EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 September 2014
EMA/24516/2014 Corr.3
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 and on the companies that have failed to comply with any of the obligations in this Regulation

Year 2013

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1. Synopsis

This Annual Report to the European Commission covers the 7th year of the Paediatric Regulation. It includes an analysis on Annual reports on deferrals, completion of PIPs and registration of deadlines to put a medicinal product on the market; these analyses started in the 2012 report, and are continued in 2013.

The data from 2013 further confirm that the development of a medicinal product is now planned better and earlier, with the use in children in mind:

- The number of scientific advices at the EMA level including paediatric questions has increased steadily from 2006 to 2013 and PDCO members are now always involved in such procedures;
- The number of applications and decisions on PIPs (including modifications) and waivers has increased in 2013.

With regard to research positive trends are continuing:

- More neonates (full term and premature) are enrolled in clinical trials in 2013.
- Enpr-EMA: more networks are enrolled bringing the number to 41 at the end of 2013.
- More inventories of paediatric needs have been finalised in 2013. This provides information for applicants on identification of unmet needs by the Paediatric Committee.
- The number of fully completed PIPs is increasing, with a very low number of negative outcomes in compliance check. This is very encouraging and indicates that more paediatric medicines will go through the regulatory process and be available for patients.

  Annual reports on deferrals indicate that a majority of paediatric plans progress without major difficulties; however, a significant percentage of annual reports do identify problems, often recruitment difficulties.
- More information on paediatric use of medicines is provided to Health Care Professionals and patients, as evidenced by the increase in paediatric information in Summaries of Product Characteristics.
- Submissions under Articles 45 and 46 continue 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.
- The Agency continues to maintain the "Register of deadlines to put a medicinal product on the market" (article 33 of the Paediatric Regulation).

More companies are receiving the reward for completion of a PIP:

- There has been an increase in Compliance procedures - in 2013 there were 16 positive final compliance checks compared to 4 in 2012 and 9 in 2011, which means that some paediatric plans are completed and that the relevant information on the use of the medicinal products in children will be reflected in the SmPC and in the Patient leaflet; this is necessary to claim the SPC (Supplementary Protection Certificate) extension.

Issues identified last year that are still present in the 2013 report include:

- As in the previous year, there are fewer late PIP/Waiver submissions but the median time of the delay remains similar.

- A few MAHs do not submit Annual Reports within the required timelines. The tracking of this activity is now fully operational and is be monitored by the Agency;
- out of 90 PIPs scheduled for completion by 30/6/2013 28 were not completed and there appears to be no valid justification or a modification to change the timelines.

Other major projects which have been completed, or have significantly progressed in 2013, include:

- Publication of more scientific guidelines with information to assist applicants with paediatric development.
- The extrapolation working group continues to meet regularly to provide advice on paediatric investigation plans with extrapolation issues. The group has also advanced on the drafting of a reflection paper that will be published in the near future.
- The framework for collecting data, including the identification of performance indicators, for the 10 year report to the EC (Art. 50.3 of the Paediatric Regulation) has been put in place and systematic collection of data has started in 2014.
- Opinions have been streamlined and new simplified templates on the scientific document (parts B-E) and key elements form are now available along with a new simplified template for Annex I of the opinion.
- The template for the Summary of the PDCO evaluation of the proposed PIP/Waiver has been finalised and these will be published in 2014.

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 (hereinafter 'the 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 the year 2013 and follows a similar structure as the previous reports prepared by the Agency for the European Commission. Previous reports covered the period from the entry into force of the Paediatric Regulation, i.e. 26 January 2007 to 31 December 2009, from 1 January 2010 to 31 December 2010, from 1 January 2011 to 31 December 2011 and from 1 January 2012 to 31 December 2012. The data are presented as a follow-up of the European Medicines Agency's five-year report to the European Commission, 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 European Commission work for which has started.

2.2. Major changes in the report and results

Some activities monitored for the first time in 2012 are continued in the 2013 report:

- the obligation of reporting annually on deferred studies, with evidence that some of these reports are not submitted, but for those submitted that the majority of developments are taking place uneventfully;
- an overview of the completion of paediatric plans, showing mixed results;
- the register to record deadlines of the placing on the market.

Generally the report follows the 2012 report format, with the same data being collected as in the previous year. The response rate from Member States improved compared to 2012, helped by increased awareness in relation to the preparation of the 10 year report to the European Commission and involvement of CMDh.

Data from 2013 confirm that the development of medicinal products is now planned from the start with children in mind. Paediatric development questions continue to be a significant part of scientific advice procedures with involvement of PDCO in all cases and very successful collaboration. In 2013 there have been more positive compliance checks which would potentially lead to more medicinal products authorised with paediatric indications or paediatric information in the SmPC.

Major projects which have significantly progressed in 2013 include: the continuation of the work of the extrapolation working group and the publication of the final version of the concept paper on extrapolation, and the establishment of the framework for the collection of the data and information for the 10-year report to the European Commission.

2.3. Data collection and methodology

In October 2013, the Agency sent a letter to all Member States requiring their contributions for the preparation of this report. The data spread sheet used for 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 2013 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 which qualifies for an SPC.

The Agency received contributions from 23 out of 28 (82%) Member States, and from 21 out of 28 (75%) National Patent Offices (NPOs) (see Annex 2). Participation was higher compared to 2012 when contribution was 18 out of 27 (67%) Member States and 16 out of 27 (60%) National Patent Offices.

From this year, most of the data for EMA procedures are reported using automated analyses provided from the EMA's databases. Due to the different distribution of procedures according to the date of submission or completion which is caused by the reporting system, and other differences in criteria, some figures for the previous years (up to 2012) may be slightly different from those in the previous annual reports. These differences are minor and do not affect the conclusions.

3. Companies and products that have benefited from any of 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 Regulation, the Agency provides free scientific advice for any request containing questions on paediatric development. The advice is provided by the Scientific Advice Working Party (SAWP) and is adopted by the CHMP. For the requests on paediatric development, members of the PDCO are routinely involved in the provision of scientific advice through the Scientific Advice procedures (see Table 1).

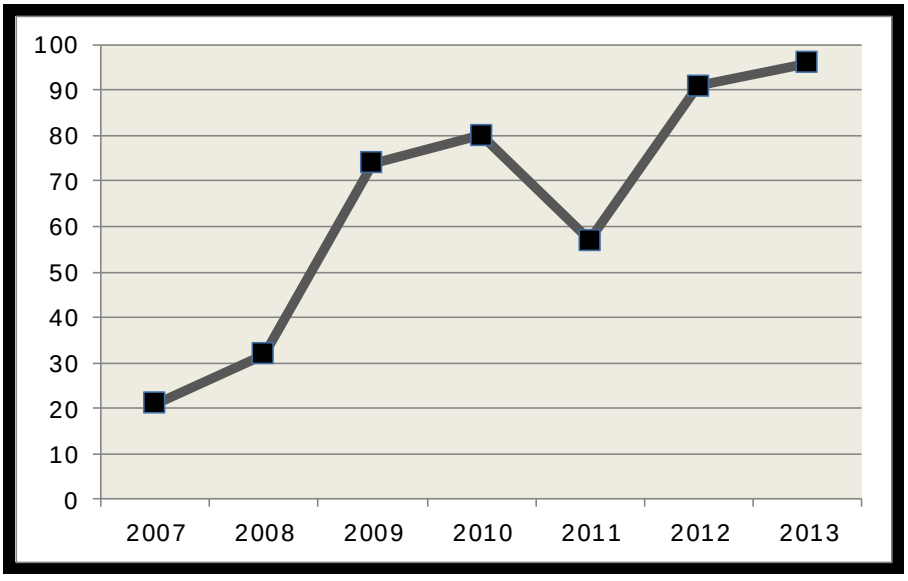
The number of scientific advice procedures including paediatric questions has increased steadily from the start of the implementation of the regulation. In 2013, 473 procedures for advice were submitted, of which 96 (20.1%) included paediatric development questions. This represents an increase of 12.6% from 2012. Almost all scientific advice procedures in paediatric development (96.8%) 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
Total number of advice (Scientific Advice and Protocol Assistance)*	388	400	433	420	473
N. of SA/PA procedures including questions on paediatric development*	74	80	57	91	96
Paediatric-only or mixed advice that involved a PDCO member(s) as expert(s)**	68	80	67	94	93

Source: EMA databases. * Year of advice letter. ** Year of start of procedure. ND = Not documented

Figure 1 - Scientific Advice and Protocol Assistance in paediatrics
Total n. of SA/PA procedures with paediatric questions



3.1.2. Advice from the National Competent Authorities

Some National Competent Authorities provide scientific advice on paediatric development. In 2013, 21 Member States reported information on scientific advices, compared to 14 in 2012 (Table 2).

Table 2 - Number of national scientific advice provided by Member States in 2013 and 2012

	2013			2012		
Member state	paed-only	Mixed	**Total**	paed-only	Mixed	**total**
Austria	0	0	**0**	0	0	**0**
Belgium				2	3	**5**
Bulgaria	0	0	**0**			
Croatia						
Cyprus	0	0	**0**	0	0	**0**
Czech Republic	0	0	**0**	0	0	**0**
Denmark	0	1	**1**	2	1	**3**
Estonia	0	0	**0**	0	0	**0**
Finland	0	1	**1**			
France	2	2	**4**			
Germany	2	9	**11**	2	16	**18**
Hungary	0	0	**0**			
Ireland						
Italy	1	1	**2**	0	2	**2**
Latvia				0	0	**0**
Lithuania						
Luxembourg	0	0	**0**			
Malta	0	0	**0**	0	0	**0**
Poland	0	0	**0**			
Portugal	0	0	**0**			
Romania	0	0	**0**			
Slovakia	0	0	**0**			
Slovenia	0	0	**0**	0	0	**0**
Spain	0	1	**1**	0	5	**5**
Sweden	0	3	**3**	0	0	
The Netherlands						
United Kingdom	2	10	**12**	3	5	**8**
Total of advices	**7**	**28**	**35**	**9**	**32**	**41**

Compared to 2012, the total number of paediatric advice procedures given nationally has decreased by 14% in 2013.

3.2. Paediatric Investigation Plans – Waivers

The table below (Table 3) is a compilation per year since the implementation of the Paediatric Regulation.

The numbers are based on EMA Decisions not Opinions, as applications with an adopted Opinion may still be withdrawn before the EMA Decision.

Table 3 - Decisions on Paediatric Investigations plans and Waivers

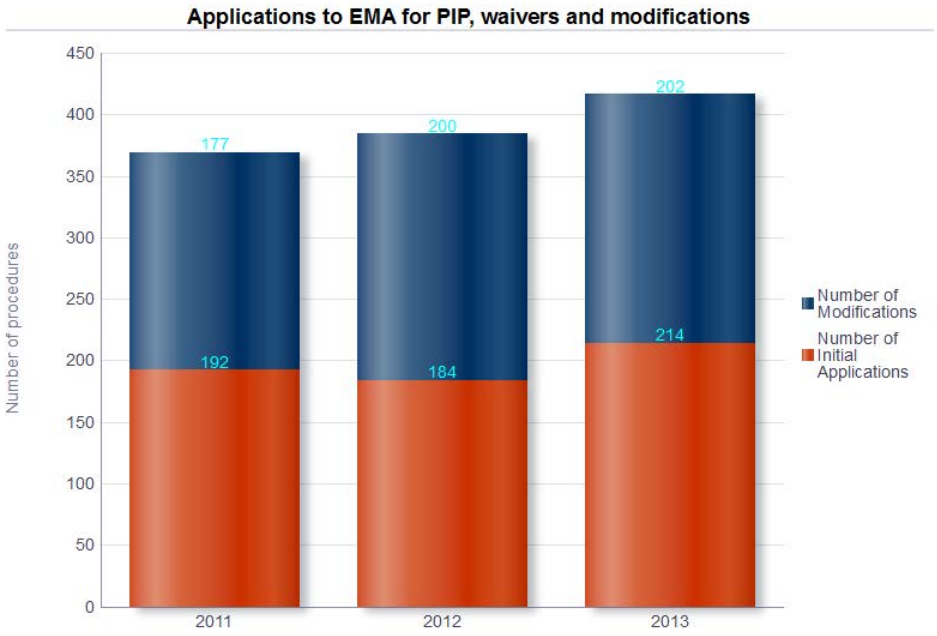
	2007	2008	2009	2010	2011	2012	2013
Number of positive decisions on first PIP applications	0	76	122	*185	116	95	92
Number of positive decisions on product-specific ("full") waivers	3	42	71	54	46	46	54
Number of positive decisions on a modification of an agreed PIP	0	5	48	95	149	169	175
Negative decisions	0	2	13	8	3	3	4
Grand total of Decisions	**3**	**125**	**254**	***342**	**314**	**313**	**325**

*Data for 2010 are influenced by approximately 100 exceptional applications received for products for immunotherapy of allergic oculorhinitis, due to changes in their classification in the German law.

3.2.1. Applications

The total number of applications for first PIPs, waivers, and PIP modifications in 2013 (416) is increased compared to 2012 (384) and 2011 (369), an 8% increase vs 2012 (Figure 2). The relatively low increase in number of first 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 has occurred.

Figure 2 - Applications for PIPs, waivers and PIPmodifications



3.2.2. Publication of Opinions / Decisions

The Decisions issued by the Agency, which include the PDCO Opinion, are published in a summarised form and can be found on the EMA website, in a specific webpage.

3.2.3. Class Waivers

The latest EMA decision on class waivers, dated 19 December 2011, can be found on the EMA website: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/12/WC500119981.pdf.

No additional EMA decision on class waivers has been published in 2012. A revision of the list is under consideration.

Table 4 - Requests of confirmation of applicability of a class waiver - 2013

	confirmed	Not confirmed	**Total**
All Requests	61	6	**67**
Of which in the therapeutic area of Oncology:	*14*	*1*	***15***
Potential use in children identified by PDCO in another condition	25	N/A	**25 (37%)**

In 2013, 67 requests for class waivers applicability were assessed and their outcomes were given during monthly PDCO meetings (Table 4):

- 90% 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 children.
- 10% of the requests were given a negative outcome (Type 2 Diabetes, COPD, lung carcinoma, primary gout, Alzheimer, myelofibrosis): for each of these requests, the proposed indication did not fall under the scope of the Agency 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 requested to submit a product specific waiver if they wished to do so.
- 22% of the requests involved products used in oncology.
- The PDCO recommended that for 37% of the requests, the products may be developed for another condition for which a therapeutic need in children has been identified.

3.2.4. Modifications of agreed PIPs

In 2013 there were 179 decisions on Modifications of agreed PIPs compared to 166 in 2012.

The number of requests for modification of agreed PIPs continues to increase moderately, but this is expected as the number of current “active” (non-completed, ongoing) 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.

The number and type of changes in modification procedures is very variable, since a full modification procedure is needed even to change a single key element, such as a single timeline for completion of a study.

However, a recent analysis shows that in fact, relative to the number of existing agreed PIPs, the number of requests for modifications is actually decreasing, with a lower ratio of requests for modification per total agreed PIPs every year (ratio shown in Figure 3; data from Table 5).

Figure 3 - Ratio of modification requests per total of existing agreed PIPs

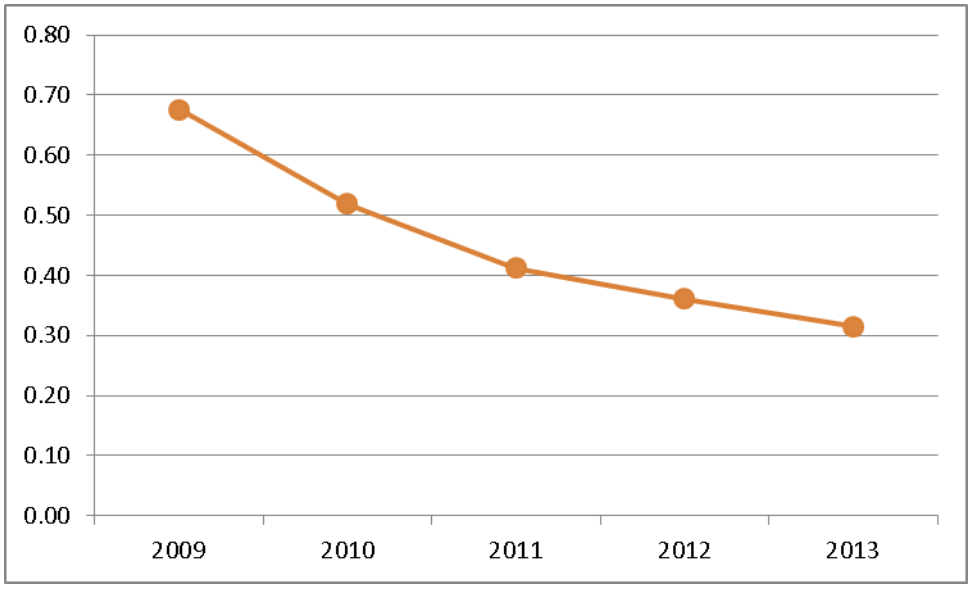


Table 5 - PIPs agreed and modifications requested

Ratio of PIP modification requests to cumulative n. of first PIPs						
	2008	**2009**	**2010**	**2011**	**2012**	**2013**
First PIPs agreed per year	76	122	185	116	95	92
Cumulative total of first PIPs agreed	76	198	383	499	594	686
Cumulative positive final CC	5	13	22	31	35	51
"Ongoing" PIPs	71	185	361	468	559	635
Modifications requested	5	48	96	149	169	176
ratio (modifications/cumulative total of ongoing PIPs in the preceding year)		**0.68**	**0.52**	**0.41**	**0.36**	**0.31**

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, is being successful in reducing the number of modification procedures per PIP.

3.3. Compliance statement included in a marketing authorisation

A compliance check is done at EMA or, potentially, by National Competent Authorities (NCA), 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 Competent Authority (European Commission, EMA or NCA in different situations).

No NCA reported having checked compliance of a PIP. This may be because the NCAs have delegated it to the EMA PDCO, or because Marketing Authorisation Holders have obtained a PDCO Opinion in advance of the regulatory procedure at he NCA.

In 2013, the PDCO adopted the highest number of positive opinions on compliance check so far (16, see Table 6).

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

	2008	2009	2010	2011	2012	2013	**Total**
PDCO negative letters on interim compliance		2		3	1	1	**7**
PDCO positive letters on interim compliance	4	18	39	47	40	40	**188**
PDCO negative opinions on full/final compliance check		1				1	**2**
PDCO positive opinions on full/final compliance check	5	8	9	9	4	16	**51**
Totals	**9**	**29**	**48**	**59**	**45**	**58**	**248**

3.3.1. Compliance statement for centrally-authorised medicinal products

In 2013, the EMA issued three compliance statements, related to regulatory submissions for authorised products in accordance with Article 8 (Table 7).

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

Companies	Products: invented name	international non-proprietary name (INN)	Date of MA	Type of procedure (referring to outcome)
Novartis Europharm Ltd	Glivec	Imatinib	27/06/2013	Type II variation
Baxter AG	Pandemic Influenza Vaccine H5N1 Baxter	pandemic influenza vaccine (H5N1) (whole virion, inactivated, prepared in cell culture)	25/11/2013	Type II variation
Janssen-Cilag International N.V.	Prezista	Darunavir	19/09/2013	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 2013 compared to 2012 (27 products in 2013 compared to 8 products in 2012). There was no reward granted following use of Article 29 paediatric referral in 2013.

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
Merck Sharp & Dohme BV	Ezetimibe	Ezetrol
Boeringher Ingelheim International GmBH	Tiotropium bromide monohydrate	Spiriva
MEDA Pharma	Azelastin/fluticasone	Synaze, Azeflu, Dymista, Xatalin, Bileni, Sycara
Ferring	Misoprostol	Misodel
MEDA Pharma	Clindamycin/tretinoin	Zanea

3.4. Extension of the Supplementary Protection Certificate (SPC) / Market Exclusivity / Data protection (PUMA)

3.4.1. Extensions of the SPC

Extensions of the Supplementary Protection Certificate (SPC) are granted by National Patent Offices.

In 2013, a similar number of active substances benefited from the 6-month extension compared to 2012 (9). Seven (7) products are mentioned in both the 2012 list and 2013 list 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 supplementary protection certificate (SPC) granted by the National Patent Office in 2013

Marketing authorisation holder	Invented name(s)	International non-proprietary name	SPC extension granted in 2013 in	SPC extension pending in
Bristol-Myers Squibb Pharma EEIG	Orencia	abatacept		Romania
Otsuka Pharmaceutical Europe Ltd	Abilify	aripiprazole		France Germany Romania United Kingdom
Merck Sharp and Dohme	Cancidas	caspofungin	Bulgaria Czech Republic Slovakia	
Genzyme Europe BV	Cholestagel	colesevelam		United Kingdom
Forest Laboratories UK	Colobreathe	colistimethate*		Germany
Pfizer Limited	Enbrel	etanercept	Finland France Germany Greece Italy United Kingdom	Austria Bulgaria

Marketing authorisation holder	Invented name(s)	International non-proprietary name	SPC extension granted in 2013 in	SPC extension pending in
Novartis Europharm Limited	Glivec	Imatinib*	Sweden	Czech Republic Finland Greece Italy Ireland
Janssen Biologics B.V.	Remicade	infliximab	Austria Germany Greece United Kingdom	
Sanofi-Aventis Deutschland GmbH	Lantus Optisulin	insulin – glargine	Finland France Germany Greece United Kingdom	
Merck Sharp & Dohme	Maxalt	rizatriptan	Austria	Czech Republic
Boehringer Ingelheim	Spiriva	tiotropium bromide	Austria Bulgaria Czech Republic Denmark Ireland Germany Greece France Slovakia Spain Sweden The Netherlands United Kingdom	Finland Italy
Otsuka Pharmaceutical Europe Ltd.	Samsca	tolvaptan	Denmark France Germany Spain Sweden The Netherlands United Kingdom Romania	

3.4.2. Orphan Market Exclusivity extension

So far, no orphan medicinal product has benefited from this reward since the entry into force of the regulation.

However, it should be noted that a medicinal product may be removed from the list of orphan-designated products, for example to benefit from the 6-month extension of the SPC as paediatric

reward, instead of the 2-year extension of the market exclusivity foreseen for orphan products. Among the products with an SPC extension pending or granted in 2013 and included in this report, two (imatinib and colistimethate) have non-active orphan designations.

3.4.3. Paediatric Use Marketing Authorisation

There were no PUMA marketing authorisations in 2013.

3.5. Marketing authorisation granted or varied with mention of waiver or deferral in the Summary of Product Characteristics

In 2013, there were more centrally authorised medicinal products with added mention on deferral or waiver in the Summary of Product Characteristics (SmPC) than in 2012 (52 for new MA in 2013 compared to 43 in 2012, a 21% increase) (see Table 10).

Further information on these medicinal products can be found in the European Public Assessment Reports with the product information available on the Agency website.

Non-centralised products whose product information has been updated to reflect waivers and deferrals are listed in Table 11. Further information on these medicinal products can be found in 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)	Date of EU CD
AMYViD	florbetapir (18f)	Eli Lilly Nederland B.V.	x		MA	14/01/2013
AUBAGIO	teriflunomide	Sanofi-Aventis Groupe	x	x	MA	26/08/2013
Adasuve	loxapine	Alexza UK Ltd.	x	x	MA	20/02/2013
BOSULIF	bosutinib	Pfizer Limited		x	MA	27/03/2013
Capecitabine SUN	capecitabine	Sun Pharmaceutical Industries Europe B.V.	x		MA	21/06/2013
Cholib	fenofibrate / simvastatine	Abbott Healthcare Products Ltd.	x		MA	26/08/2013
Erivedge	vismodegib	Roche Registration Ltd	x		MA	12/07/2013
HyQvia	human normal immunoglobulin	Baxter Innovations GmbH		x	MA	16/05/2013
IMVANEX	modified vaccinia ankara virus	Bavarian Nordic A/S	x	x	MA	31/07/2013
Iclusig	ponatinib	ARIAD Pharma Ltd	x		MA	01/07/2013
Imnovid	pomalidomide	CELGENE EUROPE LIMITED	x		MA	05/08/2013
Inflectra	infliximab	HOSPIRA UK LIMITED	x		MA	10/09/2013
JETREA	ocriplasmin	ThromboGenic NV	x		MA	13/03/2013
Krystexxa	pegloticase	Savient Pharma Ireland Ltd.		x	MA	08/01/2013
Lemtrada	alemtuzumab	Genzyme Therapeutics Ltd	x	x	MA	12/09/2013
Lojuxta	lomitapide	Aegerion Pharmaceuticals		x	MA	31/07/2013
Lonquex	lipegfilgrastim	Teva Pharma B.V		x	MA	25/07/2013
Lyxumia	lixisenatide	Sanofi-Aventis		x	MA	01/02/2013
MACI	autologous cultured chondrocytes	Genzyme Europe BV		x	MA	27/06/2013
Nuedexta	dextromethorphan / quinidine	Jenson Pharmaceutical Services Ltd	x		MA	24/06/2013
PROVENGE	autologous peripheral blood mononuclear cells activated with pap-gm-csf (sipuleucel-t)	Dendreon UK LTD	x		MA	06/09/2013
Remsima	infliximab	Celltrion Healthcare Hungary Kft.	x		MA	26/08/2013

Invented name	International non-proprietary name	Marketing authorisation holder	Waiver stat. added	Deferral stat. added	Procedure (MA / variation)	Date of EU CD
Ryzodeg	insulin degludec and insulin aspart (idegasp)	Novo Nordisk A/S	x	x	MA	21/01/2013
Selincro	nalmefene	H. Lundbeck A/S	x		MA	25/02/2013
Spedra	avanafil	VIVUS BV	x		MA	21/06/2013
Stivarga	regorafenib	Bayer Pharma AG	x		MA	26/08/2013
Stribild	elvitegravir / cobicistat / emtricitabine / tenofovir disoproxil	Gilead Sciences International Ltd		x	MA	24/05/2013
Tafinlar	dabrafenib	GlaxoSmithKline Trading Services		x	MA	26/08/2013
Tresiba	insulin degludec	Novo Nordisk A/S	x		MA	21/01/2013
Voncento	human coagulation factor viii / human von willebrand factor	CSL Behring GmbH		x	MA	12/08/2013
Xtandi	enzalutamide	Astellas Pharma Europe B.V.	x		MA	21/06/2013
Zaltrap	aflibercept	Sanofi-Aventis Groupe	x		MA	01/02/2013
ABILIFY MAINTENA	aripiprazole	Otsuka Pharmaceutical Europe Ltd	x		MA	15/11/2013
EVARREST	human fibrinogen / human thrombin	Omrix Biopharmaceuticals N. V.		x	MA	25/09/2013
Giotrif	afatinib	Boehringer Ingelheim International GmbH	x		MA	25/09/2013
Imatinib medac	imatinib	Medac	x		MA	25/09/2013
Incresync	alogliptin / pioglitazone	Takeda Pharma A/S	x		MA	19/09/2013
Invokana	canagliflozin	Janssen-Cilag International N.V.		x	MA	15/11/2013
Kadcyla	trastuzumab emtansine	Roche Registration Ltd	x		MA	15/11/2013
Lidocaine/Prilocaine Plethora	lidocain / prilocaine	Plethora Solutions Ltd.	x		MA	15/11/2013
Relvar Ellipta	fluticasone furoate / vilanterol	Glaxo Group Ltd	x	x	MA	13/11/2013
Tybost	cobicistat	Novartis Europharm Ltd		x	MA	19/09/2013
Ultibro Breezhaler	indacaterol / glycopyrronium bromide	Sandoz Pharmaceuticals GmbH	x		MA	19/09/2013

Invented name	International non-proprietary name	Marketing authorisation holder	Waiver stat. added	Deferral stat. added	Procedure (MA / variation)	Date of EU CD
Vipdomet	alogliptin / metformin	Takeda Pharma A/S	x		MA	19/09/2013
Vitekta	elvitegravir	Gilead Sciences International Ltd		x	MA	13/11/2013
Vipidia	alogliptin	Takeda Pharma A/S		x	MA	19/09/2013
Xofigo	radium-223	Bayer Pharma AG	x		MA	13/11/2013
Xoterna Breezhaler	indacaterol / glycopyrronium bromide	Novartis Europharm Ltd	x		MA	19/09/2013
Brintellix	vortioxetine	H. Lundbeck A/S	x	x	MA	18/12/2013
Ilaris	canakinumab	Novartis Europharm Ltd	x		VA	18/02/2013
Lucentis	ranibizumab	Novartis Europharm Ltd	x		VA	04/07/2013
Revlimid	lenalidomide	Celgene Europe Ltd	x		VA	13/06/2013
Tysabri	natalizumab	Biogen Idec Ltd		x	VA	09/07/2013
Stelara	ustekinumab	Janssen-Gilag International N.V.		x	VA	19/09/2013
Thymanax	agomelatine	Servier (Ireland) Industries Ltd.		x	VA	13/11/2013
Valdoxan	agomelatine	Les Laboratoires Servier		x	VA	13/11/2013
Xeloda	capecitabine	Roche Registration Ltd	x		VA	29/11/2013
Yervoy	ipilimumab	Bristol-Myers Squibb Pharma EEIG		x	VA	31/10/2013

For medicinal products authorised through national/decentralised/mutual recognition procedure, statement on deferral or waiver was added in 21 procedures (9 initial MAs and 12 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 (Mark. Author. Or Variat.)	Date of MA/outcome
Austria	Icomb	ramipril, amlodipine	Midas Pharma GmbH	x		MA	10/06/2013

Member State	Invented name	International non-proprietary name	Marketing authorisation holder	Waiver stat. added	Deferral stat. added	Procedure (Mark. Author. Or Variat.)	Date of MA/outcome
Cyprus	EZETROL	ezetimibe	Merck Sharp & Dohme Bv	x		VA	30/07/2013
Cyprus	ATACAND	candesartan cilexetil	Astrazeneca Ab	x		VA	22/11/2013
Cyprus	SPIRIVA INHALATION CAPS	tiotropium bromide	Boehringer Ingelheim International Gmbh	x		VA	21/05/2013
Cyprus	Spiriva	tiotropium bromide	Boehringer Ingelheim International Gmbh	x		VA	16/05/2013
Cyprus	TOBREX	tobramycin	A Potamitis Medicare Ltd	x		VA	14/11/2013
Denmark	Spiriva Respimat	tiotropium	Boehringer Ingelheim	x		VA	16/05/2013
Estonia	Spiriva Respimat	tiotropium	Boehringer Ingelheim	x	x	VA	21/05/2013
Estonia	Spiriva	tiotropium	Boehringer Ingelheim	x	x	VA	21/05/2013
Estonia	Eziclen	mineral salts in combination)	Ipsen Pharma		x	MA	Not provided
Estonia	Striverdi Respimat	olodaterol	Boehringer Ingelheim	x		MA	Not provided
Estonia	Mysodelle	misoprostol	Ferring Lääkkeet Oy	x		MA	Not provided
Finland	Striverdi Respimat 2.5mikrog, inhalaationeste, liuos	olodateroli hydrochloridum	Boehringer Ingelheim International GmbH	x		MA	08/11/2013
Finland	Axiron 30mg/1.5ml liuos iholle	testosteronum	Eli Lilly Finland Oy Ab	x		MA	18/11/2013

Member State	Invented name	International non-proprietary name	Marketing authorisation holder	Waiver stat. added	Deferral stat. added	Procedure (Mark. Author. Or Variat.)	Date of MA/outcome
France	FLUARIXTETRA	influenza virus fragmented, inactived, strain A/California/7/2009 (H1N1)pdm09 - analogue strain used NIB-74xp derived from A/Christchurch/16/2010	GLAXOSMITHKLINE		x	MA	19/06/2013
Slovenia	SPIRIVA	tiotropium	Boehringer Ingelheim International GmbH	x		VA	21/05/2013
Slovenia	SPIRIVA RESPIMAT	tiotropium	Boehringer Ingelheim International GmbH	x		VA	16/05/2013
Sweden	Misodel	misoprostol	Ferring Läkemedel AB	x		MA	21/11/2013
Sweden	Spiriva Respimat	tiotropium	Boehringer Ingelheim International GmbH	x		Line extension	30/07/2013
Sweden	Zevtera	ceftobiprole medocaril	Basilea Medical Ltd		x	MA	09/12/2013

3.6. Price / reimbursement benefits

The Agency has received information on price or reimbursement benefits for paediatric medicines in the Member States, which is listed under National Initiatives.

3.7. Research incentives

3.7.1. EU Framework Programme

Funding of studies into off-patent medicinal products has been made available since 2007 (Article 40). The funding was provided through the EU Framework Programmes for Research and Technological Development; it covers the development of off-patent medicinal products with a view to the submission of a PUMA.

In agreement with the European Commission, the PDCO maintains a priority list of off-patent products for which studies are needed.

An updated priority list (http://bit.ly/xMS4LE) was published in 2013 as a base for potential future funding within the Horizon2020 programme. The Agency collaborates continuously with the Commission's Directorate General for Research of the European Commission, to foster development of off-patent medicinal products for paediatric use.

3.7.2. European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA)

Enpr-EMA[1] is still expanding. Based on the Enpr-EMA self-assessment forms, the paediatric networks are classified in four categories[1].

In 2013:

- a national Swiss paediatric network (SwissPedNet) joined as Category 3;
- a Spanish centre (Hospital Sant Joan de Deu) joined as Category 3;
- RED SAMID (Red de Investigación en Salud Materno-Infantil y del Desarrollo), a Spanish national paediatric network specialised on Maternal and Child Health and Development was upgraded to Category 2.

At the end of the year, Enpr-EMA had 41 registered networks:

- 18 networks (44%) were recognised as Enpr-EMA Category 1 (full Enpr-EMA members);
- 3 networks (7%) were recognised as Category 2;
- 16 networks (39%) were recognised as Category 3.
- 4 networks (10%) were recognised as Category 4

[1] 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.
[2] 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.

There is a future need for the creation and establishment of an European paediatric clinical trial network specialised in nephrology as well as a network of European Paediatric Pharmacists.

A searchable network database providing easy access to data about each individual registered network and their expertise in paediatric research was created in 2013. 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. This database is now published on the EMA website (Enpr-EMA Network Database).

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	
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		

Type of network	Category 1	Category 2	Category 3	Category 4
Neonatology	GNN		EuroNeoNet Neo-circulation INN	
European Paediatric Pharmacists				
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

Other Enpr-EMA activities throughout 2013 included:

- The election of a new Chair of the Enpr-EMA coordinating group, Dr Mark Turner, Associate Director for International Affairs, NIHR-MCRN, further to completion of the previous Chair's term of office.
- The establishment of 10 Enpr-EMA Working Groups (WG), including network and industry representatives, tasked with addressing the most important needs identified during the Enpr-EMA June 2013 workshop:
  - WG 1: Approaches to priority setting
  - WG 2: Broad engagement in priority setting
  - WG 3: How to establish communication between Enpr-EMA, networks and industry (merged with WG 5)
  - WG 4: Dialogue and interaction with Ethics Committees
  - WG 5: Sharing good practices within Enpr-EMA and with industry partners (merged with WG 3)
  - WG 6: A framework for networks to interact with industry and regulators when implementation/conduct of clinical trials agreed in PIPs is no longer possible:
  - WG 7: Neonatology
  - WG 8: Joint Enpr-EMA/ENCePP WG on paediatric Pharmacovigilance
  - WG 9: Strategies for funding and maintaining a paediatric research network
  - WG 10: FP7 Projects
- The Enpr-EMA Coordinating Group submitted a corporate Enpr-EMA commentary to the European Commission during the public consultation on the Commission guideline on the format and content of applications for paediatric investigation plans. It was proposed to add a recommendation to consult Enpr-EMA members, i.e. networks, in the development of a PIP.
- Enpr-EMA members participated at a meeting with members of the European Parliament to discuss paediatric research related to the Clinical Trial Directive.

- An invitation was sent to EFPIA (European Federation of Pharmaceutical Industries and Associations) requesting a discussion meeting to better identify industry needs, and to explore opportunities for collaboration.
- Collaboration with the EMA Healthcare Professional Working Party (HCPWP) was strengthened with the nomination of an HCPWP observer member of the Enpr-EMA Coordinating Group.
- The task force and core groups of the 3 emerging paediatric networks: i.e. Cardiology: Task Force of the AEPC (Association for European Paediatric Cardiology); Gastroenterology: PEDDCReN (Paediatric European Digestive Diseases Clinical Research Network); Endocrinology/diabetes: EUCADET (European Children and Adolescent Diabetes and Endocrine Trial) were fully established, potential investigators and centres were invited to join these emerging networks and some projects on paediatric studies have already started.
- Preliminary results of a survey, created by the Enpr-EMA secretariat, on collaboration between industry and Enpr-EMA networks for the conduct of paediatric clinical trials was presented at the Enpr-EMA June 2013 workshop; there was an identified need to revise the survey and this work has been taken over by WG3-5: an updated survey on ways to improve communication between industry and networks has been designed by the WG and sent to industry/networks at a larger scale; analysis of the updated survey results is awaited in mid-2014.
- At the Enpr-EMA June 2013 Network meeting, a session focused on the provision of practical tips and training on strategies and guidance to involve young people and families in the activities of the Enpr-EMA networks. It is now envisaged the possibility link up existing European Young Person Advisory Groups with established North American ones into a Communicating International Network for worldwide involvement of young people in research.

3.7.3. Inventory of paediatric needs

As announced in the previous Annual report, the inventory of paediatric medicines in cardiovascular area was adopted in April 2013:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000096.jsp&mid=WC0b01ac05800260a1

The draft inventories of paediatric medicines in nephrology and infectious diseases were published for public consultation in 2013 and the draft inventory of paediatric medicines in neurology was adopted by the PDCO and will be published in 2014.

The PDCO is currently working on the inventory of paediatric medicines in ophthalmology and oncology.

3.7.4. National initiatives on paediatric medicines

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

France:

A new legislative framework with the aim to reduce and regulate off-label drug use was implemented in France (Law number 2011-2012, December 29, 2011) together with a related decree for "Temporary Recommendations for Use" (RTUs; Decree number 2012-743, May 9, 2012).

The legislation has provided "a regulatory process for temporarily supervising the prescribing of drugs for indications for which they are not licensed".

This legislation applies for any medicinal product and may have an impact on use of medicines in children for which the off label use is frequent.

At this time, no RTU has yet been granted and it is too early to assess any impact of this new legislation in paediatrics.

Poland

Priority review of paediatric data decided on a case-by-case basis.

Spain

Paediatrics and perinatal medicines are considered priorities by "Istituto de Salud Carlos III" in a decision on 11th June 2013 to fund strategic health actions as part of a state programme for investigation of social objectives.

UK

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 2013, the MCRN has supported a total of 280 industry studies, 61 of which were taken on in 2013. 209 public (academic/health service) studies have been taken on by the Network since 2006, 27 in 2013, with grants awarded under a number of European, UK and other research programmes (further information can be found on the webpage http://www.mcrn.org.uk/ and MCRN-supported studies:

http://public.ukcrn.org.uk/Search/Portfolio.aspx?level1=4).

Of the 27 publicly-sponsored studies taken on in 2013, funding was provided by:

- UK government (NIHR, MRC etc; 13 studies, 48%)
- Charities (6 studies, 22%; for 2 studies this funding was in partnership with companies or a Royal College)
- European Commission FP7 (3, 11%)
- Companies (2, 7%; not including study jointly funded with a charity)
- Professional societies (2 study, 7%)
- US government (NIH; 1 study, 4%).

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 European Commission guidance on the protocol-related information and results-related information concerning paediatric clinical trials to be entered into the EudraCT database, 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, but the official "finalisation of the programming" date has not yet occurred. Therefore, according to the 2012 guidelines pharmaceutical companies are not yet obliged to post results of paediatric trials in EudraCT. Some minor aspects of the system will only go live in July 2014, which is expected to be the

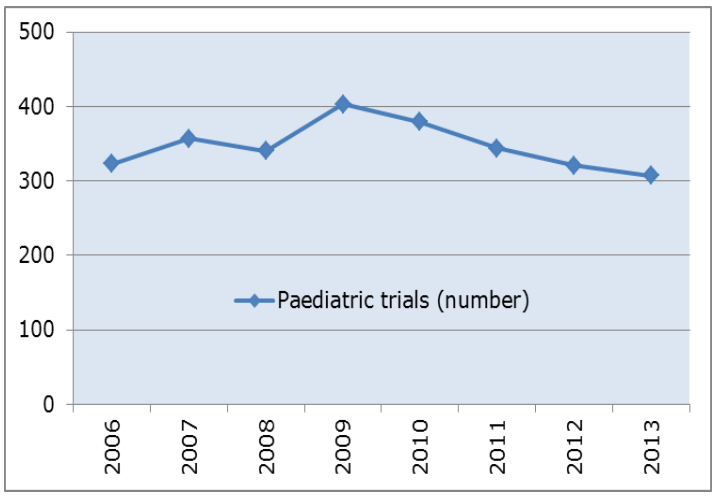
"finalisation of the programming" date. Therefore, no results of paediatric studies have been entered in EudraCT so far.

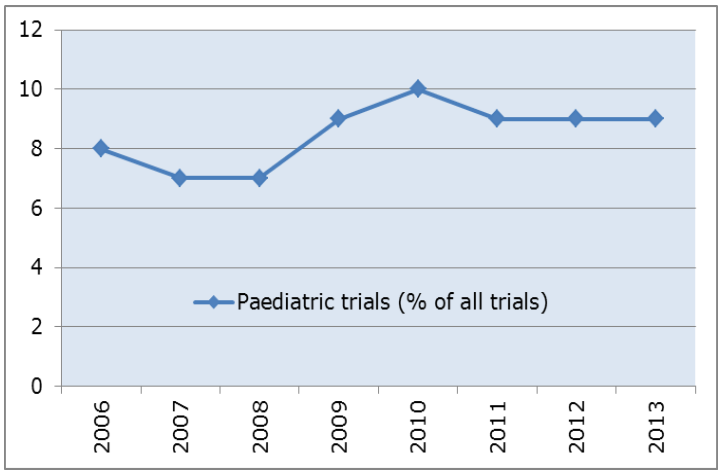
The data presented in the Table 13 and Table 14 have been extracted from the protocol-related information in the EudraCT database. It is important to note that the compilation of most of the data fields in EudraCT is not mandatory, including some that are relevant for paediatric information, and that these data are provided by sponsors, and entered by national competent authorities (for studies conducted in the EU). Small differences between the data reported for previous years in the following tables and in the report to the European Commission for the year 2012 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
Paediatric[1] trials (number)	323	357	340	403	379	344	321	307
Paediatric trials that are part of an agreed PIP* (number)	2	3	7	17	32	73	77	66
Proportion of paediatric trials that are part of an agreed PIP	*0%*	*1%*	*2%*	*4%*	*8%*	*21%*	*24%*	*21%*
Total number of trials (adults and / or children)	4,074	4,818	4,602	4,509	4,072	3,901	3,690	3,306
Proportion of paediatric trials of all trials	*8%*	*7%*	*7%*	*9%*	*10%*	*9%*	*9%*	*9%*
Exclusively[2] paediatric trials (number)	190	186	183	138	221	203	169	189
Exclusively paediatric trials, that are part of an agreed PIP* (number)	1	2	4	13	21	55	55	51
Proportion of exclusively paediatric trials, that are part of an agreed PIP	*1%*	*1%*	*2%*	*9%*	*10%*	*27%*	*33%*	*27%*

* This information could only be provided as of 2011.
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
Source: EudraCT Data (25 February 2014).





Source: EudraCT Data (25 February 2014).

From the data shown above, the proportion of paediatric trials is stable in the last 3 years, but there is a general decrease in numbers of clinical trials included in EudraCT (adults and children). More than 27% of exclusively paediatric trials (and 21% of all studies including children) are now labelled as being part of an agreed PIP.

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

Number of subjects	2006	2007	2008	2009	2010	2011	2012	2013
Preterm newborns	0	0	0	327	82	2,511	1,288	4,444
Newborns	0	98	5	184	169	1,235	1,231	1,459
Infants and toddlers	330	119	20	54,715	2,063	12,353	18,884	15,166
Children	2,378	706	200	3,310	2,436	20,053	25,486	21,559
Adolescents	472	32,458	215	2,307	4,569	18,487	15,799	13,392
Sum of above	**3,180**	**33,381**	**440**	**60,843**	**9,319**	**54,639**	**62,688**	**56,020**

Source: EudraCT Data (25 February 2014). 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, with a peak of more than 60,000 in 2012, without significant increase in number of trials. In 2013 the numbers decreased slightly, with the exception of (preterm and term) newborns, whose numbers still increased. This slight overall decrease in numbers may be

linked to the fact that more recently the PDCO has in many PIPs implemented strategies to extrapolate efficacy from adults to children, reflecting the need to limit the exposure of children in paediatric trials.

However, a limitation of this indicator is that it is 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 specific year may significantly skew the data, as shown by the wide changes in the number of infants and toddlers included in trials between 2008 (20), 2009 (54,715) and 2010 (2063).

3.9. Procedures for Paediatric Use Marketing Authorisation (PUMA)

There were no PUMA marketing authorisations in 2013. Since the beginning of the paediatric regulation only one PUMA has been authorised via the centralised procedure in 2011. A second PUMA application was discussed in 2013 (and obtained a positive opinion in February 2014).

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). Due to the large number of studies concerning mostly nationally approved products, the assessment is undertaken by waves and worksharing between Member States.
- In 2013, 4 additional waves (18 to 21) have been agreed, corresponding to 24 active substances. The assessment of the data has been finalised for 43 active substances.
- 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 (MAH) has to submit to the Competent Authority 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, 91 studies have been submitted to the Agency to fulfil the obligations of Article 46, and 80 procedures of evaluation have concluded in 2013. The CHMP recommended a change in the product information in 19 cases, corresponding to 15 medicinal products. The list of products and the resulting amendments of the Summary of Product Characteristics is presented in Annex 5. A change in a therapeutic indication was recommended in one medicinal product. The proportion of changes in 2013 is higher than in 2012, 26% versus 17.5%.
- For nationally authorised medicinal products, 94 studies were submitted in 2013, and the assessment has been finalised for 22 procedures with published public assessment reports. 50% 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 Summary of Product Characteristics 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 marketing-authorisation holders (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 marketing authorisation holder (MAH) to transfer the MA 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, than 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 submissions 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 an 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 some cases, the delay is such that the PIP was submitted when the paediatric studies had already been started or even completed.

Table 15 - Time lag between completion of adult PK studies and submission of PIPs and waivers (months) applications in 2010, 2011, 2012 and 2013

Delayed applications *(submissions 6 months or more later than deadline)*	2010	2011	2012	2013
Number of delayed PIP applications	65 (*74%*)	44 (*59%*)	34 (*39%*)	18 (*20%*)
All PIP applications	*88*	*74*	*87*	*91*
Time lag (months) median (range)	 22	 35 (9-159)	 35 (9-241)	 28 (9-66)
Number of delayed applications for full waiver	26 (*59%*)	13 (*42%*)	11(*23.5%*)	6 (*11%*)
All applications for full waiver	*44*	*31*	*47*	*56*
Time lag (months) median (range)	 18	 35 (9-137)	 61 (19-179)	 33 (14-60)

Source: EMA Paediatric database.

In 2013 fewer applications for PIPs and waivers were submitted late, and this finding is welcome. The median delay remains similar as in the previous years.

Among the 18 applications for first PIP that were submitted late:

- 5 included a valid justification (26%);
- 13 included a justification that was not acceptable or no justification at all (72%).

Among the 6 applications for a product-specific waiver that were submitted late:

- 1 included a valid justification (16%);
- 5 included a justification that was not acceptable or did not include a justification (83%).

From these data, there is a lack of appropriate justifications provided by applicants when submitting more than 6 months after the completion of the human pharmacokinetic (PK) studies in adults.

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

The reasons given for late submissions include a concern for the resources needed to prepare Paediatric plans for products which development might be discontinued, or uncertainties and fear of potential multiple modifications of agreed PIPs.

The earlier submission of plans (by end of phase 2) to the FDA according to the new 2012 Act (FDA Innovation and Safety Act) may provide a further incentive for applicants to come earlier.

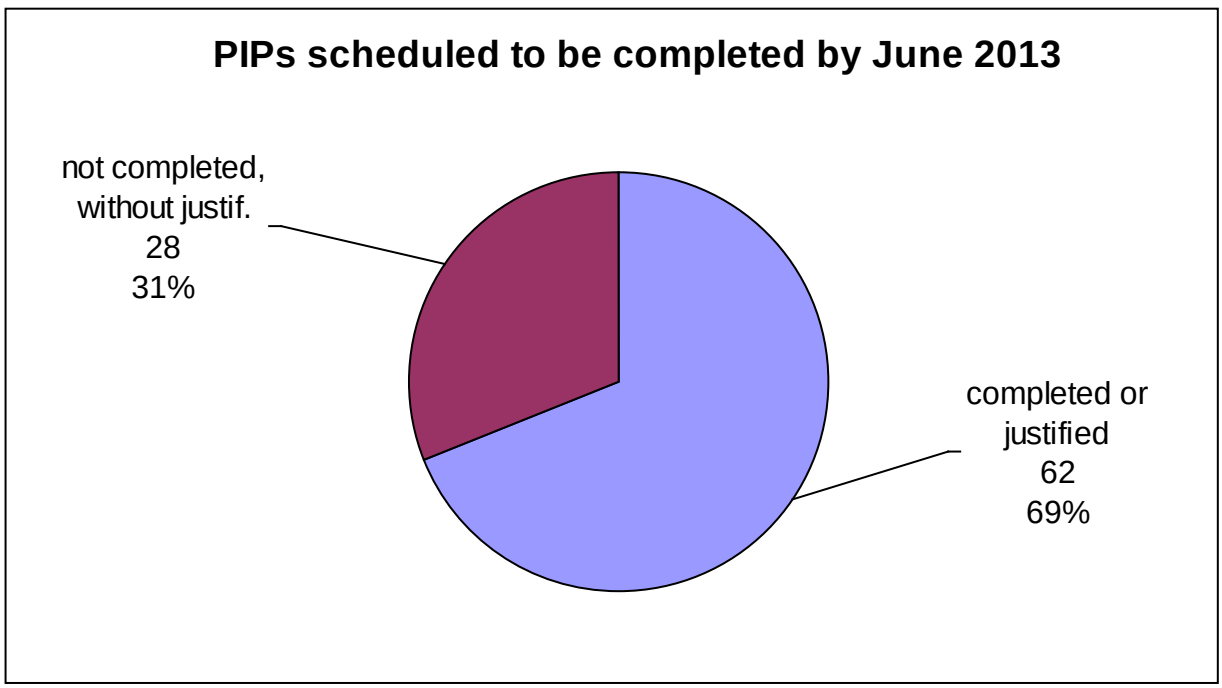
4.2. Completion of PIPs

The EMA Decisions include dates of PIP completion.

The Agency made an analysis of the PIPs with a completion date scheduled before 30 June 2013. 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 2013 might not have been subjected to compliance check.

Ninety PIPs were scheduled to be finished by 30 June 2013. Of those, 28 were not completed and have not provided a justification or submitted a modification to change the timelines.

Figure 4 - Completion of agreed PIP



The detailed lists are in Annexes 8 and 9.

4.3. Compliance with the agreed PIP

When a regulatory application 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 2013 the EMA performed 58 compliance check procedures (Table 6, Figure 5, Figure 6, Figure 3), of which 41 were interim/partial and 17 were full/final. One interim/partial compliance check procedure had negative outcome in 2013 (Tamiflu); one full/final compliance check procedure had a negative outcome (Rupafin and associated names) but successively obtained a positive opinion in 2014 after a modification of the agreed PIP.

Since the start of the Paediatric Regulation, no application for marketing authorisation or variation/extension has been refused validation because of non-compliance with the agreed PIP. In the few instances of initially negative compliance check, a successive procedure of modification of the agreed PIP has allowed to modify the issues at stake, with a following positive compliance check outcome.

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

Figure 5 - EMA compliance check procedures

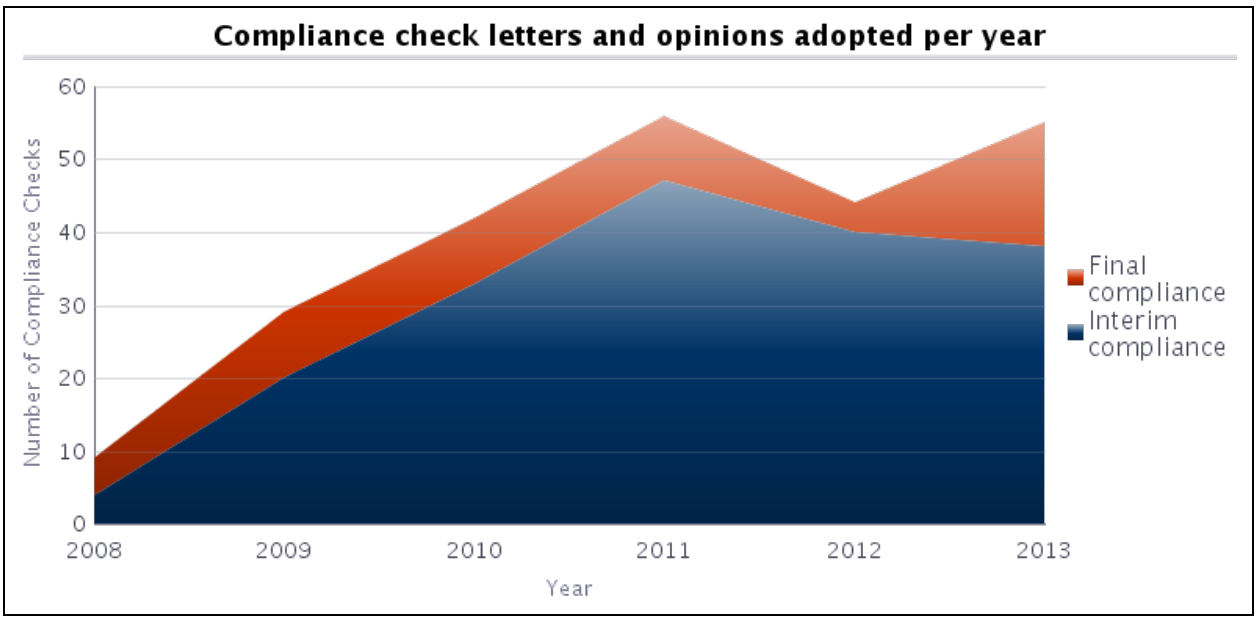
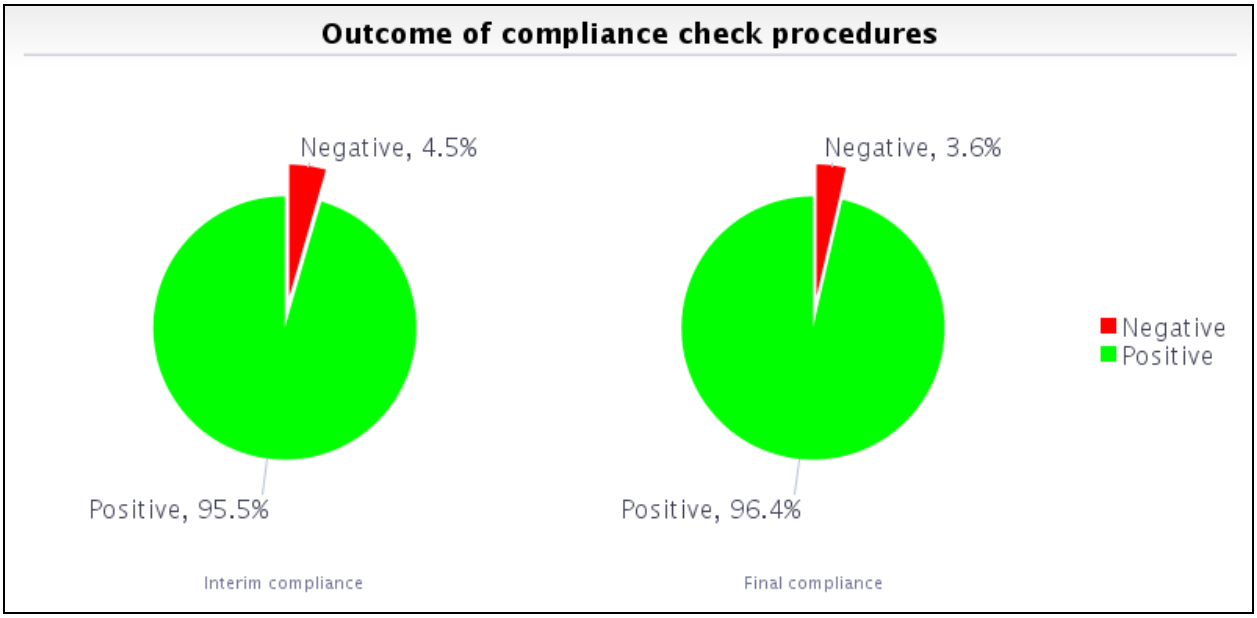


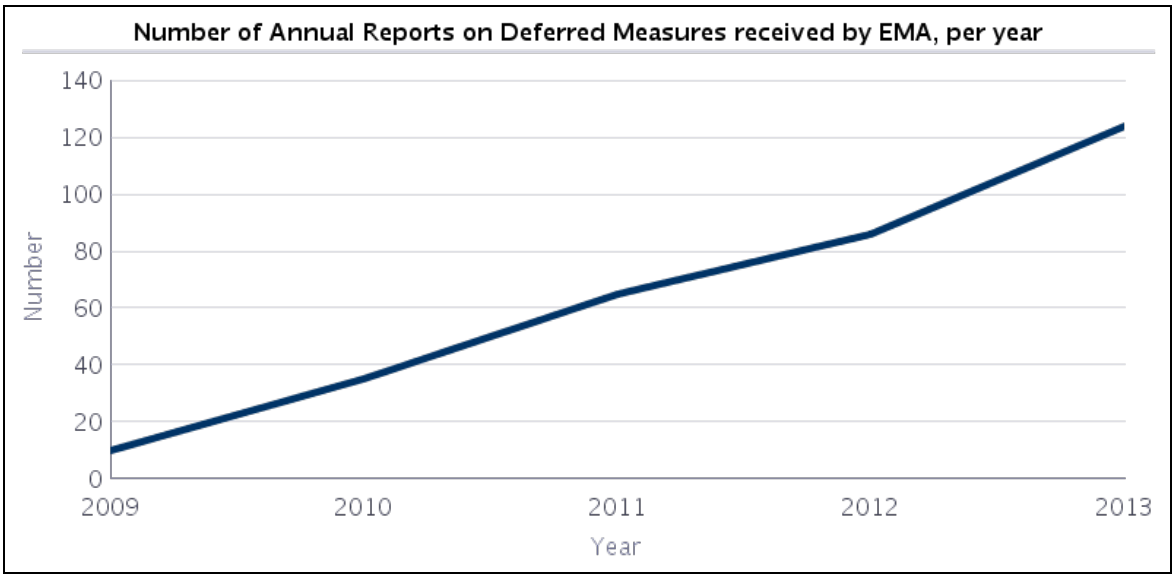
Figure 6 - Global outcome of compliance check procedures (partial on the left, final on the right)



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 7).

Figure 7 - Trend for Annual reports



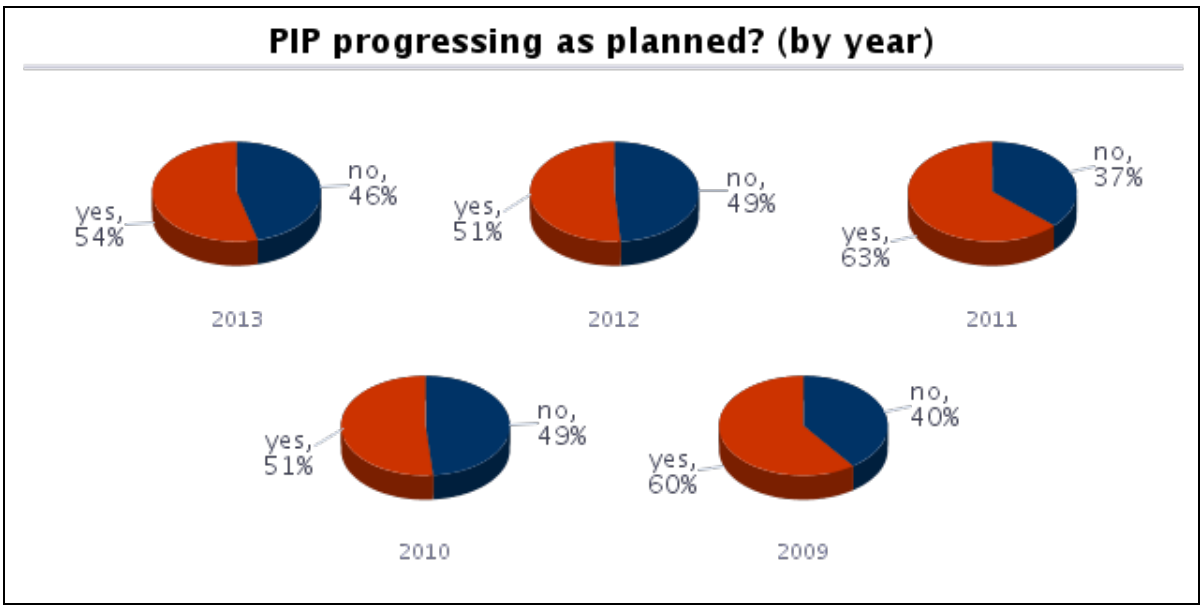
EMA has received 124 annual reports on deferrals in 2013 (86 in 2012 and 65 in 2011). The total numbers of annual reports is in Table 16, and data are analysed according to the difficulties reported.

Over the years, more than half of the reports stated that the PIP was proceeding as planned; this figure is substantially stable over the years (Figure 8). The type of issues is in Table 16. A list of the companies having submitting the annual reports is available in Annex 10.

Table 16 - Annual reports on deferred measures

		2009	2010	2011	2012	2013	Total	% of total
No problems reported	**Total**	6	18	41	44	67	**176**	65%
problems reported	**Total**	4	17	24	42	57	**144**	**45%**
	difficulties in developing age-related formulation(s)		*1*	*3*	*2*	*6*	***12***	*3.7%*
	economic problems					*1*	***1***	*0.3%*
	efficacy concerns	*2*	*4*	*1*	*2*	*1*	***10***	*3.1%*
	organizational issues (e.g. acquisitions, mergers, applicant's internal restructuring,.. etc.)			*2*	*1*	*1*	***4***	*1.2%*
	other quality issues				*3*	*1*	***4***	*1.2%*
	other(s)		*9*	*10*	*17*	*26*	***62***	*19.4%*
	recruitment difficulties	*2*	*10*	*15*	*29*	*35*	***91***	*28.4%*
	refusals/problems with National Competent Authority(ies)	*1*	*5*	*1*	*13*	*9*	***29***	*9.1%*
	refusals/problems with ethics committees		*6*	*3*	*9*	*6*	***24***	*7.5%*
	safety concerns		*5*	*3*	*2*	*5*	***15***	*4.7%*
Grand total		**10**	**35**	**65**	**86**	**124**	**320**	100%

Figure 8 - Percentage of annual reports stating whether the PIP is progressing as planned



There are a number of Marketing Authorisation Holders who have not submitted the reports. The list of companies not submitting one or more annual reports is AMENDED

Table 17.

AMENDED

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

Applicant	2009	2010	2011	2012	2013
Merck Sharp & Dohme (Europe) Inc.	1	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		
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
Totals	**1**	**8**	**11**	**9**	**14**

The complete list of annual reports not submitted is in Annex 11 Overall, non-compliance with this obligation is limited; additionally, a few missing reports mentioned above for 2013 were in fact subsequently submitted, either after the scheduled deadline, or after companies were informed of their inclusion in this list.

Following an amendment to the 'Penalties Regulation' (EC) No 658/2007, which is applicable since July 2012, not submitting an 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.

4.5. Non-compliance with the requirements of Art.46

The Agency is not aware of any violation of the obligation contained in art. 46 of the Paediatric Regulation.

Annex 1 - List sent to the Member States regarding information to be provided

Annex

Preparation of the annual report to the European Commission

Guidance to complete the collection data sheets

- The information to be provided should cover the period from **1 January 2013 to 31 December 2013**.
- All confidential information shall be highlighted. Please note that they will be disclosed solely for the purpose of the Annual report presented to the European Commission and removed prior to its publication.
- We are aware that not all of your responses may be under your direct responsibility, nevertheless, kindly ensure that all questions are answered.
- All questions on the SME status have been removed. An attempt will be made to merge the national data with the European Medicines Agency SME database based on the name of the MAH.
- Following the proposal from some of the Member states to use data available in the internal databases, two additional questions have been included in the questionnaire.
- Please use the Excel spreadsheet provided. Where available, please use a drop down menu to fill relevant information such as the name of Member State and possible answers to various questions. Please note that the colours used are for simplification of data management only.
- **No data** is required on any medicine authorised on a legal basis that corresponds to generic, biosimilar, hybrid, well-established use, homoeopathic or traditional herbal medicines.

I - Compliance, Marketing Authorisation, Variations

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 2013 either through national (N) or decentralised (DC) or mutual recognition procedure (MRP).

For each procedure identified (initial MA, line extension or variation with compliance statement) and for each of the initial MA, line extension or variation of MA granted in 2012 where paediatric information were added or amended in the SmPC and/or the PL, please list or specify (please use one row per procedure):

- **The Member State**;
- 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);
- If the marketing authorisation (**MA**) **included** (before the reported procedure) *adult indication(s) only*, p*aediatric indication(s) only* or *Adult and Paediatric indication(s)*;
- The **therapeutic area** of the medicinal product (if several therapeutic areas, the one which was primarily concerned by the procedure);
- If requirements under the Paediatric regulation were applied when validating the procedure application (*Article 7*, *Article 8* or *not validated under Paediatric Regulation*). Please see "scope of medicines" above for information on which medicines is sought;
- 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 *Other variation of the MA*);
- The **main outcome** of the reported procedure on the SmPC according to categories used by the CMD(h) (*No change to SmPC, Paediatric information clarified, New paediatric study data, New paediatric safety information, New paediatric indication*);
- If a **statement on compliance** of the completed PIP has been issued;
- The **number of the EMA Decision** on the PIP leading to the compliance statement on compliance;
- In case of variation of the MA, please specify if this procedure is linked to the ***Article 36*** of the paediatric regulation, meaning the Paediatric indication cannot be granted but all paediatric information are included in the SmPC in accordance with a completed PIP, which verification of compliance has been performed. These Article 36 procedures are submitted as variation of the MA and can be called “Failed paediatric indication”. Please in the excel sheet specify *Yes* or *No*;
- In case of variation of the MA, please specify if this procedure is linked to the ***Article 45* or *46*** of the paediatric regulation by selecting *Yes* or *No* in the appropriate column;
- Please provide information if the **Package Leaflet** was changed in order to reflect paediatric information. This is a new question that is necessary to capture where paediatric information is made available;
- In which **sections of the SmPC** paediatric information was added or amended in this specific procedure (for example, addition/modification or deletion paediatric indication in 4.1 of the SmPC, addition/modification or deletion of dosage recommendation or extension of use to children in section 4.2, addition/modification or deletion of contraindication in children in section 4.3);
- If a **statement on full *waiver*** (meaning waiver in all paediatric subsets) **or *deferral*** has been included in the SmPC (section 5.1) and in case of a waiver, whether this was also reflected in section 4.2 (using SmPC template wording). For statements on waiver and deferral, please refer to the “Mutual Recognition, decentralised and referral product information template version 2” available on the EMA website at the following address: http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2011/08/WC500111055.doc.

II - Scientific advice

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

For each National Scientific Advice, please list or specify:

- The **Member State**;
- 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;
- When the **outcome** was given;
- The name of the **pharmaceutical company applying** for this Scientific Advice at National level;
- 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*);
- Is there a **fee waiver** for paediatric-only scientific advice in your Agency: (*Yes* / *No*).

III - Benefits and infringements

- Only a single entry (row) in the spreadsheet is expected per Member State.
- **Infringements:**
  - Was a Marketing authorisation application submission validated without Article 7 or 8 fulfilled?
  - Was a statement on compliance statement included in SmPC without any paediatric data added to SmPC?
  - Was authorisation obtained without a waiver or deferral statement being added to SmPC?
  - Was any other situation of infringement detected?
  - If "Yes" to any of the questions above, please provide details.
- **Incentives and benefits:**
  - Is a fee waiver or fee reduction available for paediatric-only National Scientific Advices? (Possible answers: *Yes, automatically for all cases / Yes, but only in certain cases / No fee waiver at all*);
  - Is a fee waiver or reduction available for a paediatric clinical trial application (CTA)? (Possible answers: *Yes, automatically for all cases / Yes, but only in certain cases / No fee waiver at all*);
  - Is there a priority review for any paediatric CTA?
  - Is a fee waiver or fee reduction available for a paediatric marketing authorisation or variation application?
  - Is there a priority review for any paediatric marketing authorisation or variation application?
  - Any benefits for reimbursement of paediatric medicines, including for PUMA (e.g., specific conditions in connection with the fixing of prices and reimbursement, including priority review for this process)? If "Yes", please provide details.

IV - National funding of paediatric research

Please specify whether any national funding to support research and development for paediatric medicinal product was provided. Please supply a list of projects/name of companies or consortium which have received funding between 1 January and 31 December 2012 (please highlight confidential information).

V – Other

1. Are you tracking Paediatric trials that are conducted / regulated in your MS?

   Yes ☐ No ☐

If yes, can you contribute to any analysis on the status of Paediatric trials to complement the picture provided by EudraCT and the National database on GCP for Paediatric trials?

   Yes ☐ No ☐

2. We are here preparing the fourth Annual report. According to your experience, would you have any comments or suggestions for this and / or futures such reports?

   Yes ☐ No ☐

If yes, please specify

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		
Bulgaria	x	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	
Ireland	x	x
Italy	x	x
Latvia		
Lithuania		x
Luxembourg	x	
Malta	x	x
The Netherlands		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

Member State	Marketing authorisation holder	Invented name(s)	International non-proprietary name	MA procedure	Date of outcome	Type of procedure
Cyprus	MERCK SHARP & DOHME BV	EZETROL TABLET 10MG	ezetimibe	MRP (Mutual recognition)	30/07/2013	Variation
Cyprus	BOEHRINGER INGELHEIM INTERNATIONAL GMBH	SPIRIVA INHALATION CAPS	TIOTROPIUM BROMIDE MONOHYDRATE	MRP (Mutual recognition)	21/05/2013	Variation
Cyprus	BOEHRINGER INGELHEIM INTERNATIONAL GMBH		TIOTROPIUM BROMIDE MONOHYDRATE	MRP (Mutual recognition)	16/05/2013	Variation
Czech Republic	Merck Sharp & Dohme	Ezetrol 10 mg tablety	ezetimibe	DC (Decentralised)	20/09/2013	Initial MA
Czech Republic	Boeringer Ingelheim	Spiriva Respimat 2,5 mikrogramu	tiotropium	DC (Decentralised)	11/07/2012	Initial MA
Denmark	Merck Sharp and Dohme Ltd.	Ezetrol	Ezetimib	MRP (Mutual recognition)	30/07/2013	Variation
Denmark	Boehringer Ingelheim Int. GmbH, Germany	Spiriva Respimat	Tiotropium bromide	MRP (Mutual recognition)	16/05/2013	Variation
Estonia	Boehringer Ingelheim	Spiriva Respimat	Tiotropium bromide	DC (Decentralised)	21/05/2013	Variation
Estonia	Boehringer Ingelheim	Spiriva	Tiotropium bromide	DC (Decentralised)	21/05/2013	Variation
Estonia	MERCK SHARP & DOHME OU	EZETROL	ezetimibe	MRP (Mutual recognition)	31/10/2013	Variation
Finland	Shire Pharmaceuticals Limited	Elvanse 40mg kapseli, kova	Lisdexamfetamini dimesylas	DC (Decentralised)	04/06/2013	Initial MA
Finland	Shire Pharmaceuticals Limited	Elvanse 70mg kapseli, kova	Lisdexamfetamini dimesylas	DC (Decentralised)	04/06/2013	Initial MA

Member State	Marketing authorisation holder	Invented name(s)	International non-proprietary name	MA procedure	Date of outcome	Type of procedure
France	GLAXOSMITHKLINE	FLUARIXTETRA	influenza virus fragmented, inactived, strain A/California/7/2009 (H1N1)pdm09 - analogue strain used NIB-74xp derived from A/Christchurch/16/2010	DC (Decentralised)	19/06/2013	Initial MA
France	MEDA PHARMA (FRANCE)	SYNAZE	azelastin (chlorhydrate) ; fluticasone (propionate)	DC (Decentralised)	25/09/2013	Initial MA
France	MEDA PHARMA (FRANCE)	AZEFLU	azelastin (chlorhydrate) ; fluticasone (propionate)	DC (Decentralised)	25/09/2013	Initial MA
France	MEDA PHARMA (FRANCE)	DYMISTA	azelastin (chlorhydrate) ; fluticasone (propionate)	DC (Decentralised)	25/09/2013	Initial MA
France	MEDA PHARMA (FRANCE)	XATALIN	azelastin (chlorhydrate) ; fluticasone (propionate)	DC (Decentralised)	25/09/2013	Initial MA
France	MUNDIPHARMA	FLUTIFORM 125 microgrammes/5 microgrammes par dose	fluticasone (propionate) ; formoterol (fumarate) dihydrated	DC (Decentralised)	16/04/2013	Initial MA
France	MUNDIPHARMA	IFFEZA 125 microgrammes/5 microgrammes par dose	fluticasone (propionate) ; formoterol (fumarate) dihydrated	DC (Decentralised)	16/04/2013	Initial MA
France	MUNDIPHARMA	AFFERA 125 microgrammes/5 microgrammes par dose	fluticasone (propionate) ; formoterol (fumarate) dihydrated	DC (Decentralised)	16/04/2013	Initial MA
France	MUNDIPHARMA	FLUTIFORM 50 microgrammes/5 microgrammes par dose	fluticasone (propionate) ; formoterol (fumarate) dihydrated	DC (Decentralised)	16/04/2013	Initial MA

Member State	Marketing authorisation holder	Invented name(s)	International non-proprietary name	MA procedure	Date of outcome	Type of procedure
France	MUNDIPHARMA	IFFEZA 50 microgrammes/5 microgrammes par dose	fluticasone (propionate) ; formoterol (fumarate) dihydrated	DC (Decentralised)	16/04/2013	Initial MA
France	MUNDIPHARMA	AFFERA 50 microgrammes/5 microgrammes par dose	fluticasone (propionate) ; formoterol (fumarate) dihydrated	DC (Decentralised)	16/04/2013	Initial MA
Germany	GlaxoSmithKline GmbH	Influsplit Tetra	A/California/07/2009(H1N1)v, , 15µg; A/California/7/2004 (H3N2)-like virus, , 15µg; B/Brisbane/60/2008, , 15µg; B/Hong Kong/330/2001-like virus, , 15µg	DC (Decentralised)	19/02/2013	Initial MA
Hungary	MEDA PHARMA HUNGARY KERESKEDELMI Kft	BILENI szuszpenziós orrspray	azelastine hydrochloride, fluticasone propionate,	DC (Decentralised)	15/02/2013	Initial MA
Hungary	MEDA PHARMA HUNGARY KERESKEDELMI Kft	DYMISTA szuszpenziós orrspray	azelastine hydrochloride, fluticasone propionate,	DC (Decentralised)	15/02/2013	Initial MA
Hungary	MEDA PHARMA HUNGARY KERESKEDELMI Kft	SYCARA szuszpenziós orrspray	azelastine hydrochloride, fluticasone propionate,	DC (Decentralised)	15/02/2013	Initial MA
Hungary	Ferring Magyarország Gyógyszerkereskedelmi Kft.	MISODEL 200 mikrogramm hüvelyben alkalmazott gyógyszerleadó rendszer	misoprostol,	DC (Decentralised)	07/11/2013	Initial MA

Member State	Marketing authorisation holder	Invented name(s)	International non-proprietary name	MA procedure	Date of outcome	Type of procedure
Malta	Merck Sharp & Dohme Limited	Ezetrol	ezetimibe	MRP (Mutual recognition)	Not provided	Line extension
Romania	Meda Pharma GmbH & Co. KG, Germania	Zanea	clindamycin phosphate/tretinoin	DC (Decentralised)	21/11/2013	Initial MA
Romania	IPSEN Pharma, France	Eziclen	magnesium sulfate/potassium sulfate/sodium sulfate	DC (Decentralised)	28/12/2013	Initial MA
Romania	Les Laboratoires Servier, France	Triplixam	perindopril/indapamide/amlodipine	DC (Decentralised)	Not provided	Initial MA
Romania	Les Laboratoires Servier, France	Natrixam	perindopril/indapamide/amlodipine	DC (Decentralised)	Not provided	Initial MA
Romania	Les Laboratoires Servier, France	Arplexam	perindopril/indapamide/amlodipine	DC (Decentralised)	Not provided	Initial MA
Romania	Les Laboratoires Servier, France	Fludexam	perindopril/indapamide/amlodipine	DC (Decentralised)	Not provided	Initial MA
Romania	Boehringer Ingelheim, Germany	Infortispir Respimat	olodaterol	DC (Decentralised)	Not provided	Initial MA
Romania	Krka, d.d., Novo mesto, Slovenia	Co-amlessa	perindopril/indapamide/amlodipine	DC (Decentralised)	Not provided	Initial MA
Romania	J. Uriach & Cía., S.A., Spain	Tamalis	rupatadine fumarate	MRP (Mutual recognition)	29/11/2013	Initial MA
Slovenia	Boehringer Ingelheim International GmbH	SPIRIVA RESPIMAT 2,5 microgram, solution for inhalation	TIOTROPIUM	MRP (Mutual recognition)	16/05/2013	
UK	Basilea Medical Limited	Zevtera 500 mg powder	CEFTOBIPROLE MEDOCARIL SODIUM	DC (Decentralised)	28/11/2013	Initial MA

Annex 4 - List of medicinal products assessed in 2013 further to submission of data through Article 45 and resulting amendment of the SmPC Medicinal 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 4.2 Posology and method of administration
Section 4.4 Special warnings and precaution for use
Section 4.5 Interactions
Section 4.6 Fertility, pregnancy and lactation
Section 4.8 Undesirable effects
Section 5.1 Pharmacodynamics properties
Section 5.2 Pharmacokinetic properties

Name of Active substance	Assessment outcome: change in SmPC (Y/N)	SmPC sections [1] to be changed
Budesonide/Formoterol	Y	section 5.1 (update on paediatric information)
Dexamethasone	Y	sections 4.4, 4.6 abd 5.3 (new safety information)
Netilmicin Sulfate	N	N/A
Rabeprazole	N	N/A
Risperidone	Y	sections 4.4 (paediatric information clarified)
Alfentanil	Y	sections 4.1, 4.2, 4.6 and 5.2 (paediatric information clarified)
Captopril	N	N/A
Daunorubicin	Y	sections 4.1, 4.2 and 5.1 (update on paediatric information)
Dexamethasone combinations	Y	sections 4.2 and 4.4 (paediatric information clarified)
Dobutamine hydrochloride	Y	sections 4.1-4.2 (paediatric information clarified)
Haloperidol	Y	section 4.4 (paediatric information clarified)
Ketoconazole	Y	sections 4.2 and 5.2 (paediatric information clarified)
Lovastatin	Y	sections 4.8, 5.1 and cross referenced 4.2 (paediatric information clarified and paediatric posology not supported)
Miconazole nitrate	Y	sections 4.2, 4.3, and 4.4 (paediatric information clarified)

Name of Active substance	Assessment outcome: change in SmPC (Y/N)	SmPC sections [1] to be changed
Phytomenadione	Y	sections 4.2, and 5.1 (paediatric information clarified)
Setraline	N	N/A
Testosterone	Y	section 4.2 (paediatric information clarified)
Trazodone	N	N/A
Ursodeoxycholic acid	Y	sections 4.1, 4.2, 4.3 and 5.1 (paediatric information clarified)
Verapamil	Y	section 4.2 (paediatric information clarified)
Zanamivir	N	N/A
Atracurium besilate	Y	sections 4.2 and 5.1 (paediatric information clarified)
Aztreonam	N	N/A
Gonadorelin	Y	section 4.8 (update on safety information)
Pentamidine	N	N/A
Vinorelbine	Y	sections 4.2, and 5.1 (paediatric information clarified)
Spironolactone	N	N/A
Alginic Acid	N	N/A
Adenosine	Y	sections 4.1, 4.2, and 5.1 (paediatric information clarified)
Biotin	N	N/A
Lamotrigine	N	N/A
Lidocaine	Y	sections 4.1 and 4.2 (paediatric information clarified)
Meropenem	N	N/A
Salmeterol + fluticasone	Y	sections 5.1, and 5.2 (paediatric information clarified)
Sumatriptan	N	N/A
Colecalciferol and sodium fluoride	Y	sections 4.1, 4.2, and 5.1 (paediatric information clarified)
Metoprolol succinate	Y	section 4.1 (new indication) sections 4.2, 5.1 and 5.2 (paediatric information clarified)
Quetapine	Y	sections 4.4, 4.8 and 5.1 (new safety information) and sections 4.2, 4.4, 4.8 and 5.1 (paediatric information clarified)
Nystatin	Y	section 4.2 (paediatric information clarified)

Name of Active substance	Assessment outcome: change in SmPC (Y/N)	SmPC sections [1] to be changed
Permethrin	Y	sections 4.1, 4.2, 4.4. and 5.1 (paediatric information clarified)
Latanoprost	N	N/A
Latanoprost/Timolol	N	N/A
Terbutaline sulfate	N	N/A

TOTAL:

- 43 active substances assessed
- 17 active substances for which no change in current SmPC is recommended
- 26 active substances for which a change in SmPC sections is recommended (1 active substance assessment lead to 1 new paediatric indication)

Annex 5 - List of medicinal products assessed in 2013 further to submission of data through Article 46

(and resulting amendment of the SmPC)

Centrally authorised medicinal products

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

[1] Section 4.1: Therapeutic indication
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

Active Substance	Brand Name	MAH	Assessment outcome: change in SmPC (Y/N)	SmPC sections [1] to be changed
aripiprazole	Abilify	Otsuka Pharmaceutical Europe Ltd	Y	Section 5.1
aripiprazole	Abilify	Otsuka Pharmaceutical Europe Ltd	further information required	See subsequent procedure
aripiprazole	Abilify	Otsuka Pharmaceutical Europe Ltd	Y	Section 4.8
pandemic influenza vaccine (h5n1) (split virion, inactivated, adjuvanted)	Adjupanrix	GlaxoSmithKline Biologicals	N	N/A
retapamulin	Altargo	Glaxo Group Ltd	N	N/A
nelarabine	Atriance	Glaxo Group Ltd	N	N/A
nonacog alfa	BeneFIX	Pfizer Limited	further information required	See subsequent procedure
nonacog alfa	BeneFIX	Pfizer Limited	N	N/A
aztreonam	Cayston	Gilead Sciences International Ltd	N	N/A

Active Substance	Brand Name	MAH	Assessment outcome: change in SmPC (Y/N)	SmPC sections [1] to be changed
human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed)	Cervarix	GlaxoSmithKline Biologicals	N	N/A
human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed)	Cervarix	GlaxoSmithKline Biologicals	N	N/A
certolizumab pegol	Cimzia	UCB Pharma SA	N	N/A
c1 inhibitor, human	Cinryze	ViroPharma SPRL	N	N/A
c1 inhibitor, human	Cinryze	ViroPharma SPRL	Y	Section 5.1
c1 inhibitor, human	Cinryze	ViroPharma SPRL	N	N/A
daptomycin	Cubicin	Novartis Europharm Ltd	N	N/A
docetaxel	Docetaxel Winthrop	Aventis Pharma S.A.	N	N/A
doripenem	Doribax	Janssen-Cilag International N.V.	N	N/A
doripenem	Doribax	Janssen-Cilag International N.V.	N	N/A
prasugrel	Efient	Eli Lilly Nederland B.V.	N	N/A
apixaban	Eliquis	Bristol-Myers Squibb / Pfizer EEIG	N	N/A
etanercept	Enbrel	Pfizer Limited	N	N/A
deferasirox	Exjade	Novartis Europharm Ltd	further information required	See subsequent procedure
deferasirox	Exjade	Novartis Europharm Ltd	N	N/A
influenza vaccine (live attenuated, nasal)	FLUENZ	MedImmune LLC	N	N/A
influenza vaccine (live attenuated, nasal)	FLUENZ	MedImmune LLC	N	N/A
human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)	Gardasil	Sanofi Pasteur MSD, SNC	further information required	See subsequent procedure
human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)	Gardasil	Sanofi Pasteur MSD, SNC	N	N/A

Active Substance	Brand Name	MAH	Assessment outcome: change in SmPC (Y/N)	SmPC sections [1] to be changed
human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)	Gardasil	Sanofi Pasteur MSD, SNC	N	N/A
human normal immunoglobulin	Hizentra	CSL Behring GmbH	Y	safety changes to the SmPC and RMP recommended
canakinumab	ILARIS	Novartis Europharm Ltd	N	N/A
mecasermin	Increlex	Ipsen Pharma	Y	
diphtheria (d), tetanus (t), pertussis (acellular, component) (pa), hepatitis b (rdna) (hbv), poliomyelitis (inactivated) (ipv) and haemophilus influenzae type b (hib) conjugate vaccine (adsorbed)	Infanrix hexa	GlaxoSmithKline Biologicals	Further information required	See subsequent procedure
diphtheria (d), tetanus (t), pertussis (acellular, component) (pa), hepatitis b (rdna) (hbv), poliomyelitis (inactivated) (ipv) and haemophilus influenzae type b (hib) conjugate vaccine (adsorbed)	Infanrix hexa	GlaxoSmithKline Biologicals	N	N/A
diphtheria (d), tetanus (t), pertussis (acellular, component) (pa), hepatitis b (rdna) (hbv), poliomyelitis (inactivated) (ipv) and haemophilus influenzae type b (hib) conjugate vaccine (adsorbed)	Infanrix hexa	GlaxoSmithKline Biologicals	N	N/A
diphtheria (d), tetanus (t), pertussis (acellular, component) (pa), hepatitis b (rdna) (hbv), poliomyelitis (inactivated) (ipv) vaccine (adsorbed)	Infanrix penta	GlaxoSmithKline Biologicals	N	N/A
rufinamide	Inovelon	Eisai Ltd	N	N/A
rufinamide	Inovelon	Eisai Ltd	N	N/A
paliperidone	Invega	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
japanese encephalitis vaccine (inactivated, adsorbed)	Ixiaro	Valneva Austria GmbH	Y	updates to SmPC when final results available
ocriplasmin	JETREA	ThromboGenic NV	Y	Sections 4.1 and 5.2
insulin detemir	Levemir	Novo Nordisk A/S	Y	Section 4.2
insulin lispro	Liprolog	Eli Lilly Nederland B.V.	N	N/A
pregabalin	Lyrica	Pfizer Limited	further information required	
meningococcal group a, c, w135 and y conjugate vaccine	Nimenrix	GlaxoSmithKline Biologicals S.A.	N	N/A
meningococcal group a, c, w135 and y conjugate vaccine	Nimenrix	GlaxoSmithKline Biologicals S.A.	N	N/A
meningococcal group a, c, w135 and y conjugate vaccine	Nimenrix	GlaxoSmithKline Biologicals S.A.	Y	
meningococcal group a, c, w135 and y conjugate vaccine	Nimenrix	GlaxoSmithKline Biologicals S.A.	Y	Section 5.1
meningococcal group a, c, w135 and y conjugate vaccine	Nimenrix	GlaxoSmithKline Biologicals S.A.	Y	Sections 4.4 and 5.1
meningococcal group a, c, w135 and y conjugate vaccine	Nimenrix	GlaxoSmithKline Biologicals S.A.	N	N/A
insulin aspart	NovoMix	Novo Nordisk A/S	N	N/A
insulin aspart	NovoRapid	Novo Nordisk A/S	Y	Section 4.2
insulin aspart	NovoRapid	Novo Nordisk A/S	N	N/A
somatropin	NutropinAq	Ipsen Pharma	N	N/A
pandemic influenza vaccine (h5n1, whole virion, vero cell derived, inactivated)	Pandemic Influenza Vaccine H5N1 Baxter	Baxter AG	Y	changes to safety and immunogenicity data in children
dabigatran etexilate	Pradaxa	Boehringer Ingelheim International GmbH	N	N/A

Active Substance	Brand Name	MAH	Assessment outcome: change in SmPC (Y/N)	SmPC sections [1] to be changed
purified antigen fractions of inactivated split virions a/indonesia/05/2005 (h5n1)/pr8-ibcdc-rg2	Prepandrix	GlaxoSmithKline Biologicals	N	N/A
pneumococcal saccharide conjugated vaccine, adsorbed	Prevenar	Pfizer Limited	N	N/A
pneumococcal saccharide conjugated vaccine, adsorbed	Prevenar	Pfizer Limited	N	N/A
pandemic influenza vaccine (h5n1) (split virion, inactivated, adjuvanted)	Pumarix	GlaxoSmithKline Biologicals	Y	
sildenafil	Revatio	Pfizer Limited	N	N/A
atazanavir sulfate	Reyataz	Bristol-Myers Squibb Pharma EEIG	Data required with future submissions	N/A
human rotavirus, live attenuated	Rotarix	GlaxoSmithKline Biologicals S.A.	Y	Section 5.1
human rotavirus, live attenuated	Rotarix	GlaxoSmithKline Biologicals S.A.	N	N/A
human rotavirus, live attenuated	Rotarix	GlaxoSmithKline Biologicals S.A.	N	N/A
telbivudine	Sebivo	Novartis Europharm Ltd	N	N/A
human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)	Silgard	Merck Sharp & Dohme Limited	further information required	See subsequent procedure
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
sunitinib	Sutent	Pfizer Limited	Y	Sections 4.2, 4.8, 5.1 and 5.2
asenapine	Sycrest	N.V. Organon	further information required	See subsequent procedure
asenapine	Sycrest	N.V. Organon	Y	Sections 4.2 and 4.8

Active Substance	Brand Name	MAH	Assessment outcome: change in SmPC (Y/N)	SmPC sections [1] to be changed
asenapine	Sycrest	N.V. Organon	Y	Sections 4.2 and 4.8
palivizumab	Synagis	AbbVie Ltd.	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
pneumococcal polysaccharide conjugate vaccine (adsorbed)	Synflorix	GlaxoSmithKline Biologicals	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
pneumococcal polysaccharide conjugate vaccine (adsorbed)	Synflorix	GlaxoSmithKline Biologicals	N	N/A
oseltamivir	Tamiflu	Roche Registration Ltd	N	N/A
docetaxel	Taxotere	Aventis Pharma S.A.	N	N/A
diphtheria (d), tetanus (t), pertussis (whole cell) (pw) and hepatitis b (rdna) (hbv) vaccine (adsorbed)	Tritanrix HepB	GlaxoSmithKline Biologicals	N	N/A
prepandemic influenza vaccine (h5n1) (whole virion, inactivated, prepared in cell culture)	Vepacel	Baxter Innovations GmbH	N	N/A
lacosamide	Vimpat	UCB Pharma SA	Y	
nevirapine	Viramune	Boehringer Ingelheim International GmbH	further information required	See subsequent procedure
nevirapine	Viramune	Boehringer Ingelheim International GmbH	N	N/A
omalizumab	Xolair	Novartis Europharm Ltd	N	N/A
eslicarbazepine acetate	Zebinix	Bial - Portela & Cª, S.A.	N	N/A

Active Substance	Brand Name	MAH	Assessment outcome: change in SmPC (Y/N)	SmPC sections [1] to be changed
stavudine	Zerit	Bristol-Myers Squibb Pharma EEIG	Further information required	See subsequent procedure
stavudine	Zerit	Bristol-Myers Squibb Pharma EEIG	N	N/A

TOTAL:

- 91 Art.46 submitted in 2013
- 80 assessment procedures concluded in 2013
- 57 active substances assessed in 2013
- 15 active substances for which a change in SmPC sections is recommended

Medicinal products authorised through national / mutual recognition / decentralised procedure

Article 46 work-sharing finalised in 2013 and published

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

[1] Section 4.1: Therapeutic indication
Section 4.2 Posology and method of administration
Section 4.4 Special warnings and precaution for use
Section 4.5 Interactions
Section 4.8 Undesirable effects
Section 5.1 Pharmacodynamics properties
Section 5.2 Pharmacokinetic properties

Name of Active substance	Brand Name	MAH	Assessment outcome: change in SmPC (Y/N)	SmPC sections [1] to be changed
Risedronate sodium	Actonel	Sanofi-aventis / Warner Chilcott	Y	sections 4.2 & 5.1 (paediatric information clarified)
Somatropin	Genotropin	Pfizer	N	N/A
Calcipotriol/bethamethasone	Daivobet	Leo Pharma A/S	Y	sections 4.2, 4.8 and 5.1 (paediatric information clarified)
Inactivated poliovirus (IPV) types 1,2 and 3	Poliorix	GlaxoSmithKline	N	N/A
A/California/7/2009 (H1N1) derived strain used NYMC X-181 A/Perth/16/2009 (H3N2)-like strain used NYMCX-187 derived from A/Victoria/210/2009 B/Brisbane/60/2008	Fluarix	GlaxoSmithKline GmbH & Co. KG	Y	section 4.8 (new safety information)
Live attenuated measles virus (Schwarz strain), Live attenuated mumps virus (RIT 4385 strain), Live attenuated rubella virus (Wistar RA 27/3 strain), Live attenuated varicella virus (OKA strain)	Priorix Tetra	GlaxoSmithKline GmbH & Co. KG	N	N/A

Name of Active substance	Brand Name	MAH	Assessment outcome: change in SmPC (Y/N)	SmPC sections [1] to be changed
Live attenuated measles virus (Schwarz strain), Live attenuated mumps virus (RIT 4385 strain), Live attenuated rubella virus (Wistar RA 27/3 strain), Live attenuated varicella virus (OKA strain)	Priorix Tetra	GlaxoSmithKline GmbH & Co. KG	N	N/A
Salmeterol/fluticasone propionate	Seretide Diskus, Viani Diskus	GlaxoSmithKline R&D	Y	section 5.1 (paediatric information clarified)
Sumatriptan	Imigran	GlaxoSmithKline R&D	Y	sections 4.2 and 5.1 (paediatric information clarified)
Triamcinolone acetonide	Nasacort	Sanofi Aventis	Y	sections 4.2, 4.4, 4.8, and 5.1 (paediatric information clarified)
Montelukast	Singulair, Montelukast, Airathon, Xaira, Imvlo, Asmanex Twisthaler	MERCK SHARP & DOHME B.V.	N	N/A
Atacand and associated names (candesartan cilexetil)	Atacand, Amias, Blopress	AstraZeneca & Takeda Ltd	Y	sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, and 5.3 (paediatric information clarified)
Avaxim 80U Pediatric (inactivated hepatitis A vaccine)	Avaxim 80U Pediatric	Sanofi Pasteur	Y	section 4.5 (update on interactions)
Purified Meningococcal Polysaccharide from Neisseria meningitidis Serogroups A and C	Meningococcal (Groups A and C) Polysaccharide Vaccine Meningo A+C®	Sanofi Pasteur	N	N/A

Name of Active substance	Brand Name	MAH	Assessment outcome: change in SmPC (Y/N)	SmPC sections [1] to be changed
Quetiapine	Seroquel	AstraZeneca	Y	sections 4.4, 4.8 and 5.1 (new safety information)
Quetiapine	Seroquel	AstraZeneca	Y	sections 4.2, 4.4, 4.8, and 5.1 (paediatric information clarified)
Haemophilus influenzae type b conjugate, Neisseria meningitidis capsular polysaccharide C, tetanus toxoid conjugates	Menitorix	GlaxoSmithKline Biologicals s.a.	Y	Variation type II to be filed (to add information on use in infants born prematurely, option of a 2+1 schedule and concomitant use with Synflorix)
Haemophilus influenzae type b conjugate, Neisseria meningitidis capsular polysaccharide C, tetanus toxoid conjugates	Menitorix	GlaxoSmithKline Biologicals s.a.	N	N/A
Haemophilus influenzae type b conjugate, Neisseria meningitidis capsular polysaccharide C, tetanus toxoid conjugates	Menitorix	GlaxoSmithKline Biologicals s.a.	N	N/A
Haemophilus influenzae type b conjugate, Neisseria meningitidis capsular polysaccharide C, tetanus toxoid conjugates	Menitorix	GlaxoSmithKline Biologicals s.a.	N	N/A
Montelukast + Mometasone furoate	Singulair, Montelukast, Airathon, Xaira, Imvlo, Asmanex Twisthaler	MERCK SHARP & DOHME B.V.	N	N/A
Somatropin	Genotropin	Pfizer	N	N/A

TOTAL:

- 22 active substances assessed in 2013
- 11 active substances for which no change in current SmPC is recommended
- 11 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]	(abbreviated) authorised Indication(s), including paediatric indication(s)	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]	(abbreviated) authorised Indication(s), including paediatric indication(s)	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	

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

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

Invented Name	PIP procedure number	Active Substance(s) [abbreviated if necessary]	(abbreviated) authorised Indication(s), including paediatric indication(s)	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*
Viramune	EMEA-000391-PIP01-08-M01	Nevirapine	Tablets and oral suspension: Viramune is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1-infected adults, adolescents, and children of any age (see section 4.4). prolonged-release tablets: Viramune is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1-infected adolescents and children three years and above and able to swallow tablets (see section 4.2 and 4.4).	05/02/1998	05/09/2011	05/09/2013	
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	

Invented Name	PIP procedure number	Active Substance(s) [abbreviated if necessary]	(abbreviated) authorised Indication(s), including paediatric indication(s)	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*
Remicade	EMEA-000549-PIP01-09-M01	infliximab	Treatment of severely active ulcerative colitis, in paediatric patients aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies.	13/08/1999	21/02/2012	21/02/2014	11/06/2012
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	

Invented Name	PIP procedure number	Active Substance(s) [abbreviated if necessary]	(abbreviated) authorised Indication(s), including paediatric indication(s)	Date of MA	Date of variation (to include the paediatric indication)	Deadline to put on the product on the market	on the market with paediatric indication*
Enbrel	EMEA-000299-PIP01-08-M03	Etanercept	Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate. Treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate. Treatment of enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy. Treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.	03/02/2000	31/07/2012	31/07/2014	

Invented Name	PIP procedure number	Active Substance(s) [abbreviated if necessary]	(abbreviated) authorised Indication(s), including paediatric indication(s)	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*
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	
Glivec	EMEA-000463-PIP01-08-M03	Imatinib mesilate	Treatment of paediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ALL) integrated with chemotherapy.	07/11/2001	27/06/2013	27/06/2015	
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	

Invented Name	PIP procedure number	Active Substance(s) [abbreviated if necessary]	(abbreviated) authorised Indication(s), including paediatric indication(s)	Date of MA	Date of variation (to include the paediatric indication)	Deadline to put on the product on the market	on the market with paediatric indication*
Prezista	EMEA-000038-PIP01-07-M03	Darunavir (as ethanolate)	In combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adult and paediatric patients from the age of 3 years and at least 15 kg body weight.	12/02/2007	19/09/2013	19/09/2015	
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 2013 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 2013 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	Substances	Opinion	Delay (months)
Diater Laboratorio de Diagnóstico y Aplicaciones Terapéuticas, S.A.	Sodium benzylpenilloate / Benzylpenicilloyl octa- L-lysine	PIP agreed	29
Cubist Pharmaceuticals (UK) Ltd	Tedizolid phosphate	PIP agreed	42
BTG International Ltd	Glucarpidase	PIP agreed	41
Roche Registration Limited	quilizumab	PIP agreed	13
Biogen Idec Ltd	daclizumab	PIP agreed	66
Estetra S.A.	Estetrol & Drospirenone	PIP agreed	16
Hyperion Therapeutics, Ltd.	glycerol phenylbutyrate (GPB)	PIP agreed	38
UCB Pharma S.A.	epratuzumab	PIP agreed	33
Eisai Europe Limited	Lenvatinib	PIP agreed	36
The Medicines Company	Oritavancin (diphosphate)	PIP agreed	35
Eli Lilly and Company	Glucagon Receptor Antagonist	PIP agreed	21
sanofi-aventis recherche & développement	Sarilumab	PIP agreed	12
Alexion Europe SAS	Asfotase alfa	PIP agreed	18
Celgene Europe Ltd	pomalidomide	Full waiver granted	14
BILLEV PHARMA ApS	acetylsalicylic acid / clopidogrel hydrogen sulphate	Full waiver granted	21
TEVA Pharma B.V.	colecalciferol / alendronic acid	Full waiver granted	31
Conventia Healthcare LLP	Omeprazole / Ketoprofen	Full waiver granted	55
QRxPharma Inc	Oxycodone hydrochloride / Morphine sulfate	Full waiver granted	19

Annex 8 - List of PIPs completed (by 30/6/13)

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	
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, Victor...	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

Annex 9 - List of PIPs not completed by the agreed date
(scheduled by 30/06/2013)

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. (AMENDED)

Substances	Invented name	Company	Latest PIP number	Obligation to complete PIP
docetaxel	TAXOTERE	AVENTIS PHARMA SA	EMEA-000029-PIP01-07	yes
Mercaptopurine monohydrate	not applicable	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
Hydrocortisone / Calcipotriol Hydrate	Picato®	LEO Pharma A/S	EMEA-000277-PIP01-08	yes
Skimmed cow's milk powder	Diallertest	DBV Technologies	EMEA-000201-PIP01-08-M01	yes
Split influenza virus, inactivated, containing antigen: A/California/7/2009 (H1N1)v like strain (X-179A)	Arepanrix	GlaxoSmithKline Biologicals S.A.	EMEA-000687-PIP01-09-M02	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
Vandetanib		AstraZeneca AB	EMEA-000052-PIP01-07	yes
Split Influenza virus, inactivated, containing antigen: A/California/7/2009 (H1N1)v like strain (X-179A)	Pandemrix	GlaxoSmithKline Biologicals S.A.	EMEA-000725-PIP01-09-M03	yes

Substances	Invented name	Company	Latest PIP number	Obligation to complete PIP
L-Tryptophan / L-Serine / L-Lysine acetate / L-Histidine / Glycine / L-Alanine / L-Valine / L-Threonine / Taurine / L-Proline / L-Phenylalanine / L-Methionine / L-Leucine / L-Isoleucine / Glycyl-L-Tyrosine / L-Arginine hydrochloride / L-Alanyl-L-Glutamine / N-Acetyl-L-Cysteine	Neoven	*Fresenius Kabi Deutschland GmbH*	EMEA-000042-PIP01-07-M01	yes
Glucose (monohydrate)	-	Cblaya & Mhuguet S.L.	EMEA-000221-PIP01-08	undetermined
thrombin alfa		Bayer HealthCare AG	EMEA-000163-PIP01-07	No
Human normal immunoglobulin	HyQvia 100 mg/ml solution for infusion	Baxter Innovations GmbH	EMEA-000872-PIP01-10-M01	yes
Formoterol fumarate / Mometasone furoate	not available at present	Merck Sharp & Dogme (Europe) Inc.	EMEA-000025-PIP01-07-M01	yes
Oseltamivir Phosphate	Tamiflu	Roche Registration Ltd	EMEA-000365-PIP01-08-M04	yes
Purified antigen fractions of inactivated split virion Influenza A/Indonesia/5/05/ (H5N1)	Arepanrix	GlaxoSmithKline Biologicals S.A.	EMEA-000134-PIP01-07	yes
Cholic acid	not available at present	FGK Representative Service GmbH	EMEA-000651-PIP01-09-M02	yes
Furosemide	not available at present	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

Substances	Invented name	Company	Latest PIP number	Obligation to complete PIP
Levonorgestrel	not available at present	Bayer Schering Pharma AG	EMEA-000606-PIP01-09	No (off-patent authorised product, intending to apply in the future for PUMA)
ritonavir / lopinavir	Kaletra	AbbVie Ltd	EMEA-001005-PIP01-10-M01	No
Casopitant	Zunrisa	Glaxo Group Limited	EMEA-000154-PIP01-07	yes
Formoterol fumarate dihydrate .	FlutiForm	Mundipharma Research Limited	EMEA-000127-PIP01-07-M02	yes
Laquinimod	Nerventra	Teva Pharma GmbH	EMEA-000972-PIP01-10-M03	No (negative MAA)
2,6-Bis-{(1-napthalenyl-3,6-di...	Vivagel	Starpharma Pty Ltd	EMEA-001354-PIP01-12	yes

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

Number of annual reports submitted	Total	2013	2012	2011	2010	2009
Company	**320**	**124**	**86**	**65**	**35**	**10**
ALEXION EUROPE SAS	3	1	1	1		
AMAG Pharmaceuticals, Inc.	1	1				
AbbVie Limited	3	1	1	1		
AbbVie Ltd	3	1	1	1		
Alexion Europe SAS	1	1				
Almirall S.A.	1	1				
Amgen Europe B.V.	9	3	3	2	1	
Astellas Pharma Europe B.V.	2	1	1			
AstraZeneca AB	8	3	2	2	1	
BIAL - Portela & Ca, SA	2	1	1			
Bayer Schering Pharma AG	15	3	3	4	5	
Biogen Idec Limited	1	1				
Boehringer Ingelheim International GmbH	10	3	2		2	3
Bristol-Myers Squibb / Pfizer EEIG	2	2				
Bristol-Myers Squibb International Corporation	9	5	4			
Bristol-Myers Squibb Pharma EEIG	9	3	3	2	1	
Bristol-Myers Squibb/AstraZeneca EEIG	4	2	1	1		
CTI Life Sciences, Ltd.	1	1				
Centocor B.V.	4	1	1	1	1	
Chiesi Farmaceutici S.p.A.	1	1				
Eisai Ltd.	4	2	2			
Eli Lilly and Company Limited	7	4	2	1		
F. Hoffmann La Roche	1	1				
FAES FARMA, S.A.	3	1	1	1		
Forest Laboratories Limited	1	1				
GW Pharma Ltd	1			1		
Genzyme Europe B.V.	3	1	1		1	
Gilead Sciences International Limited	8	3	3	2		
Glaxo Group Limited	8	4	2	2		
GlaxoSmithKline Biologicals S.A.	**13**	5	4	3	1	
GlaxoSmithKline Trading Services Limited	**4**	2	2			

Number of annual reports submitted	Total	2013	2012	2011	2010	2009
Grünenthal GmbH	**12**	6		6		
Janssen Biologics B.V.	**2**	1	1			
Janssen-Cilag International NV	**19**	5	6	4	2	2
Johnson & Johnson PRD	**6**	1	1	1	3	
Laboratoire HRA Pharma	**3**		1	1	1	
Les Laboratoires Servier	**8**	4	2	2		
MSD-SP Limited	**2**			1	1	
Merck Sharp and Dohme (Europe), Inc.	**15**	3	3	2	4	3
Mitsubishi Pharma Europe Ltd	**1**	1				
N.V. Organon	**6**	2	2	2		
Novartis Europharm Limited	**31**	10	8	7	5	1
Novartis Vaccines and Diagnostics S.r.l.	**3**	2		1		
Novo Nordisk A/S	**7**	4	1	1	1	
Nycomed Danmark ApS	**1**	1				
Otsuka Pharmaceutical Europe Ltd.	**2**	1	1			
Pfizer Limited	**9**	4	3	1	1	
Pharming Group N.V.	**3**	1	1	1		
Rapidscan Pharma Solutions (RPS) EU Ltd	**3**	1	1	1		
Roche Products Ltd	**1**	1				
Roche Registration Ltd	**11**	3	3	3	1	1
SP Europe	**2**	1	1			
Sanofi Pasteur SA	**2**			2		
Sanofi Pharma Bristol-Myers Squibb SNC	**1**				1	
Shire Pharmaceutical Contracts Ltd	**2**	1	1			
Shire Pharmaceuticals Ireland Limited	**3**	1	1	1		
Shire-Movetis NV	**1**		1			
Takeda Global Research and Development Centre (Europe) Ltd	**3**	2	1			
The Medicines Company	**2**	1	1			
Tibotec BVBA	**2**	1	1			
UCB Pharma SA	**1**	1				
Valeant Pharmaceuticals Ltd.	**2**	1	1			
Vertex Pharmaceuticals Incorporated	**1**	1				
ViiV Healthcare UK Ltd	**1**	1				
ViroPharma SPRL	**2**	1	1			
Wyeth Europa Limited	**2**		1	1		
Wyeth Lederle Vaccines S.A.	**6**	1	1	2	2	

Annex 11 - List of due annual reports on deferred measures that have not been submitted in 2013

PIP Number	Product Name	Substances	Company Name	Original MA Date	Annual Report Due Date
EMEA-001149-PIP01-11	Evarrest, Evicel	human fibrinogen / human thrombin	Omrix Biopharmaceuticals SA	06/10/2008	06/10/2013
EMEA-000128-PIP01-07	Victoza	liraglutide	Novo Nordisk A/S	30/06/2009	30/06/2013
EMEA-000128-PIP02-09	Victoza	liraglutide	Novo Nordisk A/S	30/06/2009	30/06/2013
EMEA-000597-PIP02-10	Betmiga	mirabegron	Astellas Pharma Europe B.V.	20/12/2012	20/12/2013
EMEA-000063-PIP01-07	Tredaptive, Trevaclyn	nicotinic acid / laropiprant	Merck Sharp and Dohme (Europe), Inc.	03/07/2008	03/07/2013
EMEA-000153-PIP01-07	Eurartesim	piperaquine phosphate anhydride / dihydroartemisinin	Sigma-Tau SpA	27/10/2011	27/10/2013
EMEA-000054-PIP01-07	Livazo	pitavastatin calcium	Kowa Pharmaceutical Europe Company Ltd	10/08/2010	10/08/2013
EMEA-000300-PIP01-08	Alipza	pitavastatin calcium	Kowa Pharmaceutical Europe Company Ltd	10/08/2010	10/08/2013
EMEA-000301-PIP01-08	Vezepra	pitavastatin calcium	Kowa Pharmaceutical Europe Company Ltd	10/08/2010	10/08/2013
EMEA-000302-PIP01-08	Pitavastatin	pitavastatin calcium	Kowa Pharmaceutical Europe Company Ltd	10/08/2010	10/08/2013
EMEA-000472-PIP01-08	Tesavel	sitagliptin phosphate monohydrate	Merck Sharp and Dohme (Europe), Inc.	10/01/2008	10/01/2013
EMEA-000239-PIP01-08	Vibativ	telavancin	Theravance, Inc.	02/09/2011	02/09/2013
EMEA-000184-PIP01-08	Tobi	tobramycin	Novartis Europharm Limited	20/07/2011	20/07/2013
EMEA-000309-PIP01-08	RoActemra	tocilizumab	Roche Registration Limited	16/01/2009	16/01/2013