollen Preparation		Allergopharma J. Ganzer KG	EMEA-000337-PIP01-08	Yes
Methoxyflurane	Penthrox	ORION Clinical Services	EMEA-000334-PIP01-08-M02	Yes
Maribavir		ViroPharma SPRL	EMEA-000353-PIP01-08	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

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

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

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

Company name	Total	2009	2010	2011	2012	2013	2014
Mitsubishi Pharma Europe Ltd	**1**					1	
N.V. Organon	**8**			2	2	2	2
Novartis Europharm Limited	**41**	1	5	7	8	10	10
Novartis Vaccines and Diagnostics S.r.l.	**5**			1		2	2
Novo Nordisk A/S	**12**		1	1	1	4	5
Nycomed Danmark ApS	**2**					1	1
Omrix Biopharmaceuticals SA	**2**						2
Otsuka Pharmaceutical Europe Ltd.	**3**				1	1	1
Pfizer Limited	**13**		1	1	3	4	4
Pharmaxis Pharmaceuticals Limited	**1**						1
Pharming Group N.V.	**4**			1	1	1	1
Rapidscan Pharma Solutions (RPS) EU Ltd	**4**			1	1	1	1
Roche Products Ltd	**2**					1	1
Roche Registration Ltd	**16**	1	1	3	3	3	5
SP Europe	**3**				1	1	1
Sanofi Pasteur SA	**3**			2			1
Sanofi Pharma Bristol-Myers Squibb SNC	**1**		1				
Shire Pharmaceutical Contracts Ltd	**4**				1	1	2
Shire Pharmaceuticals Ireland Limited	**4**			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
Teva Pharma B.V.	**1**						1
The Medicines Company	**3**				1	1	1
Tibotec BVBA	**3**				1	1	1
UCB Pharma SA	**3**					1	2
Valeant Pharmaceuticals Ltd.	**3**				1	1	1
Vertex Pharmaceuticals Incorporated	**2**					1	1

Company name	Total	2009	2010	2011	2012	2013	2014
ViiV Healthcare UK Ltd	**2**					1	1
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
Number of annual reports submitted	**476**	**10**	**35**	**65**	**86**	**124**	**156**

Annex 11 - List of due annual reports on deferred measures that have not been submitted in 2014

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	13/02/2014