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Report to the European Commission

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

Year 2017

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[1] REGULATION (EC) No 1901/2006 of the EUROPEAN PARLIAMENT AND OF THE COUNCIL on medicinal products for paediatric use (Regulation (EC) No 1901/2006 Regulation (EC) No 1902/2006)

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Acronyms, abbreviations

CHMP	Committee for Medicinal Products for Human Use
CML	Chronic myelogenous leukaemia
EC	European Commission
EMA, the Agency	European Medicines Agency
INN	International non-proprietary name
MA	Marketing authorisation
MAH	Marketing authorisation holder(s)
MS	Member States
NCA	National Competent Authorities
NPO	National patent offices
PA	Protocol assistance
Paediatric Regulation	REGULATION (EC) No 1901/2006 of the EUROPEAN PARLIAMENT AND OF THE COUNCIL on medicinal products for paediatric use
PDCO	Paediatric Committee
PIP	Paediatric investigation plan
PUMA	Paediatric use marketing authorisation
SA	CHMP scientific advice
SAWP	Scientific Advice Working Party
SPC	Supplementary protection certificate

1. Introduction

1.1. Scope of the report

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

Article 50(1) states:

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

This report covers year 2017 and lists the companies benefiting from and infringing the regulation.

1.2. Data collection and methodology

In October 2017 the Agency contacted the national patent offices (NPO) of each Member State (MS) with regards to the medicinal products that had obtained a six-month extension of the supplementary protection certificate (SPC) in 2017.

The Agency received contributions from the following Member State NPOs: Austria, Belgium, Bulgaria, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden.

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

In January 2018, companies identified as potentially infringing the Paediatric Regulation in 2017 with regard to non-completion of a PIP by the agreed date and non-submission of an annual report on deferred measures by the due date, were given an opportunity to provide comments on the finding before publication of the identified infringement. All information received by 15 February 2018 was considered for finalisation of this report.

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

2.1. Scientific advice

2.1.1. Advice from the EMA

In accordance with Article 26 of the Paediatric Regulation, the Agency provides free scientific advice (SA) on any question related to paediatric development of a medicinal product. The advice is prepared by the Scientific Advice Working Party (SAWP) and is adopted by the Committee for Medicinal Products for Human Use (CHMP). For the requests on paediatric development, members of the paediatric committee (PDCO) routinely contribute as experts to the provision of scientific advice through the SA procedures (Table 1).

The number of SA procedures including paediatric questions has been increasing steadily from the implementation of the Paediatric Regulation. In 2017, 20% of the requests for scientific advice or protocol assistance (PA) were of paediatric relevance. PDCO members are involved in procedures relating to paediatric development and, in 2017, PDCO members were also involved in procedures that did not directly include paediatric questions but paediatric development could be affected.

Table 1 - Scientific advice and protocol assistance, incl. follow-ups (by the EMA, SAWP and CHMP, p/a 2009-2016)

	2009	2010	2011	2012	2013	2014	2015	2016	2017
Total no. of advice (SA and PA)	388	400	433	420	473	551	510	582	630*
No. of SA/PA/qualification of biomarker procedures that included questions on paediatric development	74	80	57	91	96	97	109	142	127
Paediatric-only or mixed advice that involved PDCO members as experts	68	80	55	91	93	88	97	138	138

Source: EMA databases. *Includes also HTA parallel advice and qualification of biomarker procedures

2.2. Rewards

2.2.1. Extensions of the supplementary protection certificate

Extensions of the supplementary protection certificate are granted by National Patent Offices therefore the data provided in this report relies on the information provided by these offices. This report provides data only for SPC extensions that have been granted, unlike in years prior to 2015 when pending SPC extensions were also reported. Furthermore, products may be mentioned in annual reports of several years because SPC expiration (and therefore extension) may not be simultaneous in all EU countries, and therefore a product may obtain SPC extension in different years in the various countries.

In 2017, 22 active substances benefited from the six-month extension (see Table 2).

Table 2 - List of companies/products receiving six-month extension in 2017

Company	**Invented name(s)**	**INN**	**SPC extension granted in 2017**
Bristol-Myers Squibb Pharma EEIG	Orencia	Abatacept	Czech Republic
Genzyme Corporation	Cholestagel	Colesevelam	Germany
Merck Sharp & Dohme	Ezetrol and associated names	Ezetimibe	Austria Belgium Hungary Slovakia Slovenia
Novo Nordisk A	Tresiba	Insulin degludec	Belgium Bulgaria Denmark Estonia Germany Italy Sweden
Sanofi Pasteur MSD	Gardasil	Vaccine against human papillomavirus	Austria Belgium Greece Italy Spain
Les Laboratoires Servier	Corlentor/ Procoralan	Ivabradine	Austria
AstraZeneca AB	Crestor and associated names	Rosuvastatin	Hungary
AbbVie Ltd	Humira	Adalimumab	Belgium Bulgaria
GSK	Menveo	Meningococcal Group A, C, W-135 and Y Conjugate Vaccine	Austria Finland Ireland Italy
Novartis	Certican/Afinitor	Everolimus	Austria Belgium Czech Republic Greece Ireland Poland Romania Spain

Company	Invented name(s)	INN	SPC extension granted in 2017
MSD	Emend	Aprepitant	Austria Belgium Finland Greece Italy Poland Romania Spain
Astellas	Vesicare and associated names	Solifenacin	Austria Germany Ireland Poland Spain Sweden
Tibotec BVBA on behalf of Janssen-Cilag International NV	Prezista	Darunavir	Austria Belgium Germany
Bristol-Myers Squibb	Reyataz	Atazanavir	Bulgaria Denmark Ireland Italy France Netherlands Portugal Romania Slovenia Spain Sweden

Company	Invented name(s)	INN	SPC extension granted in 2017
Genentech	Avastin	Bevacizumab	Austria Cyprus Czech Republic Denmark Hungary Ireland Italy Latvia Lithuania Netherlands Slovakia Slovenia Sweden
Novartis	Ilaris	Canakinumab	Cyprus Denmark Ireland Italy Netherlands Poland Portugal Romania Slovakia Slovenia Sweden
Biogen	Tysabri	Natalizumab	Denmark Hungary Ireland Italy Sweden
Laboratoire Theramex		Nomegestrol acetate and estradiol	Austria Denmark Finland Ireland Italy Portugal Sweden

Company	Invented name(s)	INN	SPC extension granted in 2017
Janssen	Simponi	Golimumab	Cyprus Denmark Ireland Italy France Latvia Lithuania Netherlands Portugal Romania Slovenia
Sanofi Pasteur	Hexacima	Diphtheria toxoid, tetanus toxoid, pertussis antigens, hepatitis B surface antigen (rDNA), poliovirus (inactivated) and haemophilus type b polysaccharide conjugate	Denmark Italy Netherlands Sweden
Amgen	Mimpara	Cinacalcet	Ireland Italy Portugal Sweden
Gilead	Stribild	Elvitegravir/cobicistat/ emtricitabine/tenofovi r disoproxil as fumarate	Ireland Sweden

Source: NPO survey

2.2.2. Orphan market exclusivity extension

In 2017, two orphan medicinal products have benefited from a two-year extension of their respective market exclusivity:

- Inovelon by Eisai for the treatment of seizures associated with Lennox-Gastaut Syndrome in paediatric patients 1 year of age and older;
- Tasigna by Novartis for adult and paediatric patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in the chronic phase, paediatric patients with chronic phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib.

2.3. Paediatric use marketing authorisation

One new paediatric use marketing authorisation (PUMA) is pending an EC decision in 2017:

- Alkindi (hydrocortisone) by Diurnal Ltd. received a positive CHMP opinion in December 2017 for replacement therapy of adrenal insufficiency in infants, children and adolescents.

2.4. Placing on the market

The Agency continues to maintain the "Register of deadlines to put a medicinal product on the market" (Article 33 of the Paediatric Regulation), established in 2012. It lists the two-year deadlines by which marketing authorisation holders (MAH) have to place their medicinal products on the market following completion of an agreed paediatric investigation plan (PIP) and obtaining a paediatric indication. The register includes information on the fulfilment of this requirement. This information is either provided voluntarily by MAHs or following requests by the Agency after expiration of the deadline.

Link to the register:
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/03/WC500139602.pdf

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

3.1. 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 a waiver no later than upon completion of the human pharmacokinetic (PK) studies in adults specified in Section 5.2.3 of Part I of Annex I to Directive 2001/83/EC, except when duly justified.

Late submissions are being reported since 2010 (Table 3) for applications with a delay greater than six months. From 2014 only those considered by the PDCO as not justified are being reported.

Table 3 - Time lag six months or longer between completion of adult PK studies and submission of PIP or waiver application

Procedure	2010	2011	2012	2013	2014	2015	2016	2017
PIPs (% of total granted)	65 (74%)	44 (59%)	34 (39%)	18 (20%)	12 (13%)	7 (10%)	20 23%)	24 (28%)
Full waivers (% of total granted)	26 (59%)	13 (42%)	11 (23%)	6 (11%)	4 (8%)	4 (8%)	14 (27%)	14 (16%)

Source: EMA Paediatric database

In 2017 a total of 87 PIPs received a positive opinion and 86 full product-specific waivers were granted.

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

3.2. Completion of PIPs

The EMA decisions on PDCO opinions contain the expected date of PIP completion.

For the analysis of timely completion, the PIPs with an expected completion date until 30 June 2017 were reviewed. This cut-off date was chosen to account for the fact that applicants must submit the completed study reports within six months of completion (Art. 46) and studies (and PIPs) completed after June 2017 may not have been subjected to a final compliance check.

In total, 261 PIPs were scheduled to finish by 30 June 2017; of those, 150 (57%) were completed; of the remaining 111 that have not been completed 31 do not have a valid justification (e.g. a modification to amend the date of completion is pending/ongoing or development has been discontinued etc). The detailed list is provided in Annex II.

3.3. Annual reports on deferrals

According to Article 34.4 of the Paediatric Regulation, MAHs should submit an annual report to the Agency providing an update on progress of deferred paediatric studies in accordance with the EMA decision agreeing the PIP and granting a deferral. In 2017 the EMA received 203 annual reports on deferred measures. Four companies did not submit their annual report on deferred measures due in 2017.

The list of companies that did not submit one or more annual reports is included in Table 4.

Table 4 - List of companies not submitting annual reports on deferred measures

Company	2011	2012	2013	2014	2015	2016	2017
Aastrom Biosciences DK Aps					1		
Actelion Registration Ltd						1	1
Aegerion Pharmaceuticals						1	1
AMAG Pharmaceuticals, Inc.					1		1
Amgen Europe B.V.			1				
Clinigen Healthcare Ltd						1	
Clinuvel (UK) Limited					1		
Eisai Ltd.	1					1	
Forest Laboratories Limited				1	1		
Genzyme Europe B.V.	1						
GlaxoSmithKline	1						
Janssen-Cilag International N.V.	1				1		
Kowa Pharmaceutical Europe Company Ltd	1	1	4				
Merck Sharp & Dohme (Europe) Inc.	2	1	2				
Novartis (Europharm Limited, Vaccines and diagnostics)		2	1				
Novo Nordisk A/S	1	1	2				
N.V. Organon						1	
Nycomed Danmark ApS						1	
Omrix Biopharmaceuticals SA			1		1		
Pfizer Limited	2						
Pharmaxis Pharmaceuticals Limited					1		
Roche Registration Limited	1	1	1		1		
Seqirus S.r.l.						1	
Sigma-Tau SpA		1	1		1		
Takeda Global Research and Dev. Centre (Europe) Ltd		1			1		
Teva Pharma GmbH						1	
Theravance, Inc.		1	1				
Totals	**11**	**9**	**14**	**1**	**11**	**8**	**3**

Source: EMA database (PedRA)

The complete list of annual reports that were not received is to be found in Annex III.

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

This list includes only applications for which a decision on a PIP or a waiver was adopted by the European Medicines Agency in 2017; applications that were withdrawn or whose discussion is ongoing are not listed.

The number of months of delay is calculated from the date of the completion of PK studies in adults as declared by the applicant in the application for a PIP or a product-specific waiver request.

The below table shows the 2017 agreed PIPs or waivers submitted with a significant delay for which none or acceptable (by the PDCO) justification, was provided. The timing of submission should not be later than the end of healthy subject or patient PK, which can coincide with the initial tolerability studies, or the initiation of the adult phase-II studies (proof-of-concept studies). In cases where a phase II study in adults is already completed by the time of the PIP submission, the submission is in principle considered delayed unless justified. Further information on the timing of a PIP application can be found on the EMA website.

Company	Substance	Application type
Jazz Pharmaceuticals Ireland Limited	Liposomal combination of cytarabine and daunorubicin	PIP
Cleveland BioLabs Inc	Entolimod	PIP
Novimmune B.V	emapalumab	PIP
BioMarin International Limited	Vosoritide	PIP
Incyte Corporation	(Z)-N-(3-bromo-4-fluorophenyl)-N'-hydroxy-4-(2-(sulfamoylamino)ethylamino)-1,2,5-oxadiazole-3-carboximidamide	PIP
Akcea Therapeutics (UK) Limited	A phosphorothioate oligonucleotide targeted to apolipoprotein C-III [ISIS 304801]	PIP
GeNeuro SA	Recombinant humanised IgG4 monoclonal antibody against MSRV-Envelope protein (GNbAC1)	PIP
Bellicum Pharma Ltd.	Expanded donor-derived allogenic T cells transduced with the retroviral vector expressing the transgenes for inducible caspase9 and the truncated CD19 selectable marker	PIP
AbbVie Ltd	Venetoclax	PIP
TRACON Pharma Limited	carotuximab	PIP
Akebia Therapeutics, Inc.	vadadustat	PIP

Company	Substance	Application type
Shire Pharmaceuticals Ireland Limited	maribavir	PIP
Merck Sharp & Dohme (Europe), Inc	Varicella-zoster virus (inactivated)	PIP
Novartis Europharm Limited	Autologous T cells transduced with lentiviral vector containing a chimeric antigen receptor directed against CD19	PIP
Kite Pharma EU B.V.	Autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor	PIP
Infant Bacterial Therapeutics AB	Lactobacillus reuteri	PIP
Sanofi Pasteur Inc.	N. meningitidis serogroup W polysaccharide conjugated to tetanus toxoid / N. meningitidis serogroup Y polysaccharide conjugated to tetanus toxoid / N. meningitidis serogroup C polysaccharide conjugated to tetanus toxoid / N. meningitidis serogroup A polysaccharide conjugated to tetanus toxoid	PIP
Orchard Therapeutics Ltd.	Autologous CD34+ hematopoietic stem cells transduced ex vivo with EFS lentiviral vector encoding for the human ADA gene	PIP
Kiadis Pharma Netherlands B.V.	T-lymphocytes enriched leukocyte preparation depleted ex vivo of host host-alloreactive T cells using photodynamic treatment	PIP
Lupin (Europe) Ltd.	Mexiletine hydrochloride	PIP
AbbVie Ltd	Venetoclax	PIP
Adimmune Corporation	Influenza virus surface antigens (haemagglutinin) of strain B (Yamagata lineage) / Influenza virus surface antigens (haemagglutinin) of strain A (H3N2) / Influenza virus surface antigens (haemagglutinin) of strain A (H1N1) / Influenza virus surface antigens (haemagglutinin) of strain B (Victoria lineage)	PIP

Company	Substance	Application type
Seqirus UK Limited	Influenza virus surface antigens (haemagglutinin and neuraminidase) of strain B (Victoria lineage) / Influenza virus surface antigens (haemagglutinin and neuraminidase) of strain B (Yamagata lineage) / Influenza virus surface antigens (haemagglutinin and neuraminidase) of strain A (H3N2) / Influenza virus surface antigens (haemagglutinin and neuraminidase) of strain A (H1N1)	PIP
GeNeuro SA	Recombinant humanised IgG4 monoclonal antibody against MSRV-Envelope protein (GNbAC1)	PIP
Pharmexon Consulting s.r.o.	Meldonium dihydrate	Waiver
Aquinox Pharmaceuticals (Canada) Inc.	(1S, 3S, 4R)-4-[(3aS, 4R, 5S,7aS)-4-(aminomethyl)-7a-methyl-1-methylidene-octahydro-1H-inden-5-yl]-3-(hydroxymethyl)-4-methylcyclohexan-1-ol; acetic acid salt	Waiver
Sylentis SAU	Small interfering RNA targeting human TRPV1	Waiver
Titan Pharmaceuticals Inc.	Buprenorphine hydrochloride	Waiver
Novartis Europharm Ltd	alpelisib	Waiver
Edge Therapeutics, Inc.	Nimodipine	Waiver
Ultragenyx Pharmaceutical Inc.	Burosumab	Waiver
Pharmaceutical Works Polpharma SA	Indapamide / Ramipril	Waiver
ERREKAPPA EUROTERAPICI S.p.A.	Amlodipine / Candesartan	Waiver
CIPROS S.r.l.	Amlodipine / Perindopril	Waiver
Neopharmed Gentili S.r.l	Ezetimibe / Rosuvastatin (calcium)	Waiver
ERREKAPPA EUROTERAPICI S.p.A.	Amlodipine / Rosuvastatin	Waiver
Biogen Idec Limited	Opicinumab	Waiver
Mundipharma Research Limited	Methylphenidate (hydrochloride)	Waiver

Source: EMA database PedRA

Annex II. List of PIPs not completed by the agreed date until 30 June 2017

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 been informed by the sponsor accordingly. For the purpose of this analysis, a PIP is considered completed if there has been a positive final compliance check by the EMA/PDCO..

Procedure number	Substance(s)	Invented name	Company
EMEA-000029-PIP01-07	docetaxel	TAXOTERE	AVENTIS PHARMA SA
EMEA-000658-PIP01-09	Estradiol / Nomegestrol	N/A	NV Organon (part of Schering Plough)
EMEA-000532-PIP01-09	Sodium bituminosulphonate / Clindamycin phosphate	Ichthoseptal N	ICHTHYOL -GESELLSCHAFT Cordes, Hermanni & Co. (GmbH & Co.) KG
EMEA-000130-PIP01-07	Paracetamol, Eur. Ph.	N/A	Baxter World Trade SA/NV
EMEA-000221-PIP01-08	Glucose (monohydrate)	N/A	Cblaya & Mhuguet S.L.
EMEA-000163-PIP01-07	thrombin alfa	N/A	Bayer HealthCare AG
EMEA-000651-PIP01-09-M02	Cholic acid	N/A	FGK Representative Service GmbH
EMEA-000982-PIP01-10	Furosemide	N/A	PonsPharma Inc.
EMEA-000487-PIP01-08	bromocriptine mesilate	Cycloset	VeroScience EU Ltd
EMEA-000337-PIP01-08	Grass Pollen Preparation	N/A	Allergopharma J. Ganzer KG
EMEA-001069-PIP01-10	secretin	Safinea	Repligen Europe Limited
EMEA-001298-PIP01-12	Azithromycin	AZYTINN	Only for children pharmaceuticals
EMEA-001134-PIP01-11	Chimeric monoclonal anti-Shiga toxin (Stx) antibodies cαStx1 and cαStx2	Shigamabs	Albany Regulatory Consulting Limited
EMEA-001324-PIP01-12-M01	Glibenclamide	GLIBENTEK	AMMTeK
EMEA-001156-PIP01-11-M07	rdESAT-6 (recombinant dimer of 6 kD early secretory antigenic target)/ rCFP-10 (recombinant 10 kD culture filtrate protein)	N/A	Statens Serum Institut

Procedure number	Substance(s)	Invented name	Company
EMEA-000044-PIP01-07	TGplPTH1-34	N/A	Kuros Biosurgery International AG
EMEA-001120-PIP01-10	Budesonide	Budiair and associated names	Neurosis Consortium
EMEA-001513-PIP01-13	Estetrol & Levonorgestrel	N/A	Estetra S.A.
EMEA-001599-PIP01-13	Ibuprofen (sodium dihydrate)	N/A	Proveca Limited
EMEA-001057-PIP01-10-M01	(S)-3'-(OH)-desazadesferrithiocin-polyether, magnesium salt (FBS0701)	N/A	Shire Pharmaceutical Development Ltd
EMEA-001238-PIP01-12	Alpha tocotrienol quinone	Vincerinone	Edison Orphan Pharma BV
EMEA-001352-PIP01-12-M01	Metformin hydrochloride	EX404 Metformin HCl 650 mg Effervescent granules	EffRx Pharmaceuticals SA
EMEA-000281-PIP01-08-M02	huMAb IGF-1R - A Recombinant Human Monoclonal Antibody to the Insulin-Like Growth Factor-1 Receptor	N/A	Roche Registration Limited
EMEA-000488-PIP02-11	Rubidium-82	CardioGen-82	Advanced Accelerator Applications
EMEA-001314-PIP01-12	Dinutuximab beta / Chimeric anti-disialoganglioside (GD2) monoclonal antibody (ch14.18/CHO)	N/A	APEIRON Biologics AG
EMEA-000649-PIP01-09	Taspoglutide	N/A	Ipsen Pharma
EMEA-001490-PIP01-13	Cholera Vaccine	N/A	PaxVax Inc.
EMEA-000973-PIP01-10-M03	recombinant human N-acetylgalactosamine-6-sulfatase	Vimizim (elosulfase alfa)	BioMarin Europe Limited
EMEA-001133-PIP01-11	Trivalent, seasonal, recombinant influenza hemagglutinin vaccine	FluBlok	Protein Sciences Europa

Procedure number	Substance(s)	Invented name	Company
EMEA-000389-PIP01-08-M01	N-[4-(3-amino-1H-indazol-4 yl) phenyl]-N1-(2-fluoro-5-methylphenyl) urea	N/A	AbbVie Ltd
EMEA-000711-PIP01-09	Morphine hydrochloride	N/A	EPMC Pharma SPRL

Annex III. List of due annual reports on deferred measures that have not been submitted in 2017

Procedure number	Invented name	Substance	Company name	Original MA Date	Annual report due date
EMEA-000373-PIP02-09	Rienso	Ferumoxytol	AMAG Pharmaceuticals, Inc.	15/06/2012	15/06/2017
EMEA-000997-PIP01-10	Uptavi	selexipag	Actelion Registration Ltd	12/05/2016	12/05/2017
EMEA-001124-PIP01-10	Lojuxta	Lomitapide	Aegerion Pharmaceuticals	31/07/2013	31/07/2017