10 June 2014
EMA/328413/2013 Corr.2
Human Medicines Development and Evaluation

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 2012

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Human Medicines Special Areas Sector
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1. Synopsis

This Annual Report to the European Commission covers the 6th year of the Paediatric Regulation and follows the "5-year report" published by the European Commission in 2012. New reporting is included on Annual reports on deferrals, completion of PIPs and registration of deadlines to put a medicinal product on the market.

All data confirms 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 2012 and PDCO members are now always involved in such procedures;
- The number of applications and decisions on PIPs and waivers remains stable and there are about 5 times more applications for new medicinal products, compared to that for already authorised medicinal products.

On the research field, results are more visible and positive in many aspects:

- The number of paediatric clinical trial participants has significantly increased to more than 60,000 in 2012, meaning that more children are now enrolled;
- Enpr-EMA is successful in stimulating the creation of new networks and 2 new to be established. Financial resources to support the infrastructure are needed if paediatric research is to be encouraged at EU level;
- New funding for studies into off-patent medicines is planned for 2013 and the priority list has been updated;
- The first inventories of paediatric needs have been finalised in 2012, with a list of cardiovascular paediatric medicines. A second list on anti-infective paediatric medicines will soon be published for consultation and the inventory of paediatric medicines in nephrology is under preparation. This is information for applicants on where the Paediatric Committee sees unmet needs;
- 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 to be made available;
- Annual reports on deferrals indicate that more than half of the Plans progress without major difficulties; this follow-up is an important source of feedback for the Paediatric Committee. The majority of the MAHs are submitting their Annual report on deferrals as requested by the legislation.

More information on paediatric use of medicines is provided to Health Care Professionals and patients:

- 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;
- More than 3200 reports on results of paediatric clinical trial with authorised medicines are readily available in the so-called Article 45 database published by the Agency, and 3000 more are made available gradually;
- The product information of new products include information on whether paediatric development is expected (waiver or deferral information).

- The Agency established and maintains 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:

- Compliance statements are included in marketing authorisations, which means that some paediatric plans are completed and that the relevant information on the use of the medicinal products in children is reflected in the SmPC and in the Patient leaflet; this is necessary to claim the SPC (Supplementary Protection Certificate) extension;
- Marketing Authorisation Holders have received more extensions of the Supplementary Protection Certificates from National Patent Offices.

However there are still issues in a few areas:

- There are fewer late submissions of PIPs or waiver applications, but the median delay is not shorter and some late submissions included either no justification, or unacceptable justifications;
- Some MAHs are not submitting Annual Reports. The tracking of this activity is now fully operational and will be monitored by the Agency;
- About 37% of PIPs have not been completed, despite a completion date for June 2012 or earler, indicating the need for the Agency to monitor more closely this indicator.

Other major projects have been completed, or have significantly progressed in 2012:

- More guidance has been published to help applicants;
- A joint procedure between the PDCO and the Scientific Advice Working Party has been created, and is piloted;
- The PDCO was the first EMA Committee to publish Agendas and Minutes in June 2012.

In 2013, the EMA together with its Paediatric Committee will work on:

- Simplification of applications and Opinions for PIPs, with new template and guidance for the scientific document (parts B-E), simplified key elements (studies) form, and a new simplified template for Annex I of the Opinion;
- More transparency on the activities of the PDCO is planned, including a "summary of the PDCO opinion";
- The expansion of the role of Enpr-EMA in facilitating and coordinating clinical trials in children;
- Increasing the monitoring of completion of PIPs and submission and analysis of the annual report on deferred studies;
- A greater involvement of children and their parents in the opinion-making process;
- Preparing for the elements to be included in the "10-year report" to the EC (Art. 50.3 of the Paediatric Regulation);
- Scientific topics of interest for paediatric medicines development (e.g. extrapolation, formulations, modelling and simulation, new approaches to neonatal medicines development).

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 2012 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 and from 1 January 2011 to 31 December 2011. 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.

2.2. Major changes in the report and results

Some activities have been monitored for the first time in 2012 and are presented:

- 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
- a new register has been set up to record deadlines of the placing on the market.

Data from 2012 confirm that the development of medicinal products is now planned from the start with children in mind. More scientific advices with paediatric questions are issues, with a systematic involvement of the members of the PDCO at centralised level. More studies are completed in line with the agreed paediatric plan (PIPs) leading to more compliance checks. More children are enrolled in clinical trials. More information is provided to the Health care professionals and the patients via regular amendments of the information on the product. More Marketing Authorisation Holders have seen this year their efforts rewarded by extension of the patent of their medicinal products.

Major projects are moving forward: the European network Enpr-EMA has expanded; a first inventory of paediatric needs has been published for cardiovascular medicines, a second one on anti-infective medicines will be soon released and one in nephrology is being prepared.

Overall there is more evidence that the Paediatric Regulation is delivering in its three main areas of paediatric research, information and availability of medicines for children, and that most companies are meeting their obligations, although often with delays. As a consequence, more companies are rewarded with products benefiting from addition protection.

2.3. Data collection

In November 2012, 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 the list of medicinal products that had obtained in 2011 a 6-month extension of the Supplementary Protection Certificate (SPC),and of 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 contribution from 18 out of 27 Member States, and from 16 out of 27 National Patent Offices (NPOs) (see Annex 2).

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 the paediatric development. The advice is provided by the Scientific Advice Working Party of the Committee for Medicinal Products for Human Use (CHMP) and is adopted by the CHMP. For the paediatric requests, members of the PDCO are now routinely involved in the Scientific Advice procedures (see table 2).

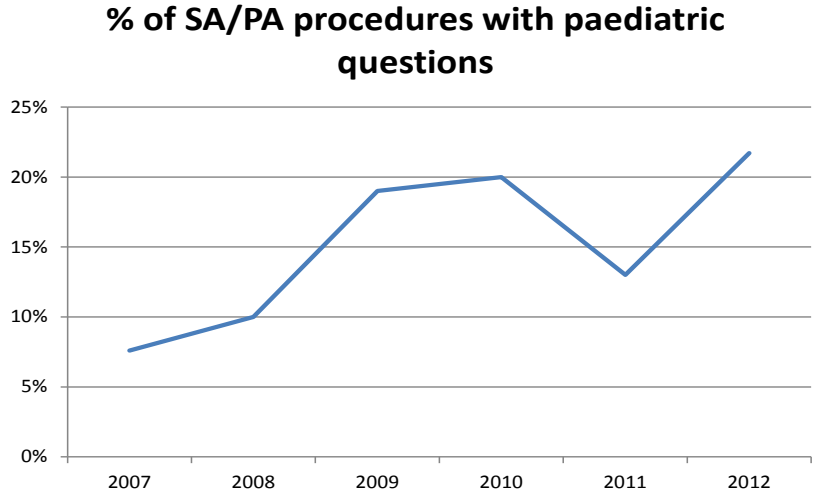
The number of advice procedures including paediatric questions has increased steadily from 2006 to 2012 and particularly from 2011 to 2012 (because of a temporary decrease in 2011: Table 1). The proportion of advices with questions on paediatrics has almost tripled in 6 years, from 7.6% in 2007 to 21.7% in 2012 (Figure 1). This confirms that the paediatric population is increasingly considered as part of the overall development of a medicinal product.

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

	2006	2007	2008	2009	2010	2011	2012
Total number of advice (Scientific Advice and Protocol Assistance)*	259	277	321	388	400	433	420
N. of SA/PA procedures including questions on paediatric development*		21	32	74	80	57	91
Paediatric-only or mixed advice that involved a PDCO member(s) as expert(s)**				68	80	67	94

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

Figure 1 - Scientific Advice and Protocol Assistance in paediatrics



3.1.2. Advice from the National Competent Authorities

Some National Competent Authorities provide scientific advice on paediatric development. In 2011, 21 Member States reported information on scientific advices, while only 14 reported in 2012 (Table 2).

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

Member State	*Paed-only 2011*	*Mixed 2011*	**Total 2011**	*Paed-only 2012*	*Mixed 2012*	**Total 2012**
Austria*	*0*	*0*	**0**	*0*	*0*	**0**
Belgium*	*0*	*5*	**5**	*2*	*3*	**5**
Cyprus*	*0*	*0*	**0**	*0*	*0*	**0**
Czech Republic*	*0*	*0*	**0**	*0*	*0*	**0**
Denmark*	*0*	*2*	**2**	*2*	*1*	**3**
Estonia*	*0*	*0*	**0**	*0*	*0*	**0**
Finland	*0*	*0*	**0**			
France	*1*	*2*	**3**			
Germany*	*0*	*32*	**32**	*2*	*16*	**18**
Hungary	*0*	*0*	**0**			
Ireland	*0*	*0*	**0**			
Italy*	*3*	*1*	**4**	*0*	*2*	**2**
Latvia				*0*	*0*	**0**
Lithuania	*0*	*0*	**0**			
Malta*	*0*	*0*	**0**	*0*	*0*	**0**
Portugal	*0*	*0*	**0**			
Romania	*0*	*0*	**0**			
Slovenia*	*0*	*0*	**0**	*0*	*0*	**0**
Spain*	*1*	*3*	**4**	*0*	*5*	**5**
Sweden*	*3*	*8*	**11**	*0*	*0*	
The Netherlands	*0*	*0*	**0**			
United Kingdom*	*3*	*12*	**15**	*3*	*5*	**8**
Total of reported advices	***11***	***65***	**76**	***9***	***32***	**41**
Total for the 13 MSs who answered in 2011 and 2012*	*10*	*60*	*70*	*9*	*27*	*36*

As compared to 2011, the number of paediatric only or mixed advices given nationally has significantly decreased. This has to be taken with caution as there are also fewer Member States who answered.

3.2. Paediatric Investigation Plans – Waiver

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 some applications may have been withdrawn before the EMA Decision.

Table 3 - Applications and Decisions on Paediatric Investigations plans and Waivers

	2007	2008	2009	2010	2011	2012
Number of Decisions on PIPs and full waivers	**12**	**124**	**189**	**252**	**151**	**134**
Total number of PIPs	2	81	121	201	106	87
PIPs agreed under Article 7 (without waivers)	0	50	73	174	86	70
Article 7 PIPs submitted	*28*	*132*	*142*	*219*	*109*	*89*
PIPs agreed under Article 8 (without waivers)	2	31	43	26	18	17
Article 8 PIPs Submitted	*37*	*81*	*61*	*27*	*20*	*19*
PIPs Agreed for a PUMA*	0	0	5	1	2	0
PIPs for PUMA Submitted	*0*	*11*	*10*	*4*	*0*	*1*
Full waivers	10	43	68	51	45	47
Full Waiver Submitted	*24*	*86*	*88*	*72*	*62*	*75*
Decision on a modification of an agreed PIP	0	8	51	108	153	166
Modifications of an agreed PIP Submitted	*0*	*12*	*88*	*110*	*177*	*200*

* NB: potential PUMAs are also submitted under article 7.

3.2.1. Applications

The number of application is comparable in 2012 to 2011. The relatively low number of applications compared to previous forecasts could be explained by late submissions of PIPs/waivers in the life cycle, i.e. after most of the attrition has occurred.

3.2.2. Opinions

The Decisions issued by the Agency are published in a summarised form and can be found on the following webpage: http://www.ema.europa.eu/htms/human/paediatrics/decisions.htm.

It is planned to increase transparency and publish the full description of the measures (key elements) contained in the opinions in 2013.

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 waiver has been published in 2012. A revision of the list is under discussion.

3.2.4. Modifications of agreed PIPs

Modifications of agreed PIPs (165 positive and 1 negative) are similar to 2011.

As expected, the number of modification is increasing, by 10% in 2012, as the number of medicines with a PIP has increased,.

3.3. Compliance statement included in a marketing authorisation

A compliance check is done at EMA or at NCA level, either as part of validation of applications for marketing authorisation, or variation/extensions, or, on request from the applicant to the PDCO, prior to the submission of such applications.

No Member State reported having checked compliance of completed PIPs. This may be because the National Competent Authorities had delegated to the EMA PDCO, or because Marketing Authorisation Holders have obtained a PDCO Opinion.

Table 4 - PDCO Opinions on compliance and letters on interim compliance check

	2010	2011	2012
PDCO positive Opinions on compliance	9	8	4
Applications for interim compliance check	40	49	51
Letters with positive outcome on interim compliance check	33	42	39
Letters with negative outcome on interim compliance check	0	3	1

3.3.1. Compliance statement for centrally-authorised medicinal products

In 2012, a single company submitted the results of all studies performed in compliance with an agreed PIP submitted in accordance with Article 8 (Table 5).

Table 5 - 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)
Pfizer Limited	Enbrel	Etanercept	31/07/2012	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 was similar to 2011 (8 products). There was no reward granted after the use of article 29 paediatric referral in 2012.

Table 6 - List of companies and products with a compliance statement (authorised through national/decentralised/mutual recognition procedure)

Companies	international non-proprietary name (INN)	Products: invented name
ASA Pharma	acetylsalicylic acid, bisoprolol	Bisoprolol Aspirin
Grünenthal GmbH	tapentadol	Palexia, Palexias, Yantil
Chiesi Pharmaceuticals	beclometasone dipropionate, formoterol fumarate dihydrate	Foster Nexthaler

Companies	international non-proprietary name (INN)	Products: invented name
GmbH		
Mundipharma GmbH, Germany	fluticasone propionate/ formoterol fumarate	Flutiform, Iffeza
Mundipharma AB	formoterol fumarate dihydrate, fluticasone propionate	Flutiform, Iffeza

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 2012, there were more active substances benefited from the 6-month extension. Six were for products that had not been rewarded before. Seven (7) products are mentioned in both the 2011 list and 2012 list because SPC extensions are granted country by country.

Table 7 - List of companies/products which have benefited from 6-months extension of the supplementary protection certificate (SPC) granted by the National Patent Office in 2012

Marketing authorisation holder	Invented name(s)	International non-proprietary name	SPC extension granted in 2012 in	SPC extension pending in
Bristol-Myers Squibb Pharma EEIG	Orencia	Abatacept	Bulgaria Italy Romania	
AstraZeneca AB	Arimidex and associated names	Anastrazole	Rejected in Romania	
Otsuka Pharmaceutical Europe Ltd	Abilify	Aripiprazole		Denmark Germany Italy Romania Sweden The Netherlands United Kingdom
Merck Sharp and Dohme	Cancidas	Caspofungin	Romania	Bulgaria Luxembourg
Sanofi BMS	Plavix and associated names	Clopidogrel	Belgium Denmark Ireland Italy Spain	Austria The Netherlands
Genzyme Europe BV	Cholestagel	Colesevelam		United Kingdom

Marketing authorisation holder	Invented name(s)	International non-proprietary name	SPC extension granted in 2012 in	SPC extension pending in
Pfizer Limited	Enbrel	Etanercept	France Ireland Italy Sweden The Netherlands	Austria Belgium Bulgaria Denmark Germany Luxembourg Spain United Kingdom
Janssen Biologics B.V.	Remicade	Infliximab	Denmark France Italy Luxembourg Sweden The Netherlands	Austria Belgium Germany Spain United Kingdom
Sanofi-Aventis Deutschland GmbH	Lantus Optisulin	Insulin – glargine	Denmark Ireland Italy Sweden	Belgium France Germany Luxembourg Spain United Kingdom
Merck Sharp & Dohme	Singulair	Montelukast	Denmark Germany Italy Luxembourg Spain	
Boehringer	Viramune	Nevirapine	Belgium Denmark Germany Italy Luxembourg Spain The Netherlands United Kingdom	
Merck Sharp & Dohme (Europe) Inc.	Maxalt	Rizatriptan	Belgium Denmark France Germany Ireland Italy Luxembourg Spain Sweden The Netherlands United Kingdom	

Marketing authorisation holder	Invented name(s)	International non-proprietary name	SPC extension granted in 2012 in	SPC extension pending in
Novartis	Zometa and associated names	Zoledronic acid	Romania	

[1,2] Some national patent offices have placed a tick in both columns as the SPC could be requested although timelines might not allow for it. Unless otherwise stated "no SPC" may indicate either that no application has been submitted when the patent qualifies for an SPC, or that no application has been submitted because no SPC was granted.

3.4.2. Orphan Market Exclusivity extension

So far no orphan medicinal product has benefited from this reward.

3.4.3. Paediatric Use Marketing Authorisation

There were no PUMA applied for or granted in 2012.

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

In 2012, there were more centrally authorised medicinal products with added mention on deferral or waiver in the Summary of Product Characteristics (SmPC) than in 2011 (43 for new MA and 7 through variation/extension) (see Table 8).

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

Table 8 - List of centrally authorised products and companies for which a deferral / waiver statement has been included in SmPC

Invented name	International non-proprietary name	Marketing authorisation holder	Waiver stat. added	Deferral stat. added	Procedure (Mark. Author. or variat.)	Date of EU CD
Sepioglin	Pioglitazone	Vaia S.A.	x		MA	09/03/2012
Esmya	Ulipristal	Gedeon Richter Plc.	x		MA	23/02/2012
Signifor	Pasireotide	Novartis Europharm Limited	x		MA	24/04/2012
Pixuvri	Pixantrone dimaleate	CTI Life Sciences Limited	x	x	MA	10/05/2012
Cuprymina	Copper (64cu) chloride	SPARKLE S.r.l.	x		MA	23/08/2012
Eklira Genuair	Aclidinium bromide	Almirall, S.A.	x		MA	20/07/2012
Picato	Ingenol mebutate	LEO Pharma A/S	x		MA	15/11/2012
Pioglitazone Accord	Pioglitazone hydrochloride	Accord Healthcare Limited	x		MA	21/03/2012
Jentadueto	Linagliptin / metformin hydrochloride	Boehringer Ingelheim International GmbH	x		MA	20/07/2012
Pioglitazone Teva	Pioglitazone	Teva	x		MA	26/03/2012

Invented name	International non-proprietary name	Marketing authorisation holder	Waiver stat. added	Deferral stat. added	Procedure (Mark. Author. or variat.)	Date of EU CD
Paglitaz	Pioglitazone	KRKA	x		MA	21/03/2012
Pioglitazone Actavis	Pioglitazone		x		MA	15/03/2012
Zoledronic acid medac	Zoledronic acid	medac GmbH	x		MA	03/08/2012
Zoledronic acid Hospira	Zoledronic acid	Hospira UK Limited	x		MA	19/11/2012
Eylea	Aflibercept	Bayer Pharma AG	x		MA	22/11/2012
Inlyta	Axitinib	Pfizer Limited	x		MA	03/09/2012
Pioglitazone Teva Pharma	Pioglitazone	Teva Pharma B.V.	x		MA	26/03/2012
Seebri Breezhaler	Glycopyrronium bromide	Novartis Europharm Limited	x		MA	28/09/2012
Zoledronic acid Teva Pharma	Zoledronic acid	Teva Pharma B.V	x		MA	16/08/2012
Zoledronic acid Teva	Zoledronic acid	Teva Pharma B.V	x		MA	16/08/2012
Pioglitazone Krka	Pioglitazone	KRKA	x		MA	21/03/2012
Jakavi	Ruxolitinib phosphate	Novartis Europharm Limited	x		MA	23/08/2012
Zoledronic acid Mylan	Zoledronic acid	Mylan S.A.S.	x		MA	23/08/2012
Zoledronic acid Actavis	Zoledronic acid	Actavis Group PTC ehf	x		MA	20/04/2012
XALKORI	Crizotinib	Pfizer Limited	x		MA	23/10/2012
Glidipion	Pioglitazone	Actavis Group PTC ehf	x		MA	15/03/2012
Tovanor Breezhaler	Glycopyrronium bromide	Novartis Europharm Limited	x		MA	28/09/2012
Enurev Breezhaler	Glycopyrronium bromide	Novartis Europharm Limited	x		MA	28/09/2012
Bretaris Genuair	Aclidinium bromide	Almirall, S.A.	x		MA	20/07/2012
Vepacel	Whole virion non-adjuvanted influenza virus, propagated in vero cells (continuous cell line of mammalian origin), inactivated, containing antigen of alvietnamll2031 2004 (h5nl)	Baxter Innovations GmbH		x	MA	17/02/2012
Glybera	Adeno-associated viral vector expressing lipoprotein lipase	uniQure biopharma B.V.		x	MA	25/10/2012

Invented name	International non-proprietary name	Marketing authorisation holder	Waiver stat. added	Deferral stat. added	Procedure (Mark. Author. or variat.)	Date of EU CD
Rienso	Ferumoxytol	Takeda Global Research and Development Centre (Europe) Ltd		x	MA	15/06/2012
Dacogen	Decitabine	Janssen-Cilag International NV		x	MA	20/08/2012
Nimenrix	Meningococcal group a, c, w135 and y conjugate vaccine	GlaxoSmithKline Biologicals S.A.		x	MA	20/04/2012
Zinforo	Ceftaroline fosamil	AstraZeneca AB		x	MA	23/08/2012
NovoThirteen	Catridecacog	Novo Nordisk A/S		x	MA	03/09/2012
Caprelsa	Vandetanib	AstraZeneca AB		x	MA	17/02/2012
Forxiga	Dapagliflozin	Bristol-Myers Squibb/AstraZeneca EEIG		x	MA	12/11/2012
Revestive	Teduglutide	Nycomed Danmark ApS		x	MA	30/08/2012
Fycompa	Perampanel	Eisai Europe Limited		x	MA	23/07/2012
Adcetris	Brentuximab vedotin	Takeda Global Research and Development Centre (Europe) Ltd		x	MA	25/10/2012
Kalydeco	Ivacaftor	Vertex Pharmaceuticals (U.K.) Limited		x	MA	23/07/2012
Constella	Linaclotide	Almirall, S.A.		x	MA	26/11/2012
Rivastigmine 1A Pharma	Rivastigmine	1 A Pharma GmbH	x	x	v	08/11/2012
Rivastigmine Hexal	Rivastigmine	Hexal AG	x	x	v	22/11/2012
Rivastigmine Sandoz	Rivastigmine	Sandoz Pharmaceuticals GmbH	x	x	v	31/10/2012
Procoralan	Ivabradine	Les Laboratoires Servier	x	x	v	25/10/2012
Corlentor	Ivabradine	Les Laboratoires Servier	x	x	v	25/10/2012
Xarelto	Rivarixaban	Bayer Pharma AG	x	x	v	25/05/2012
Pandemrix	Pandemic influenza vaccine (h1n1) (split virion, inactivated, adjuvanted) a/california/7/2009 (h1n1)v like strain (x-179a)	GlaxoSmithKline Biologicals		x	v	24/10/2012

For medicinal products authorised through national/decentralised/mutual recognition procedure, statement on deferral or waiver was added in 11 procedures (7 initial MAs and 4 variations of MA, see Table 9).

Table 9 - 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
Estonia	Medabon	Mifepristone + Misoprostol	Sun Pharmaceutical Industries Europe B.V.	x		MA	08/05/2012
Finland	Sativex sumute suuonteloon	Cannabis sativae folium cum flore extr.spiss, Delta-9-tetrahydrocannabinolum	GW Pharma Ltd	x		MA	22/11/2012
Finland	Pliaglis 70 mg/g + 70 mg/g emulsiovoide	Lidocainum, Tetracainum	Galderma Nordic AB	x		MA	02/07/2012
Finland	Medabon yhdistelmäpakkaus tabletti ja emätinpuikko, tabletti	Mifepristonum, Misoprostolum	Sun Pharmaceutical Industries	x		MA	22/11/2012
Slovenia	Rupafin 1 mg/ml oral solution	Rupatadin fumarate	J.Uriach & Cía., Avda Camí Reial 51-57, Palau, Spain	x		v	25/07/2012
Slovenia	Omnic Ocas 0,4 mg prolonged release tablets	Tamsulosine	Astellas Pharma Europe B.V.,Elisabethhof 19, Leiderdorp, Netherlands	x		v	14/11/2012
Slovenia	TOBRADEX 1 mg/3 mg v 1 g eye ointment	Tobramycin and dexamethasone	S.A. Alcon-Couvreur N.V.,Rijksweg 14, Puurs, Belgium	x		v	01/10/2012
Slovenia	TOBRADEX 1 mg/3 mg v 1 ml eye drops suspension	Tobramycin and dexamethasone	S.A. Alcon-Couvreur N.V.,Rijksweg 14, Puurs, Belgium	x		v	01/10/2012
Sweden	Medabon	Mifepristone + misoprostol	SUN Pharmaceutical Industries Europe B.V	x		MA	02/08/2012
Sweden	Palexia	Tapentadol	Grünenthal GmbH		x	MA	11/11/2012
Sweden	Yantil	Tapentadol	Grünenthal GmbH		x	MA	11/11/2012

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.

Of note in this context, one of the several reasons for the relative lack of success of the PUMA seems to be that pricing may not reflect that paediatric forms are bringing benefit to the patients .

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 DG Research, 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 2012 in advance of the 7th Call of FP7, work programme 2013, for which funding will be provided in 2013.

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

The European network of existing national and European networks, investigators and centres with specific expertise in the performance of studies in the paediatric population is growing. Based on self-assessment, the networks are classified in:

- category 1: networks fulfilling all minimum quality criteria for membership of Enpr-EMA;
- category 2: networks potentially fulfilling all minimum criteria but in need of clarifying some issues before becoming a member of Enpr-EMA;
- category 3: networks not currently fulfilling minimum criteria.

Two (2) new National networks (SwissPedNet, Red SAMID) have joined in 2012, bringing the total numbers to eighteen (18) networks recognised as category 1; 2 recognised as category 2; and 16 recognised as category 3.

Table 10 - Enpr-EMA networks

Type of network	Category 1	Category 2	Category 3
National	NIHR-MCRN, FinPedMed MCRN-NL MICYRN Scotmcn CICPed		IPCRN NCCHD BLF RIPPS Futurenest CR BPDN SwissPedNet Red SAMID
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

Type of network	Category 1	Category 2	Category 3
Stem Cell and Organ Transplantation / Haematology (non malignant) / Haemostaseology	EBMT		IPTA
Respiratory diseases / Cystic Fibrosis	ECFS-CTN		
Cardiovascular diseases / Nephrology			
Psychiatry / Neurology	EUNETHYDIS		
Infectious diseases / Vaccinology	PENTA UKPVG		PENTI
Special Activities / Age groups			
Intensive Care / Pain / Anaesthesiology / Surgery		Network of Excellence for research in paediatric clinical care-NL	
Neonatology	GNN		EuroNeoNet Neo-circulation INN
European Paediatric Pharmacists			
Special Activities (pharmacovigilance, long-term follow up, community paediatricians)	FIMP-MCRN		
Expertise in Clinical Trial Methodology			TEDDY* PRIOMEDCHILD* ECRIN* GRIP*

* Criteria not applicable to these networks

Enpr-EMA does not cover all paediatric therapeutic areas. In 2012, a major activity focused on stimulating new European-wide clinical trial networks in paediatric cardiology, gastroenterology, and diabetes. Task forces and core groups of interested investigators in these three areas were established; for gastroenterology start-up funding for two years was obtained.

Another activity in 2012 focused on involvement of young people in clinical research in line with the PDCO strategy in this area. Engaging young people in clinical research has many benefits including greater understanding of young people's perspectives and improvements in study design and the quality of clinical research. A survey was sent to all 39 members of the European network of paediatric research at the EMA (EnprEMA), to analyse how paediatric networks in Europe support the engagement of young people in research. The results of the survey indicate that, while a majority of paediatric research networks clearly see the needs and benefits of involving young people/families in research activities, only a minority has dedicated resources and strategies to this objective. The need for training on how to establish and maintain young people's advisory groups was clearly expressed. Enpr-EMA, as an umbrella network of existing networks, is well placed to encourage those networks with involvement strategies in place to share these with others in order to increase expertise and knowledge and to ensure ethical, responsible and effective involvement of young people/family in paediatric clinical research. This will be addressed in the next years by Enpr-EMA.

3.7.3. Inventory of paediatric needs

As announced in the previous Annual report, the draft inventory of paediatric medicines in cardiovascular area has been published on the EMA website in August 2012:

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/08/WC500131636.pdf

After a consultation phase ending in October 2012 the inventory of paediatric medicines in cardiovascular area was adopted by the PDCO and will be published in 2013.

The inventory of paediatric medicines in infectious disease has been adopted by the PDCO in 2012. This list will be published in 2013 for public consultation.

The PDCO is working on the inventory of paediatric medicines in nephrology.

3.7.4. National initiatives on paediatric medicines

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

Member state	Incentives and benefits
Austria	Prioritised review of clinical trial applications Clinical trial applications with "Yes" in section F.1.1 of the application form ("trial subjects under 18") are flagged automatically in the national database of the NCA. Applications are then immediately screened by an assessor, and a prioritized scientific review is performed, if necessary.
Italy	Reimbursement of paediatric medicines: Several medicines, not licensed in Italy for specific paediatric indications, have been included in a list according to Italian Law 648. Law 648 allows physicians to prescribe a medicine where no therapeutic alternatives are available, including for paediatric patients, in specific therapeutic indications, and after having received a positive opinion from the Italian Medicine Agency's Commissione Tecnico Scientifica. The medicine will be reimbursed by the National Health System (Servizio Sanitario Nazionale). Law 648 may apply to off-label indications for products marketed in Italy, or for products not (yet) marketed in Italy. Importantly, the inclusion in the Law 648 list does not modify the SmPC and therefore the paediatric indications remain unauthorised and not extendable to other Member States.
Spain	Special measures for pricing of paediatric medicines: Since the entry into force of Royal Decree 16/2012 pharmaceutical forms specifically intended for the treatment of the paediatric population are excluded from the system of prices of reference.
Slovenia	Fee waiver for clinical trials with the paediatric population: EudraCT: 2010-019722-13; sponsor: University of Debrecen, Hungary; INN: daunorubicin, doxorubicin EudraCT: 2012-004270-26; sponsor: Oshadi Drug Administration, Israel; INN: oral insulin

3.8. Authorisation of paediatric clinical trials

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

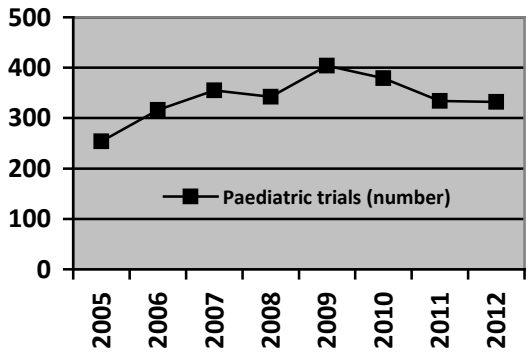
The Agency (with its Scientific Committees) has been contributing to the European Commission guidance on the protocol-related information and on the results concerning paediatric clinical trials to be entered as well as the information to be made public in Eudra-CT. Release of results related information is expected in 2013.

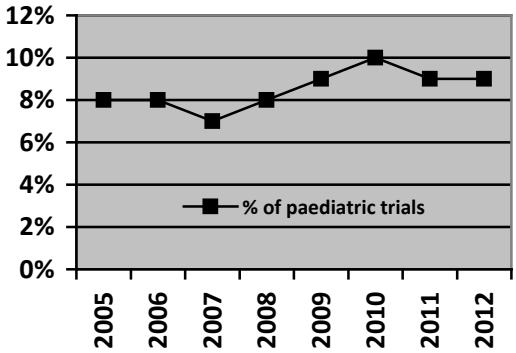
The data presented in the 2 following tables (Table 11 and Table 12) have been extracted from EudraCT. It is important to note that the compilation of most of the data fields in EudraCT is not mandatory, including some that are relevant for paediatric information, and that the input of these data is not performed by the European Medicines Agency.

Table 11 - Paediatric clinical trials by year of authorisation

	2005	2006	2007	2008	2009	2010	2011	2012
Paediatric trials (number)	254	316	355	342	404	379	334	332
Paediatric trials that are part of an agreed PIP* (number)	2	1	2	6	16	30	76	76
*Proportion of paediatric trials that are part of an agreed PIP among paediatric trials**	*1%*	*0%*	*1%*	*2%*	*4%*	*8%*	*23%*	*23%*
Total number of trials (adults and / or children)	3 350	3 979	4 749	4 512	4 445	4 026	3809	3698
Proportion of paediatric trials of all trials	*8%*	*8%*	*7%*	*8%*	*9%*	*10%*	*9%*	*9%*

* This information could only be provided as of 2011.





Source: EudraCT Data Warehouse (6 March 2013)

From the data shown above, the number and proportion of paediatric trials are stable despite the general decrease in numbers of clinical trials in EudraCT (adults and children).

Table 12 - Number of children planned to be enrolled in clinical trials, by age.

Number of subjects	2006	2007	2008	2009	2010	2011	2012
Preterm newborns	0	0	0	207	82	2 115	1474
Newborns	0	98	5	64	169	1 055	1172
Infants and toddlers	330	98	20	54 595	2039	10 798	18 776
Children	2 326	663	200	2 988	2 423	17 091	25 033
Adolescents	368	32 430	205	2 055	4 408	18 203	15 879
Sum of above	**3 025**	**33 289**	**430**	**59 702**	**9 121**	**49 262**	**62 433**
Reference: number of paediatric trials	318	351	340	398	379	330	328
Reference: number trials in PIP	1	2	6	16	30	76	78

Source: EudraCT Data (April 2013). All clinical trials have been reported in this table, including clinical trial for immunological medicinal products.

Since the implementation of the Paediatric Regulation, the number of paediatric study participants in clinical trials has significantly increased to more than 60,000 in 2012, without significant increase in number of trials. The main increase is for children. Some of the apparent increases may be related to the possibility to indicate the age of participants, but overall, there is an increase in the number of paediatric participants.

3.9. Procedures for paediatric use marketing authorisation

An application for a PUMA, for Fluad Paediatric, was submitted to EMA on 13 December 2010. In 2012, the applicant decided to withdraw the marketing authorisation application as it was unable to address the questions of the CHMP within the required timeline. An EMA press release was released in February 2012.

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 1000 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 2012, 4 additional waves (14 to 17) have been agreed, corresponding to 42 active substances . The assessment of the data has been finalised for 34 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.

When regulatory action is necessary MAHs are advised to submit straightaway a variation containing the Article 46 paediatric study(ies)

- For centrally authorised products, 80 procedures of evaluation of studies submitted through this Article have been finalised in 2012. The CHMP recommended a change in the product information in 14 cases, corresponding to 17 medicinal products. The list of products and the resulting amendments of the SmPCs is presented in Annex 5. The proportion of changes in 2012 is slightly lower than in 2011, 17.5% versus 25%.
- For nationally authorised medicinal products, 45 studies were submitted in 2012 and the assessment has been finalised for 14 procedures with 11 public assessment reports. Two recommend changes in product information were adopted (18% in 2012 versus 24% in 2011). The list of assessment reports products and amendments of the SmPCs are 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 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. However, the first medicinal products have only been authorised recently following the completion of a PIP.

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; it is considered that this corresponds approximately to the end of phase 1.

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. This puts the PDCO in a difficult situation as the evaluation may conclude that insufficient or inappropriate studies or trials have been performed (underpowered studies, wrong endpoints, insufficient duration), but the PDCO is unable to request further data for ethical reasons, i.e. to avoid exposing children in repeat trials.

Late submissions of PIP/waiver are reported since 2010 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 were completed.

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Table 13a - Time lag between completion of adult PK studies and submission of PIPs and waivers (months) applications in 2010 and 2011

Delayed applications (submissions 6 months or more later than deadline)	2010	2011
Number of delayed PIP applications	65 (*74%*)	44 (*59%*)
All PIP applications	*88*	*74*
Time lag median (range)	 22	 35 (9-159)
Number of delayed applications for full waiver	26 (*59%*)	13 (*42%*)
All applications for full waiver	*44*	*31*
Time lag median (range)	 18	 35 (9-137)

Source: EMA Paediatric database.

Table 14b - Time lag between completion of adult PK studies and submission of PIPs and waivers (months) agreed in 2012

Delayed applications with Decision given in 2012 (submissions 6 months or more later than deadline)	**2012**
Number of delayed PIP applications	34 (*39%*)
*All **agreed** PIP*	*87*
Time lag median (range)	 35 (9-241)
Number of delayed applications for full waiver	11 (*23.5%*)
*All **agreed** full waiver*	*47*
Time lag median (range)	 61 (19-179)

Source: EMA Paediatric database.

It should be noted that the data reported for 2012 have been calculated in a different way than in 2010 and 2011. While in 2010 and 2011, we looked at late submissions in the mentioned year; in 2012 we looked at decisions made in 2012, independently of the year of submission. As a consequence, PIPs may be mentioned both in 2011 Annual report and in the 2012 Annual report. The 9 concerned PIPs are flagged with a ***** in Annex 7.

In 2012 fewer PIPs were submitted late and this finding is welcome. However the median delay remains identical.

Fewer waivers were submitted late but for those, the delay has almost doubled in 2012.

Among the 34 PIPs submitted more than 6 months after the deadline:

- 17 included a valid justification (50%),
- 1 included a justification that was not acceptable (3%),
- 16 did not include a justification (47%).

Among the 11 waivers submitted late:

- 2 included a valid justification (18%),
- 1 included a justification that was not acceptable (9%),
- 8 did not have any justification (73%).

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 in Annex 7.

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

On the other hand, there are benefits from early dialogue, including a better integration of paediatric needs in adult development including for formulations and pharmaceutical forms, toxicology (reproduction toxicity), animal models and juvenile animal data, modelling and simulation for PK and

pharmacodynamic studies. Discussing the paediatric plan has in fact in some cases helped companies to define their strategy for the adult development.

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

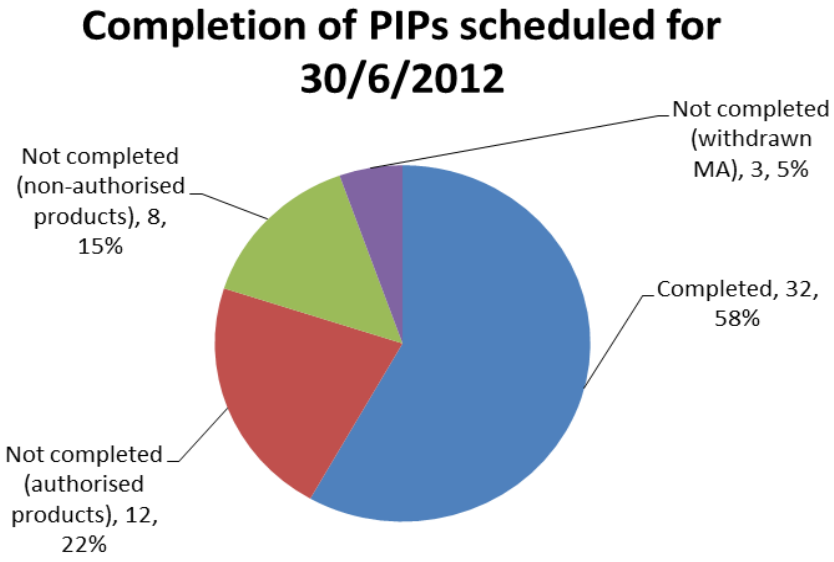
The PIP Decisions include dates of completion.

The Agency made an analysis of the PIPs with a completion date scheduled before 30 June 2012. The cut-off date was chosen as end of June 2012, as applicants must submit the complete study reports within 6 months of completion, and studies (and PIPs) completed after June 2012 might not have been submitted yet. All PIPs that are completed have a PDCO compliance Opinion.

Fifty five (10%) of all 560 PIPs agreed between July 2007 and December 2012 had a date of completion before 30 June 2012. Figure 2 shows that the majority (58%) has indeed been completed; of the remaining 23, 3 are for products whose marketing authorisation has been withdrawn.

The detailed lists are in Annexes 8 and 9.

Figure 2 - PIPs with completion scheduled on or before 30 June 2012



4.3. Validation of applications for marketing authorisation / extension

There were no reports of applications falling under Article 7 or 8 that were validated without having complied with the requirements at the Agency or at national level.

4.4. Compliance with the paediatric requirements and rewards

So far there is no indication that a company has benefited from the reward without having complied with the requirements set out in the Regulation.

4.5. Compliance with the agreed PIP

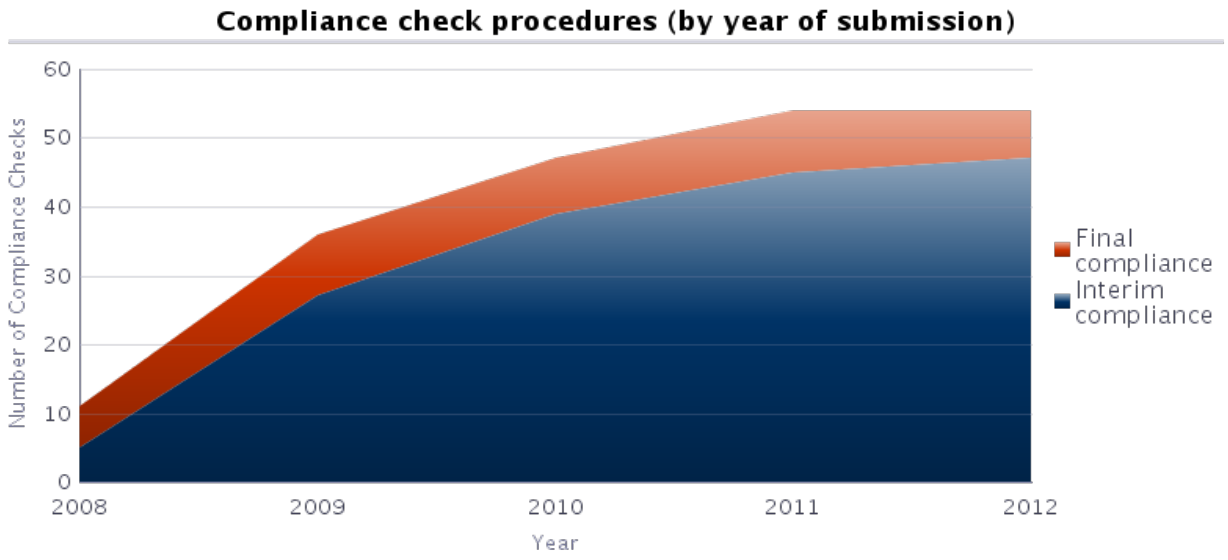
When submitting a regulatory application falling under the scope of Articles 7, 8, or 30 of the Paediatric Regulation, compliance with the agreed PIP will be checked as part of the validation.

Up to 31 December 2012, the EMA has performed a total of 202 compliance check procedures, of which 39 were final/full (i.e. after completion of all measures in the PIP) and 163 were interim (after completion of some but not all measures in the PIP).

From 2008 to 2011 the number of compliance check procedures increased steadily; data from 2012 are stable, compared to 2011 (see Figure 3).

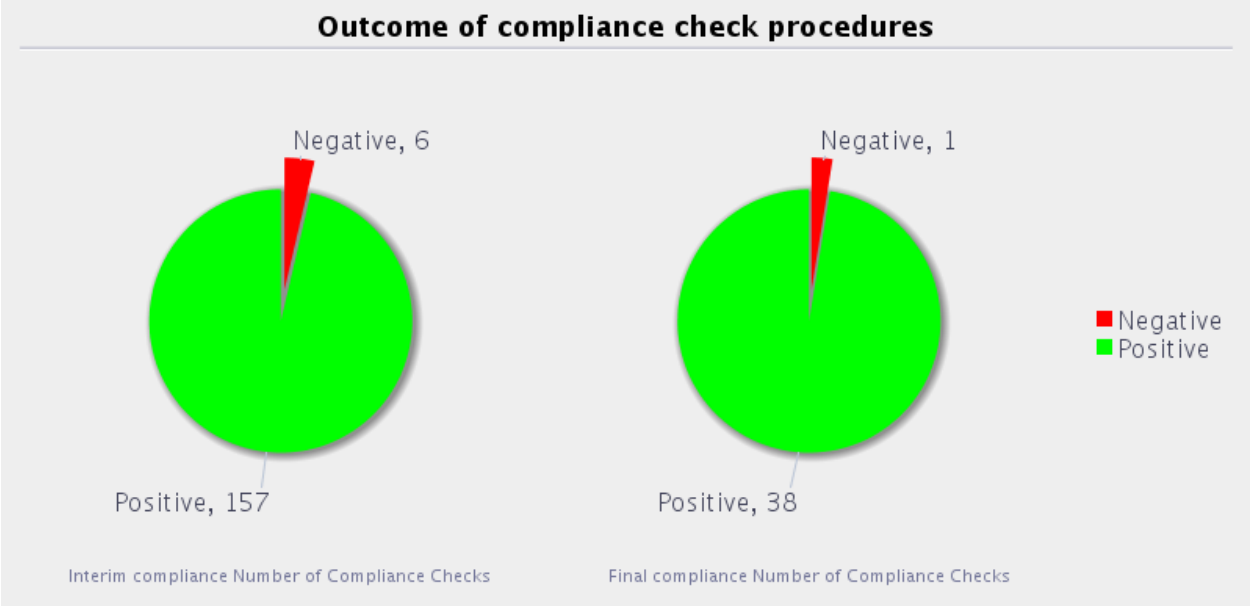
So far, no National Competent Authority has reported the finalisation of a compliance check procedure for a nationally approved product.

Figure 3 - EMA compliance check procedures



Only one final compliance check procedure was negative but was followed by a modification of the agreed PIP for a relatively minor issue, and resulted in a positive opinion (Figure 4).

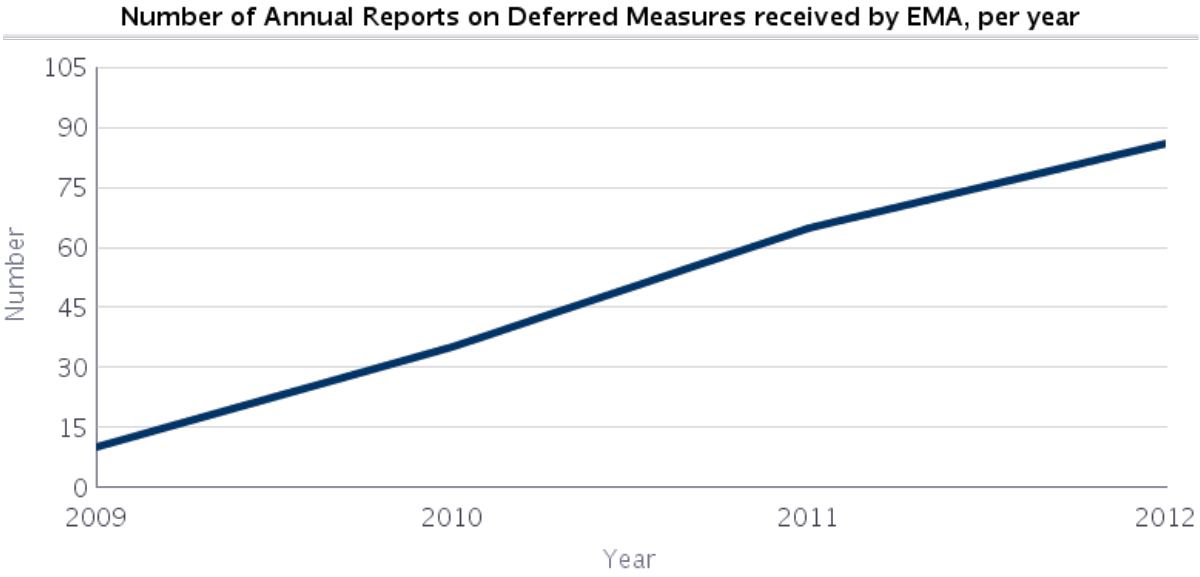
Figure 4 - Compliance check procedures outcome (partial on the left, final on the right)



4.6. Annual reports on deferrals

The number of annual reports on deferred measures (for authorised medicinal products) is increasing every year (Figure 5).

Figure 5 – Trend for Annual reports



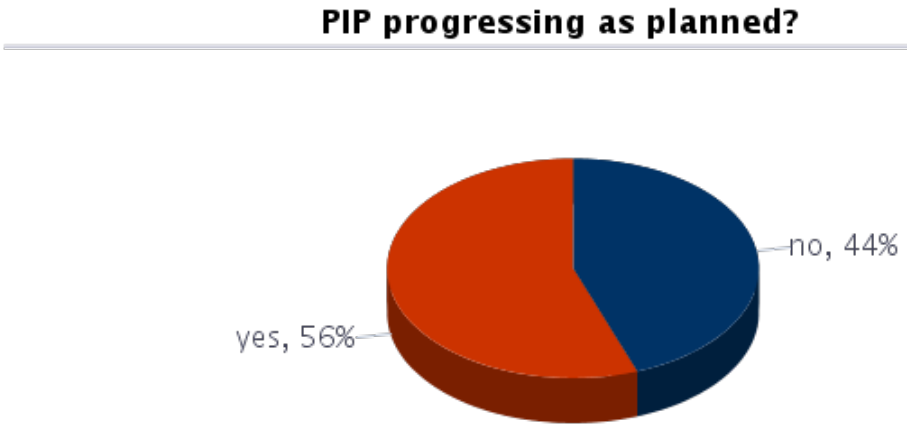
EMA has received 84 annual reports on deferral in 2012 (56 in 2011 and 31 in 2010). The total numbers of annual reports is in table 14, and data are analysed according to whether the PIP is proceeding as planned or not.

Over the years, more than half of the reports stated that the PIP was proceeding as planned (Figure 6). The type of issues is in Table 14. A list of the companies having submitting the annual reports is available in Annex 10.

Table 15 - Annual reports on deferred measures

	2009	2010	2011	2012	Total	% N=196
Number of annual reports indicating no difficulties	**6**	**18**	**41**	**44**	**109**	
Number of annual reports indicating difficulties	**4**	**17**	**24**	**42**	**87**	
Type of issue						
Recruitment difficulties	2	10	15	29	**56**	*28.6%*
Other(s)		9	10	17	**36**	*18.4%*
Refusals/problems with National Competent Authority(ies)				13	**20**	*10.2%*
Safety concerns		5	3		**10**	*5.1%*
Efficacy concerns	2	4	1	2	**9**	*4.6%*
Difficulties in developing age-related formulation(s)		1	3	2	**6**	*3.1%*
Applicant's organizational issues (e.g. acquisitions, mergers, applicant's internal restructuring, etc.)			2		**3**	*1.5%*
Other quality issues				3	**3**	*1.5%*

Figure 6 - 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 Table 15.

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Table 16 - List of companies not submitting annual reports on deferred measures

Applicant	2009	2010	2011	2012	Total
Merck Sharp & Dohme (Europe) Inc.	1	1	2	1	**5**
Novartis (Europharm Limited, Vaccines and diagnostics)		1		2	**3**
GlaxoSmithKline		2	1		**3**
Pfizer Limited		1	2		**3**
Roche Registration Limited		1	1	1	**3**
Novo Nordisk A/S			1	1	**2**
Kowa Pharmaceutical Europe Company Ltd			1	1	**2**
Bristol-Myers Squibb/AstraZeneca		1			**1**
Eli Lilly and Company		1			**1**
Janssen-Cilag International N.V.			1		**1**
Eisai Ltd.			1		**1**
Genzyme Europe B.V.			1		**1**
Sigma-Tau SpA				1	**1**
Takeda Global Research and Dev. Centre (Europe) Ltd				1	**1**
Theravance, Inc.				1	**1**
Totals	**1**	**8**	**11**	**9**	**29**

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

Following a recent 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.

4.7. International exchange of information in view of global development

Under the confidentiality arrangements with the FDA, Japan and Canada, the Agency is holding monthly teleconferences to discuss PIP applications or Written Requests, or any information, with a view to facilitating global development of paediatric medicinal products.

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 2012 to 31 December 2012**.
- 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 2012 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	X	X
Bulgaria		X
Cyprus	X	
Czech Republic	X	
Denmark	X	X
Estonia	X	X
Finland	X	
France		X
Germany	X	X
Greece		
Hungary	X	
Ireland		X
Italy	X	X
Latvia	X	
Lithuania		
Luxembourg		X
Malta	X	
The Netherlands		X
Poland		
Portugal	X	
Romania	X	X
Slovakia		
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	Marketing authorisation (MA) granted through procedure	Date of MA / outcome of procedure	Type of procedure (referring to outcome)
Hungary	ASA Pharma	Bisoprolol Aspirin 5/75mg kapszula	acetylsalicylic acid, bisoprolol	MRP (Mutual recognition)	03/04/2012	Initial MA
Hungary	ASA Pharma	Bisoprolol Aspirin 5/100mg kapszula	acetylsalicylic acid, bisoprolol	MRP (Mutual recognition)	04/04/2012	Initial MA
Hungary	ASA Pharma	Bisoprolol Aspirin 10/75mg kapszula	acetylsalicylic acid, bisoprolol	MRP (Mutual recognition)	05/04/2012	Initial MA
Hungary	ASA Pharma	Bisoprolol Aspirin 10/100mg kapszula	acetylsalicylic acid, bisoprolol	MRP (Mutual recognition)	06/04/2012	Initial MA
Hungary	Grünenthal GmbH	PALEXIAS 25 mg retard tabletta	tapentadol	DC (Decentralised)	11/07/2012	Initial MA
Hungary	Grünenthal GmbH	YANTIL 25 mg retard tabletta	tapentadol	DC (Decentralised)	11/07/2012	Initial MA
Hungary	Chiesi Pharmaceuticals GmbH	Foster Nexthaler 100mcg/6mcg inhalációs por	beclometasone diproprionate, formoterol fumarate dihydrate	DC (Decentralised)	05/11/2012	Initial MA
Romania	Mundipharma GmbH, Germany	FLUTIFORM	fluticasone propionat/ formorterol fumarate	DC (Decentralised)	06/08/2012	Not specified
Romania	Mundipharma GmbH, Germany	IFFEZA	fluticasone propionat/ formorterol fumarate	DC (Decentralised)	06/08/2012	Not specified
Sweden	Mundipharma AB	Flutiform	formoterol fumarate dihydrate, fluticasone propionate	DC (Decentralised)	23/08/2012	Initial MA
Sweden	Mundipharma AB	Iffera	formoterol fumarate dihydrate, fluticasone propionate	DC (Decentralised)	23/08/2012	Initial MA
Sweden	Grünenthal	Palexia	Tapentadol	DC	11/11/2012	Initial MA

Member State	Marketing authorisation holder	Invented name(s)	International non-proprietary name	Marketing authorisation (MA) granted through procedure	Date of MA / outcome of procedure	Type of procedure (referring to outcome)
	GmbH			(Decentralised)		
Sweden	Grünenthal GmbH	Yantil	Tapentadol	DC (Decentralised)	11/11/2012	Initial MA

Annex 4 - List of medicinal products assessed in 2012 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.

International Non-proprietary name	Outcome of assessment	Recommended Change in the Summary of Product Characteristics (and corresponding sections of the Package Leaflet when appropriate)[1]	Years
Alendronic acid	Paediatric information clarified	Sections 4.2 & 5.1	2009-2011
Amikacin	Paediatric information clarified	Sections 4.1, 4.2, 4.4, 4.5, 4.6 & 5.2	2010-2011
Amiodarone	Paediatric information clarified	Sections 4.2, 4.3, 4.4, 5.1 & 5.2	2011
Amlodipine	New indication	Sections 4.2, 5.1 & 5.2	2010-2011
Amoxicillin	Paediatric information clarified	Sections 4.2, 4.4 and 5.2	2010-2012
Baclofen	New indication	Sections 4.1, 4.2 & 4.4	2011
Bisacodyl	New indication	Section 4.2	2010-2011
Calcitonin (salmon synthetic)	No change	Section 4.2	2009-2011
Chondroitin sulfate	Paediatric information clarified	Section 4.2	2011
Clarithromycin	Paediatric information clarified	Sections 4.1 & 4.2	2011
Clobazam	Paediatric information clarified	Section 4.2	2011
Clonidine		Sections 4.2 & 5.1	2011
Diclofenac	Paediatric information clarified	Sections 4.2, 4.3 & 4.8	2011
Ethosuximide	Paediatric information clarified	Syrup formulation Sections 4.2 & 5.1 Capsule formulation Sections 4.2 & 5.1	2011
Famciclovir	Paediatric information clarified	See outcome of Art.30 Procedure in April 2010	2011

[1] 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

International Non-proprietary name	Outcome of assessment	Recommended Change in the Summary of Product Characteristics (and corresponding sections of the Package Leaflet when appropriate)[1]	Years
Felodipine	New study data	Sections 5.1 & 5.2	2010-2011
Fentanyl	Paediatric information clarified	Fentanyl patches Sections 4.1 & 4.2 Fentanyl Injection Sections 4.2, 4.3 & 4.4 Fentanyl Lozenge Sections 4.1, 4.2, 5.1, 5.2 & 5.3	2009-2011
Flumazenil	New indication	Sections 4.1, 4.2 & 5.2	2011
Gentamicin	New safety information	Intravenous and intramuscular use Sections 4.1, 4.2, 4.4, 5.2 Topical otic Section 4.4 Topical use other than otic None Intrathecal use None	2010-2011
Itraconazole	Paediatric information clarified	Sections 4.2, 4.8, 5.1 & 5.2	2011
Levothyroxine	Paediatric information clarified	Section 4.2	2009-2011
Lisinopril	New indication	Sections 4.2, 4.8, 5.1 & 5.2	2009-2011
Mepivacaine	Paediatric information clarified	Section 4.2 & 4.3	2010-2011
Mesalazine	Paediatric information clarified	Section 4.2	2010-2011
Metoclopramide	New safety information	i.v. Form Sections 4.1, 4.2, 4.3, 4.4, 4.8 & 4.9 Oral & Rectal Forms Sections 4.1, 4.2, 4.3, 4.4, 4.8 & 4.9	2008, 2011, 2012
Metronidazole, Metronidazole / Spiramycin	Paediatric information clarified	Sections 4.1, 4.2 & 4.8	2010-2011
Milrinone	New indication	Sections 4.1, 4.2 4.4, 4.8, 5.1, 5.2 & 5.3	2011
Mirtazapine	New study data	Sections 4.2, 4.8 & 5.1	2010-2011
Oxybutynin	Paediatric information clarified	Section 4.1 & 4.4	2010-2011
Paclitaxel	Paediatric information clarified	Section 4.2	2010-2011

International Non-proprietary name	Outcome of assessment	Recommended Change in the Summary of Product Characteristics (and corresponding sections of the Package Leaflet when appropriate)[1]	Years
Propofol	Paediatric information clarified	Sections 4.4 & 5.2	2010-2011
Propranolol	New indication	Sections 4.2 & 4.8	2011
Quinapril	New study data	Sections 5.1 & 5.2	2011-2012
Remifentanil	Paediatric information clarified	Sections 4.1, 4.2, 4.4 & 5.1	2010-2011
Risedronic acid[2]	New study data	Sections 4.2 & 5.1	2010-2011
Timolol	Paediatric information clarified	Sections 4.2, 4.4, 5.1 & 5.2	2011
Topiramate	New study data	Sections 4.4, 4.8 & 5.1	2010-2011
Tranexamic acid	New study data	Section 4.2, 4.3, 4.4, 4.8, 5.1 & 5.2	2010-2011
Triptorelin	Paediatric information clarified	Sections 4.2, 4.4 and 4.8	2010-2011

[2] Covers also the sequential treatment with risedronic acid, calcium and colecalciferol

Annex 5 - List of medicinal products assessed in 2012 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.

International Non-proprietary name	Invented name	Marketing authorisation holders	Recommended change in SmPC[3]
Flutocasine Furoate	Avamys	Glaxo Group Ltd	Sections 4.4, 4.8 & 5.1
Rasburicase	Fasturtec	Sanofi-Aventis Groupe	Sections 4.1 & 5.1
Adefover Dipivoxil	Hespera	Gilead Sciences International Ltd	Sections 4.2 & 5.1

Medicinal products authorised through national / mutual recognition / decentralised procedure

Article 46 work-sharing finalised in 2012 and published

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

- **Actonel (risedronate sodium)**
  End of procedure: 20/12/2012
  Date of publication: 24/01/2013

- **Engerix B**
  End of Procedure: 22/02/2012
  Date of Publication: 02/07/2012

- **Fluarix**

  DE/W/0052/pdWS/001
  End of Procedure: 26/07/2012
  Date of Publication: 25/10/2012

  DE/W/0053/pdWS/001
  End of Procedure: 29/05/2012
  Date of Publication: 28/09/2012

  DE/W/0054/pdWS/001
  End of Procedure: 29/05/2012
  Date of Publication: 28/09/2012

- **Genotropin and associated names (somatropin)**

  DK/W/008/pdWS/003

[3] Section 4.2 Posology and method of administration
Section 5.1 Pharmacodynamics properties
Section 5.2 Pharmacokinetic properties
5.3 Preclinical safety data

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End of Procedure: 27/11/2012
Date of Publication: 24/01/2013

- **Poliorix**
  End of Procedure: 03/09/2012
  Date of Publication: 06/03/2013

- **Priorix Tetra**
  End of Procedure: 12/10/2012
  Date of Publication: 22/11/2012

- **Strattera (atomoxetine)**

  UK/W/010/pdWS/004
  End of Procedure: 08/10/2012
  Date of Publication: 22/11/2012

- **Tetravac and associated names**

  IE/W/0005/pdWS/002
  End of Procedure: 29/03/2012
  Date of Publication: 03/07/2012

- **Voluven (Poly (O-2 hydroxethyl) starch)**
  End of Procedure: 17/10/2012
  Date of Publication: 19/12/2012

Procedures finalised in 2012 resulting in changes to the Product Information following Article 46 work-sharing

Member States	INN	Invented name	Type of change
Finland	Tamsulosini hydrochloridum	Omnic 0.4 depotkapseli	
	Tamsulosini hydrochloridum	Omnic Ocas 0.4 depottabletti	
	TAMSULOSIN HYDROCHLORIDE	Prosurin XL 400 micrograms Capsules	Paediatric information clarified
Slovenia	Tamsulosine	Omnic Ocas 0,4 mg prolonged release tablets	New paediatric study data
Spain	Acid Gadobenic	MULTIHANCE 529 mg/ml SOLUCIÓN INYECTABLE	Paediatric information clarified
	Gadobenate dimeglumine	MULTIHANCE 529 mg/ml SOLUCION INYECTABLE EN JERINGA PRECARGADA	Paediatric information clarified
	Tamsulosin hydrochloride	OMNIC 0,4 mg CAPSULAS DE LIBERACION MODIFICADA	Paediatric information clarified
	Tamsulosin hydrochloride	OMNIC OCAS 0,4 mg COMPRIMIDOS DE LIBERACION PROLONGADA RECUBIERTOS CON PELICULA	Paediatric information clarified
Sweden	benzoyl peroxide, hydrous, adapalene	Tactuo	New paediatric indication
	benzoyl peroxide, hydrous, adapalene	Epiduo	New paediatric indication
	Alfuzosin hydrochloride	Dazular XL 10 mg Tablets	Paediatric information clarified
France	Alfuzosin hydrochloride	Fuzatal XL 10mg prolonged release tablets	Paediatric information clarified

Member States	INN	Invented name	Type of change
Denmark	Alfuzosin hydrochloride	Taurazil SR 5 mg Tablets	Paediatric information clarified
	Alfuzosin hydrochloride	Taurazil XL 10 mg Tablets	Paediatric information clarified
The Netherlands	Alfuzosin hydrochloride	Vasran XL 10 mg prolonged-release tablets	Paediatric information clarified
Germany	Glimepiride	Glimepiride 1mg Tablets	Paediatric information clarified
	Glimepiride	Glimepiride 2mg Tablets	Paediatric information clarified
	Glimepiride	Glimepiride 3mg Tablets	Paediatric information clarified
	Glimepiride	Glimepiride 4mg Tablets	Paediatric information clarified
United Kingdom	Rocuronium bromide	Esmeron Vials, Esmeron 10mg/ml solution for injection	Paediatric information clarified
	Ropinirole hydrochloride	Ropinirole 0.25mg Film-coated Tablets	Paediatric information clarified
	Tamsulosin hydrochloride	Omnic MR,Flomax MR 367mcg Capsules	Paediatric information clarified
	Tamsulosin hydrochloride	Flomaxtra XL 400 micrograms	Paediatric information clarified
	Tamsulosin hydrochloride	Tamurex 400 mcg prolonged release capsules	Paediatric information clarified
	Tamsulosin hydrochloride	Flectone XL 400 microgram prolonged-release tablets	Paediatric information clarified
	Tamsulosin hydrochloride	Tamsulosin 400 microgram Prolonged-release Tablets	Paediatric information clarified
	Tamsulosin hydrochloride	Tamsulosin 400 microgram Prolonged-release Tablets	Paediatric information clarified
	Tamsulosin hydrochloride	Tamsulosin 400 microgram Prolonged-release Tablets	Paediatric information clarified
	Tamsulosin hydrochloride	Tamsulosin 400 microgram Prolonged-release Tablets	Paediatric information clarified
	Tamsulosin hydrochloride	Faramsil 400 microgram Prolonged-release Tablets	Paediatric information clarified

Source: Data received from Member States

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

This list is available at:
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/03/WC500139602.pdf

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

These lists only include 2012 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.

Company name	Substances	Opinion)	Delay (months)**
GE Healthcare	Ioforminol	PIP agreed	18
Mpex London Limited	Levofloxacin hemihydrate	PIP agreed	30
Novartis Europharm Ltd.	serelaxin	PIP agreed	241
Glaxo Group Limited	migalastat hydrochloride*	PIP agreed	31
Roche Products Limited	lebrikizumab	PIP agreed	9
Gilead Sciences International Limited	Elvitegravir*	PIP agreed	41
GlaxoSmithKline Trading Service Limited	N-[3-[3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]- 6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-D]pyrimidin-1(2H)-yl]phenyl]acetamide, dimethylsulfoxide solvate*	PIP agreed	21
GlaxoSmithKline Trading Service Limited	N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzene sulfonamide, methanesulfonate salt*	PIP agreed	11
Takeda Global Research & Development Centre (Europe) Ltd.	lurasidone hydrochloride*	PIP agreed	70
Navidea Biopharmaceuticals Limited	Dextran, 3 [(2-aminoethyl)thio]propyl 17-carboxy-10,13,16-tris(carboxymethyl)-8-oxo-4-thia-7,10,13,16-tetraazaheptadec-1-yl 3-[[2-[[1-imino-2-(D-mannopyranosylthio)ethyl]amino]ethyl]thio]propyl ether	PIP agreed	42
Bayer Pharma AG	Regorafenib	PIP agreed	39
Exelixis, Inc.	Cabozantinib*	PIP agreed	34
UCB Pharma S.A.	olokizumab	PIP agreed	13
Celgene Europe Limited	Apremilast*	PIP agreed	57
BAXTER Innovations GmbH	Vonicog alfa (recombinant human von Willebrand Factor)*	PIP agreed	11
Ablynx NV	ALX-0081, anti-von Willebrand Factor Nanobody	PIP agreed	20
Pfizer Limited	tofacitinib (as tofacitinib citrate)*	PIP agreed	24
Merck Sharp & Dohme (Europe), Inc.	atorvastatin calcium / ezetimibe	Full waiver granted	50
GALDERMA R&D	Ivermectin	Full waiver granted	36

Company name	Substances	Opinion)	Delay (months)**
Endocyte Europe B.V.	Folic acid	Full waiver granted	118
Endocyte Europe B.V.	etarfolatide	Full waiver granted	118
Takeda Pharma A/S	azilsartan medoxomil / chlortalidone	Full waiver granted	31
Merck Sharp & Dohme (Europe), Inc.	atorvastatin / sitagliptin	Full waiver granted	27
AB Science	masitinib mesylate	Full waiver granted	37
Intendis GmbH	Deoxycholic acid	Full waiver granted	33
Menarini Ricerche SpA	Tramadol hydrochloride / Dexketoprofen (as trometamol)	Full waiver granted	19

* PIPs mentioned in both the 2011 Annual report (late submission in 2011) and the 2012 Annual report (late submission in any year resulting in a decision in 2012). This is due to a change in the calculation between 2011 and 2012 (see title *4.1. Submission of PIP and waiver applications to the PDCO*).

** 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.

Annex 8 - List of PIPs completed

Substances	Company	Latest PIP number	Condition / Indication
Valsartan	Novartis Europharm Limited	EMEA-000005-PIP01-07-M01	Hypertension
Ezetimibe	Merck Sharp & Dohme Limited	EMEA-000007-PIP01-07-M02	Treatment of hypercholesterolaemia
Losartan potassium	Merck Sharp & Dohme (Europe) Inc.	EMEA-000008-PIP01-07	Hypertension Proteinuria
caspofungin acetate	Merck Sharp & Dohme (Europe) Inc.	EMEA-000010-PIP01-07	Fungal infections
Montelukast sodium	Merck Sharp & Dohme Inc.	EMEA-000012-PIP01-07-M01	Chronic Asthma Episodic (Intermittent) Asthma Persistent Asthma Seasonal Allergic Rhinitis
r-L-Asparaginase	medac Gesellschaft für klinische Spezialpräparate	EMEA-000013-PIP01-07-M01	Acute lymphoblastic leukaemia (ALL) Lymphoblastic lymphoma (LBL)
zoledronic acid	Novartis Europharm Limited	EMEA-000024-PIP01-07	Osteogenesis imperfecta
Darunavir	Janssen-Cilag International NV	EMEA-000038-PIP01-07-M03	Human immunodeficiency virus-infection
ribavirin	Schering-Plough Europe	EMEA-000070-PIP01-07	Rebetol is intended for use, in a combination regimen with peginterferon alfa-2b, for the treatment of children and adolescents 3 years of age and older, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for serum HCV-RNA.
Peginterferon alfa-2b	Schering-Plough Europe	EMEA-000071-PIP01-07	peginterferon alfa-2b is intended for use, in a combination regimen with ribavirin, for the treatment of children and adolescents 3 years of age and older, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for serum HCV-RNA.
atorvastatin calcium	Pfizer Limited	EMEA-000073-PIP01-07	Heterozygous hypercholesterolaemia
Rizatriptan benzoate	Merck Sharp & Dohme (Europe) Inc.	EMEA-000084-PIP02-10	Treatment of migraine
Soya-bean oil, refined,	Baxter World	EMEA-000112-	Parenteral Nutrition

Substances	Company	Latest PIP number	Condition / Indication
Ph. Eur. / Olive oil, refined, Ph. Eur. / Glucose monohydrate, Ph. Eur. / Sodium glycerophosphate, hydrated, Ph. Eur. / Magnesium acetate tetrahydrate, Ph. Eur. / Calcium chloride dihydrate, Ph. Eur. / Potassium acetate, Ph. Eur. / Sodium chloride, Ph. Eur. / Valine, Ph. Eur. / Tyrosine, Ph. Eur. / Tryptophan, Ph. Eur. / Threonine, Ph. Eur. / Taurine, Ph. Eur. / Serine, Ph. Eur. / Proline, Ph. Eur. / Phenylalanine, Ph. Eur. / Ornithine HCl / Methionine, Ph. Eur. / Lysine monohydrate / Leucine, Ph. Eur. / Isoleucine, Ph. Eur. / Histidine, Ph. Eur. / Glycine, Ph. Eur. / Glutamic acid, Ph. Eur. / Cysteine / Aspartic acid, Ph. Eur. / Arginine, Ph. Eur. / Alanine, Ph. Eur.	Trade SPRL	PIP01-07-M01	
abatacept	Bristol-Myers Squibb Pharma EEIG	EMEA-000118-PIP01-07-M01	Juvenile Idiopathic Arthritis (JIA)
Antigen of pre-pandemic strain* A/Vietnam/1203/2004 *propageted in Vero cells (continuous cell line of mammalian origin)	Baxter Innovations GmbH	EMEA-000156-PIP01-07-M02	Influenza infection caused by an influenza strain contained in the vaccine or related to a strain contained in the vaccine
Human Normal Immunoglobulin	LBF Biotechnologies	EMEA-000167-PIP01-07-M02	Neonatal heamolytic disease (ABO-Rh incompatibility)
Estradiol / Nomegestrol	N.V. Organon	EMEA-000250-PIP01-08-M02	Pregnancy in healthy females
Vaccinum poliomyelitidis inactivatum stirpe 3 (Saukett) / Vaccinum pertussis sine cellulis ex	Sanofi Pasteur MSD SNC	EMEA-000278-PIP01-08-M01	For the active immunisation against infectious diseases caused by Haemophilus influenzae type b, Corynebacterium diphtheriae, Clostridium tetani, Bordetella pertussis and

Substances	Company	Latest PIP number	Condition / Indication
elementis praeparatum adsorbatum (FIM) / Vaccinum haemophili type b conjugatum / Vaccinum poliomyelitidis inactivatum stirpe 2 (MEF 1) / Vaccinum poliomyelitidis inactivatum stirpe 1 (Mahoney) / Vaccinum pertussis sine cellulis ex elementis praeparatum adsorbatum (PRN) / Vaccinum pertussis sine cellulis ex elementis praeparatum adsorbatum (FHA) / Vaccinum pertussis sine cellulis ex elementis praeparatum adsorbatum (PT) / Vaccinum tetani adsorbatum / Vaccinum diphtheriae adsorbatum			poliovirus types 1, 2 and 3.
anastrozole	AstraZeneca AB	EMEA-000283-PIP01-08	Treatment of short stature in pubertal boys with growth hormone deficiency, in combination with exogenous growth hormone Treatment of testotoxicosis
Etanercept	Pfizer Limited	EMEA-000299-PIP01-08-M03	Treatment of chronic idiopathic arthritis (including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylarthritis and juvenile idiopathic arthritis). Treatment of plaque psoriasis
Human Papillomavirus1 Type 18 L1 protein / Human Papillomavirus1 Type 16 L1 protein / Human Papillomavirus1 Type 11 L1 protein / Human Papillomavirus1 Type 6 L1 protein	Sanofi Pasteur MSD SNC	EMEA-000375-PIP01-08-M02	Gardasil is indicated for the prevention of premalignant genital lesions (cervical, vulvar, vaginal, anal, perineal, perianal, penile), cervical, anal, perineal, and perianal cancer, and external genital warts (condyloma acuminata) causally related to Human Papillomavirus (HPV) types 6, 11, 16 and 18. The indication is based on the demonstration of efficacy of qHPV vaccine in adult females 16 to 26 years of age and males 16 to 26 years of age and on the demonstration of immunogenicity of qHPV vaccine in 9- to 15-year-old children and adolescents.
Peginterferon alfa-2b	Schering-Plough Europe	EMEA-000384-PIP01-08	Chronic viral hepatitis C

Substances	Company	Latest PIP number	Condition / Indication
insulin glargine	Sanofi-Aventis Deutschland GmbH	EMEA-000387-PIP01-08	Treatment of type 1 diabetes mellitus
Midazolam (as the Hydrochloride salt)	Auralis Limited	EMEA-000395-PIP01-08	Epileptic seizures
insulin glargine	Sanofi-Aventis Deutschland GmbH	EMEA-000396-PIP01-08	Treatment of type 1 diabetes mellitus
Imatinib mesilate	Novartis Europharm Limited	EMEA-000463-PIP01-08-M03	Treatment of Philadelphia chromosome (BCR-ABL translocation)-positive acute lymphoblastic leukaemia Treatment of dermatofibrosarcoma protuberans Treatment of hypereosinophilic syndrome and/or chronic eosinophilic leukaemia with FIP1L1-platelet-derived growth factor receptor alpha gene re-arrangement Treatment of kit (CD 117)-positive gastrointestinal stromal tumours Treatment of myelodysplastic / myeloproliferative diseases associated with platelet-derived growth factor receptor gene re-arrangements
Propranolol hydrochloride	PIERRE FABRE DERMATOLOGIE	EMEA-000511-PIP01-08-M03	Treatment of haemangioma
Colesevelam	Genzyme Europe B.V.	EMEA-000543-PIP01-09	Heterozygous familial hypercholesterolaemia
Infliximab	Centocor B.V.	EMEA-000549-PIP01-09-M01	Ulcerative colitis
Clindamycin Phosphate / Tretinoin	MEDA Pharma GmbH & Co. KG	EMEA-000892-PIP01-10	Acne vulgaris
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	Prevention of Rotavirus infection
Misoprostol	Ferring pharmaceuticals A/S		Induction of labour

Annex 9 - List of PIPs not completed by the agreed date (scheduled for completion by 30/06/2012)

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 have the information.

Substances	Invented name	Company	Latest PIP number	Comments
Dexamethasone / Ciprofloxacin hydrochloride	CILODEX	Alcon Pharma GmbH	EMEA-000444-PIP01-08	
Motavizumab	not available at present	Abbott Laboratories Limited	EMEA-000352-PIP01-08-M01	
docetaxel	TAXOTERE	AVENTIS PHARMA SA	EMEA-000029-PIP01-07	
Mercaptopurine monohydrate	not applicable	Nova Laboratories Limited	EMEA-000350-PIP01-08	
Estradiol / Nomegestrol (acetate)*	not available at present	NV Organon (part of Schering Plough)	EMEA-000658-PIP01-09	
Sodium bituminosulphonate / Clindamycin phosphate	Ichthoseptal N	ICHTHYOL - GESELLSCHAFT Cordes, Hermanni & Co. (GmbH & Co.) KG	EMEA-000532-PIP01-09	
CYSTEAMINE HYDROCHLORIDE	CYSTADROPS	ORPHAN EUROPE SARL	EMEA-000322-PIP01-08	Modification (M02) ongoing / on timelines
Hydrocortisone / Calcipotriol Hydrate	Picato®	LEO Pharma A/S	EMEA-000277-PIP01-08	
Skimmed cow's milk powder	Diallertest	DBV Technologies	EMEA-000201-PIP01-08-M01	
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	

Substances	Invented name	Company	Latest PIP number	Comments
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	MA withdrawn
Split influenza virus, inactivated containing antigen equivalent to A/California/7/2009 (H1N1)-like strain (A/California/7/2009)), non-adjuvanted	Panenza (INN: Pandemic Influenza vaccine (H1N1) (split virion, inactivated))	Sanofi Pasteur SA	EMEA-000670-PIP01-09-M02	
Paracetamol, Eur. Ph.		Baxter World Trade SA/NV	EMEA-000130-PIP01-07	
Everolimus	Afinitor, Votubia	Novartis Europharm Ltd	EMEA-000019-PIP02-07-M02	
Vandetanib		AstraZeneca AB	EMEA-000052-PIP01-07	
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	
L-Tryptophan / L-Serine / L-Lysine acetate (corresponds to L-Lysine) / L-Histidine / Glycine / L-Alanine / L-Valine / L-Threonine / Taurine / L-Proline / L-Phenylalanine / L-Methionine / L-Leucine / L-Isoleucine / Glycyl-L-Tyrosine (corresponds to Glycine and L-Tyrosine) / L-Arginine hydrochloride (corresponds to L-Arginine) / L-Alanyl-L-Glutamine (corresponds to L-Alanine and L-Glutamine) / N-Acetyl-L-Cysteine (corresponds to L-Cysteine)	Neoven	Fresenius Kabi Deutschland GmbH	EMEA-000042-PIP01-07-M01	

Substances	Invented name	Company	Latest PIP number	Comments
Glucose (monohydrate)	-	Cblaya & Mhuguet S.L.	EMEA-000221-PIP01-08	PUMA
Titanium dioxide / Bisoctrizole	Not available at present	ORFAGEN	EMEA-000585-PIP01-09	
thrombin alfa		Bayer HealthCare AG	EMEA-000163-PIP01-07	MA withdrawn
Human normal immunglobulin	HyQvia 100 mg/ml solution for infusion	Baxter Innovations GmbH	EMEA-000872-PIP01-10-M01	
Formoterol fumarate / Mometasone furoate	not available at present	Merck Sharp & Dogme (Europe) Inc.	EMEA-000025-PIP01-07-M01	MA withdrawn
Oseltamivir Phosphate	Tamiflu	Roche Registration Ltd	EMEA-000365-PIP01-08-M04	Modification (M05) ongoing

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

Number of annual reports submitted	Total	2012	2011	2010	2009
Company	**196**	**86**	**65**	**35**	**10**
Novartis (Europharm+Vaccines)	**22**	8	8	5	1
Janssen-Cilag (incl. Biologics)	**15**	7	4	2	2
Glaxo Group Limited	**14**	8	5	1	
Merck Sharp and Dohme (Europe), Inc.	**14**	3	3	5	3
Bayer Schering Pharma AG	**12**	3	4	5	
Pfizer (incl. Wyeth)	**12**	5	4	3	
Bristol-Myers Squibb Pharma EEIG	**10**	7	2	1	
Roche Registration Ltd	**8**	3	3	1	1
Boehringer Ingelheim International GmbH	**7**	2		2	3
Amgen Europe B.V	**6**	3	2	1	
Grünenthal GmbH	**6**		6		
AstraZeneca AB	**5**	2	2	1	
Gilead Sciences International Limited	**5**	3	2		
Johnson & Johnson PRD	**5**	1	1	3	
AbbVie Limited	**4**	2	2		
Les Laboratoires Servier	**4**	2	2		
N.V. Organon	**4**	2	2		
Shire Pharmaceuticals (incl. Shire-Movetis)	**4**	3	1		
Centocor B.V.	**3**	1	1	1	
Eli Lilly and Company	**3**	2	1		
Laboratoire HRA Pharma	**3**	1	1	1	
Novo Nordisk A/S	**3**	1	1	1	
Sanofi Pharma	**3**		2	1	
ALEXION EUROPE SAS	**2**	1	1		
Eisai Ltd.	**2**	2			
FAES FARMA, S.A.	**2**	1	1		
Genzyme Europe B.V.	**2**	1		1	
Pharming Group N.V.	**2**	1	1		
Rapidscan Pharma Solutions (RPS) EU Ltd	**2**	1	1		
Astellas Pharma Europe B.V.	**1**	1			
BIAL - Portela & Ca, SA	**1**	1			
GW Pharma Ltd	**1**		1		
Otsuka Pharmaceutical Europe Ltd.	**1**	1			
SP Europe	**1**	1			
Takeda Global Research and Development Centre (Europe) Ltd	**1**	1			
The Medicines Company	**1**	1			
Tibotec BVBA	**1**	1			
Valeant Pharmaceuticals Ltd.	**1**	1			
ViroPharma SPRL	**1**	1			

AMENDED

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

Year	PIP Number	Product Name	Substances	Company Name	Original MA Date	PIP decision date	Annual Report Due Date
2009	EMEA-000279-PIP01-08	Isentress	raltegravir	Merck Sharp & Dohme (Europe), Inc.	20/12/2007	19/05/2009	20/12/2009
2010	EMEA-000200-PIP01-08	Onglyza	Saxagliptin	Bristol-Myers Squibb/AstraZeneca EEIG	01/10/2009	07/09/2009	01/10/2010
	EMEA-000689-PIP01-09	Byetta	exenatide	Eli Lilly and Company	20/11/2006	30/11/2009	20/11/2010
	EMEA-000160-PIP01-07	Pandemrix, Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted)	Purified antigen fractions of inactivated split virion Influenza A/Vietnam/1194/2004 (H5N1)	GlaxoSmithKline Biologicals S.A.	19/10/2009	24/04/2009	19/10/2010
	EMEA-000472-PIP01-08	Tesavel	Sitagliptin phosphate monohydrate	Merck Sharp and Dohme (Europe), Inc.	10/01/2008	27/03/2009	10/01/2010
	EMEA-000599-PIP01-09	Focetria and associated names, Aflunov and associated names	Influenza virus surface antigens (haemagglutinin and neuraminidase)* of H5N1 strain * propagated in eggs	Novartis Vaccines and Diagnostics S.r.l.	19/10/2009	05/08/2009	19/10/2010
	EMEA-000671-PIP01-09	Revatio	Sildenafil citrate	Pfizer Limited	28/10/2005	17/03/2010	28/10/2010
	EMEA-000434-PIP01-08	Volibris	ambrisentan	Glaxo Group Limited	21/04/2008	04/11/2009	21/04/2010

Year	PIP Number.	Product Name	Substances	Company Name	Original MA Date	PIP decision date	Annual Report Due Date
	EMEA-000309-PIP01-08	Tocilizumab Roche	Tocilizumab	Roche Registration Limited	16/01/2009	25/03/2009	16/01/2010
2011	EMEA-000709-PIP01-09	Inovelon	rufinamide	Eisai Ltd.	16/01/2007	27/08/2010	16/01/2011
	EMEA-000174-PIP01-07	Mozobil	Plerixafor	Genzyme Europe B.V.	31/07/2009	23/02/2009	31/07/2011
	EMEA-000170-PIP01-07	Revolade	Eltrombopag	GlaxoSmithKline Trading Services Limited	11/03/2010	14/10/2008	11/03/2011
	EMEA-000311-PIP01-08	Stelara	ustekinumab	Janssen-Cilag International NV	16/01/2009	04/02/2009	16/01/2011
	EMEA-000128-PIP01-07	Victoza	Liraglutide	Novo Nordisk A/S	30/06/2009	28/11/2008	30/06/2011
	EMEA-000469-PIP01-08	Ecalta	anidulafungin	Pfizer Limited	20/09/2007	31/03/2010	20/09/2011
	EMEA-000191-PIP01-08	Vfend	voriconazole	Pfizer Limited	19/03/2002	31/03/2010	19/03/2011
	EMEA-000054-PIP01-07, EMEA-000300-PIP01-08, EMEA-000301-PIP01-08, EMEA-000302-PIP01-08	Alipza, Vezepra, Liv azo, Pitavastatin	Pitavastatin calcium	Kowa Pharmaceutical Europe Company Ltd	10/08/2010	24/06/2008	10/08/2011
	EMEA-000063-PIP01-07	Pelzont, Tredaptive, Trevaclyn	Laropiprant / nicotinic acid	Merck Sharp and Dohme (Europe), Inc.	03/07/2008	23/06/2008	03/07/2011
	EMEA-000472-PIP01-08	Tesavel	Sitagliptin phosphate monohydrate	Merck Sharp and Dohme (Europe), Inc.	10/01/2008	27/03/2009	10/01/2011

Year	PIP Number.	Product Name	Substances	Company Name	Original MA Date	PIP decision date	Annual Report Due Date
	EMEA-000309-PIP01-08	Tocilizumab Roche	Tocilizumab	Roche Registration Limited	16/01/2009	25/03/2009	16/01/2011
2012	EMEA-000472-PIP01-08	Tesavel	Sitagliptin phosphate monohydrate	Merck Sharp and Dohme (Europe), Inc.	10/01/2008	27/03/2009	10/01/2012
	EMEA-000054-PIP01-07, EMEA-000300-PIP01-08, EMEA-000301-PIP01-08, EMEA-000302-PIP01-08	Alipza, Vezepra, Livazo, Pitavastatin	Pitavastatin calcium	Kowa Pharmaceutical Europe Company Ltd	10/08/2010	24/06/2008	10/08/2012
	EMEA-000019-PIP02-07	Votubia, Afinitor and associated names	Everolimus	Novartis Europharm Limited	02/09/2011	05/12/2008	02/09/2012
	EMEA-000599-PIP01-09	Focetria and associated names, Aflunov and associated names	Influenza virus surface antigens (haemagglutinin and neura-minidase)* of H5N1 strain * propagated in eggs	Novartis Vaccines and Diagnostics S.r.l.	19/10/2009	05/08/2009	19/10/2012
	EMEA-000128-PIP01-07	Victoza	Liraglutide	Novo Nordisk A/S	30/06/2009	28/11/2008	30/06/2012
	EMEA-000309-PIP01-08	Tocilizumab Roche	Tocilizumab	Roche Registration Limited	16/01/2009	25/03/2009	16/01/2012
	EMEA-000153-PIP01-07	Eurartesim	Piperaquine phosphate anhydride / Di-hydroartemisinin	Sigma-Tau SpA	27/10/2011	20/04/2009	27/10/2012

Year	PIP Number.	Product Name	Substances	Company Name	Original MA Date	PIP decision date	Annual Report Due Date
	EMEA-000237-PIP01-08	Edarbi, Ipreziv	Azilsartan medoxomil	Takeda Global Research and Development Centre (Europe) Ltd	07/12/2011	15/06/2009	07/12/2012
	EMEA-000239-PIP01-08	Vibativ	Telavancin	Theravance, Inc.	02/09/2011	14/07/2009	02/09/2012