Year	Procedure(N / DC / MRP)	Marketing Authorisation Holder	Invented name	Active substance (INN)	Paediatric indication	Member State
			0,005%, XALATAN		reflux disease Treatment of endoscopically-proven erosive reflux oesophagitis Long-term management of patients with healed oesophagitis to prevent relapse Children > 4 years old In combination with antibiotics in the treatment of duodenal ulcer caused by Helicobacter pylori Reduction of elevated intraocular pressure in paediatric patients with elevated intraocular pressure and paediatric glaucoma	
2011	NATIONAL	Antigen International Limited	Antigen metoclopramide injection bp 10mg/2ml	Metoclopramide hydrochloride	Not reported	United Kingdom
2011		Glaxosmithkline AB, Sweden	Zofran, 4 mg, 8 mg Film-coated tablet tablet,	Ondansetron	Barn Profylax och behandling av illamående och kräkningar inducerade av kemoterapi hos barn ≥ 6 månader. Profylax och behandling av postoperativt illamående och kräkningar hos barn ≥ 1 månad.	Sweden

Year	Procedure(N / DC / MRP)	Marketing Authorisation Holder	Invented name	Active substance (INN)	Paediatric indication	Member State
2011	N & MRP	Tillomed Laboratories Limited, Synthon Bv	Oxybutynin hydrochloride tablets 2.5, 5mg, urimin tablets 5mg	Oxybutynin hydrochloride	Not reported	United Kingdom

7.3. New route of administration or new pharmaceutical form for paediatric use

Summary:

- Overall the medicines for which Member States (12 in total) have reported the variation to authorise a new route of administration, or a new pharmaceutical form, correspond to medicines with an agreed PIP (7 out of the 11 active substances), that underwent an Article 29 referral procedure (section 5.) or that have been captured in Article 45 (section 8.1.2.).
- For in total 11 active substances, new pharmaceutical forms and / or new routes of administration were becoming available since coming into force of the Paediatric Regulation. In the majority, this was linked to requirements under the Paediatric Regulation.

Table 20: List of paediatric relevant line extensions (addition of new route of administration or a new pharmaceutical form) authorised in Member States.

Year	Procedure? (N / DC / MRP)	Marketing authorisation holder	Invented name	Active substance (INN)	Paediatric formulation / route of administration	Member States
2010		Pfizer Corporation Austria GmbH	Sortis and associated names	Atorvastatin	Chewable tablets	Austria, Cyprus, Czech Republic, Estonia, Lithuania, Slovenia, Spain, United Kingdom
2011	DCP	Sanofi Pasteur SA	Pediacel	DTP/Hib/Polio vaccine	New route of administration, Prefilled syringe	Poland, United Kingdom
2007	N	AstraZeneca AB	Nexium and associated names	Esomeprazole	Paediatric formulation: Granules for oral suspension in sachet	Sweden
2011		Abbott Laboratories	Brufen	Ibuprofen*	New paediatric formulation: oral suspension	Slovenia
2009	MRP	Merck Sharp & Dohme	Cozaar and associated	Losartan	Paediatric formulation:	Cyprus, Estonia, Italy,

Year	Procedure? (N / DC / MRP)	Marketing authorisation holder	Invented name	Active substance (INN)	Paediatric formulation / route of administration	Member States
			names		Powder for oral solution, oral suspension	Spain, United Kingdom,
2009	DCP	Merck Santé, s.a.s.	Glucophage	Metformin hydrochloride*	New paediatric formulation: Powder for oral solution in sachets	Poland, Sweden
2008		GlaxoSmithKline GmbH & Co. KG	Priorix-Tetra	MMRV vaccine*		Italy
2009		Merck Sharp & Dohme GmbH	Singulair	Montelukast	Granules, Chewable tablet	Austria, Czech Republic, Lithuania
2011	MRP/RUP	Merck Sharp & Dohme	Maxalt	Rizatriptan	Tablet, oral lyophilisate, oral use	Lithuania
2009		Ferring	Zomacton	Somatropin*		Italy
2010	MRP	Novartis Pharma GmbH	Diovan and associated names	Valsartan	Paediatric formulation: oral solution, divisibility of the tablet	Austria, Cyprus, Czech Republic, Estonia, Finland, Italy, Romania, Slovenia, Spain, Sweden, United Kingdom

* No agreed PIP available

7.4. Variation to include statement on waiver or deferral

- The statement on a waiver or deferral would be added to the section 5.1 of the SmPC.
- Data were provided by only 6 Member States and in each case, for no more than 1 year in between 2009 and 2011. Information from the UK on 2 active substances for which statements on a waiver were included had been included in the 2010 Report to the European Commission (Table 7, p 13).
- The EMA Report to the European Commission (2010) had identified 2 nationally authorised medicinal products, for which the statement on deferral and / or waiver had been inadvertently omitted. Since, the statement could be added in a variation for 1 medicine (Sativex [Tetranabinex / Nabidiolex]).

7.5. Variation to include paediatric dosing information or recommendations

Summary:

- The statement on a waiver or deferral would be added to the section 4.2 of the SmPC.
- In total 9 Member States provided information (219 data entries) covering the years 2007 to 2011, corresponding to in total 80 active substances. Scrutinising the data, some data entries were for medicines that had no relevant use in the paediatric population and therefore no dosing information. No all data entries reported the year of the variation.
- The number of active substances were summarised per year of the variation and whether there was an agreed PIP and therefore a link to the Paediatric Regulation, see Table 8 in core report (section 5.1).

7.6. Variation with paediatric data linked to off label use included into SmPC

No Member State presented data specifically on this question.

7.7. Variations under Article 36.1.2 - data of completed PIP, which study results failed to lead to a paediatric indication

Table 21: Variations assessing paediatric data that were in compliance with a completed, agreed PIP, but which study results did not lead to any paediatric indication

No.	Procedure? (N / DC / MRP)	INN (Invented Name)	Marketing authorisation holder	Condition that was targeted in the PIP but no paediatric use but was authorised	Year of variation	Member State(s) reporting variation
1	MRP, N	Anastrozole (Arimidex)	AstraZeneca AB	Treatment of short stature in pubertal boys with growth hormone deficiency, in combination with exogenous growth hormone, Treatment of testotoxicosis	2009	Spain, Sweden, united Kingdom
2	MRP	Montelukast (Singulair and associated names)	Merck Sharp and Dohme	Treatment of episodic (intermittent) asthma (6 months to less than 6 years)	2010	Slovenia, Spain, Sweden, United Kingdom
3	MRP	Rizatriptan (benzoate) (Maxalt and assoiated names)	Merck Sharp and Dohme	Treatment of migraine	2011	Slovenia, Spain

* Not all Member States may have reported variations.

8. Article 45 and 46 outcomes

New paediatric indications granted subsequent to variations triggered by assessments of studies submitted under Article 45 or 46 of the Paediatric Regulation. The new paediatric indications for the centrally authorised medicines are listed in section 4.2. of this report. The new paediatric indications of medicinal products authorised through national / decentral / mutual recognition procedure were:

1. Amlodipine: SmPC section 4.2: "Children with hypertension from 6 years to 17 years of age: The recommended antihypertensive oral dose in pediatric patients ages 6-17 years is 2.5 mg once daily as a starting dose, up-titrated to 5 mg once daily if blood pressure goal is not achieved after 4 weeks. Doses in excess of 5 mg daily have not been studied in pediatric patients (see section 5.1 Pharmacodynamic Properties and section 5.2 Pharmacokinetic Properties)."
2. Baclofen: SmPC Section 4.1: "Paediatric population: Baclofen Intrathecal is indicated in patients aged 4 to <18 years with severe chronic spasticity of cerebral origin or of spinal origin (associated with injury, multiple sclerosis, or other spinal cord diseases) who are unresponsive to orally administered antispastics (including oral baclofen) and/or who experience unacceptable side effects at effective oral doses."
3. Bisacodyl: SmPC Section 4.2: "Children aged 10 years or younger with chronic constipation should only be treated under the guidance of a physician. Bisacodyl should not be used in children aged 2 years or younger."
4. Flumazenil: SmPC Section 4.1: "For the reversal of conscious sedation induced with benzodiazepines in children > 1 year of age"
5. Lisinopril: SmPC Section 4.2: "Use in Hypertensive Paediatric Patients aged 6-16 years: The recommended initial dose is 2.5 mg once daily in patients 20 to <50 kg, and 5 mg once daily in patients .50 kg. The dosage should be individually adjusted to a maximum of 20 mg daily in patients weighing 20 to <50 kg, and 40 mg in patients .50 kg."
6. Milrinone: SmPC Section 4.1: "In paediatric population <National approved name> is indicated for the short-term treatment (up to 35 hours) of severe congestive heart failure unresponsive to conventional maintenance therapy (glycosides, diuretics, vasodilators and/or angiotensin converting enzyme (ACE) inhibitors), and for the short-term treatment (up to 35 hours) of paediatric patients with acute heart failure, including low output states following cardiac surgery."
7. Propranolol: SmPC Section 4.2: "Arrhythmias: Dosage should be individually determined and the following is only a guide: Children and adolescents: 0.25 - 0.5mg/kg 3-4 times daily, adjusted according to response. Max 1 mg/kg 4 times daily, total daily dose not to exceed 160 mg daily. Intravenous Dosage: [...] The intravenous injection is intended for the emergency treatment of cardiac arrhythmias only. Children and adolescents: 0.025-0.05mg/kg injected slowly, preferably under ECG control and repeated if necessary every 6-8 hours"

Before the entry into force of the Paediatric Regulation (2005-2008) and in a process similar to the assessments under Article 45 of the Paediatric Regulation, the CMD(h) has conducted in its "worksharing project" the assessment of paediatric studies submitted by Marketing Authorisation Holders for 21 active substances used in the paediatric population. The reports have been made public here: http://www.hma.eu/270.html.

8.1. Article 45

In accordance with Article 45 of the Paediatric Regulation, marketing authorisation holders were required to submit to the competent authorities all paediatric studies completed by the date of entry into force of the Regulation. These studies were to be submitted by 26 January 2008. Upon assessment of the data, the competent authority may update the SmPC and package leaflet and may vary the marketing authorisation.

For products authorised through national/decentralised/mutual recognition procedure, the extent of information received has been enormous. Information has been received for almost one thousand active substances, with several documents for each of them (some may relate to the same study). To cope with the workload, there is an ongoing worksharing exercise between Member States and the assessment is being performed in waves, co-ordinated by the CMD(h).

8.1.1. Centrally authorised medicines

Summary:

- For centrally authorised medicinal products, data (study results) were submitted for 55 active substances, corresponding to 61 medicinal products. In 2011, the CHMP completed the assessment of the last submitted data. In total, the SmPCs of 12 medicinal products were changed subsequent to the assessment. The publication of all assessment reports / outcomes of the assessment of studies submitted through Article 45 is made in the respective EPAR web pages of the EMA website (see http://www.ema.europa.eu/).

Table 22: List of Article 45 CAP outcomes resulting in changes of the SmPC.

No.	Year	Active substance	Trade name	Marketing authorisation holder	Outcome of assessment, recommended SmPC change(s)
1	2009	Pegfilgrastim	Neulasta	Amgen Europe B.V.	Section 4.2, 4.8, 5.1 and 5.2
2	2009	Ritonavir	Norvir	Abbott Laboratories Limited	Section 5.1
3	2009	Mangafodipir	Teslascan	GE Healthcare AS	Section 4.2
4	2009	Interferon beta-1a	Avonex	Biogen Idec Limited	Sections 4.2, 4.8 and 5.1
5	2009	Oseltamivir	Tamiflu		Sections 4.1, 4.2, 4.8 and 5.2
6	2010	Interferon beta-1a	Avonex	Biogen Idec Ltd.	Sections 4.2, 4.8 and 5.1
7	2010	Perflutren	Optison	GE Healthcare AS	Sections 4.2 and 5.1
8	2010	Zonisamide	Zonegran	Eisai Ltd.	Section 5.2

8.1.2. Medicinal products authorised through national/mutual recognition/decentralised procedure

Summary:

- The following table is based on the CMD(h) reporting the completion of the assessment of studies submitted under Article 45 of the Paediatric Regulation ("List of active substances for which data has been submitted in accordance with Article 45 of the Paediatric Regulation (January 2012)", available here: http://www.hma.eu/99.html). The reports on the assessments under Article 45 are made public by the CMD(h) on this webpage: http://www.hma.eu/269.html.

- Information provided by the Member States was added to the table to indicate the years and the Member States' implementation of recommendations to change the SmPC according to the CMD(h) assessment outcome and recommendations. Data on variations in relation to Article 45 or 46 were provided by only 13 Member States (Austria, Belgium, Cyprus, Finland, France, Hungary, Italy, Portugal, Romania, Slovenia, Spain, Sweden and United Kingdom).
- Of 89 active substances for which the CMD(h) completed the assessment by 31 December 2011 of studies submitted under Article 45, 73 assessment reports were made public, some of which are for more than 1 active substance. The main outcome of the assessment and the most important recommended changes to the SmPCs were, across the 73 active substances: safety information to be added (3 active substances); new paediatric study results to be added (9); a new paediatric indication to be added (7) and clarifications on paediatric use (34).
- For 18 active substances, no change to the SmPC was necessary subsequent to the assessment of paediatric studies submitted under Article 45. These active substances appear to correspond to medicines that are already authorised for a paediatric use.
- In total, the various sections of SmPCs were recommended to be changed: for 8 active substances in section 4.1 (indication), for 22 active substances in 4.2 (posology and administration), for 10 active substances in 4.4 (warnings), for 7 active substances in section 4.8 (undesirable effects), for 11 active substances in section 5.1 (pharmacodynamics) and for 11 active substances in section 5.2 (pharmacokinetics).

Table 23: Outcomes resulting in changes to the SmPC and implementation of assessment of paediatric studies submitted under Article 45 for medicinal products authorised through national/mutual recognition/decentralised procedure

Active substance (INN)	**Recommended changes to product information**	**Outcome of assessment and recommended changes**	**Years**	**Member States reporting variation implementing recommendations**
Alendronic acid	Sections 4.2 & 5.1	Paediatric information clarified	2009-2011	Italy, Hungary, Slovenia, Sweden, United Kingdom
Amikacin	Sections 4.1, 4.2, 4.4, 4.5, 4.6 & 5.2	Paediatric information clarified	2010-2011	Belgium, Finland, Italy, United Kingdom
Amiodarone	Sections 4.2, 4.3, 4.4, 5.1 & 5.2	Paediatric information clarified	2011	Belgium, Finland, Slovenia, Spain, United Kingdom
Amlodipine	Sections 4.2, 5.1 & 5.2	New indication	2010-2011	Belgium, Finland, Italy, Romania, Slovenia, Sweden, United Kingdom
Amoxicillin	Sections 4.2, 4.4 and 5.2	Paediatric information clarified	2010-2012	Austria, Belgium, Italy, Slovenia, Sweden, United Kingdom
Apis mellifera - Lyophilised bee venom[1]	Sections 4.1, 4.2, 4.3 & 4.4	Paediatric information clarified	2010	United Kingdom
Baclofen	Sections 4.1, 4.2	New indication	2011	Belgium, Finland, Romania, United

[1] Covers also vespula spp. / lyophilised wasp venom

Active substance (INN)	Recommended changes to product information	Outcome of assessment and recommended changes	Years	Member States reporting variation implementing recommendations
	& 4.4			Kingdom
Betula verrucosa (pendula), allergen extracts from birch/alder/ hazel (betula), allergen extract from birch (betula)	Section 4.2	Paediatric information clarified	2010	United Kingdom
Bisacodyl	Section 4.2	New indication	2010-2011	Belgium, Italy, Slovenia, Sweden, United Kingdom
Calcitonin (salmon synthetic)	Section 4.2	No change	2009-2011	Finland, Slovenia, United Kingdom
Canis familiaris (553)	Section 4.2	Paediatric information clarified	2010	United Kingdom
Chondroitin sulfate	Section 4.2	Paediatric information clarified	2011	Italy
Clarithromycin	Sections 4.1 & 4.2	Paediatric information clarified	2011	Belgium, Finland, Hungary, Italy, Romania, United Kingdom
Clobazam	Section 4.2	Paediatric information clarified	2011	United Kingdom
Clonidine	Sections 4.2 & 5.1		2011	Belgium, Sweden, United Kingdom
Dermatophagoides pteronyssinus	Section 4.2	Paediatric information clarified	2010	United Kingdom
Dermatophagoides farinae / Dermatophagoides pteronyssin	Section 4.2	Paediatric information clarified	2010	United Kingdom

Active substance (INN)	Recommended changes to product information	Outcome of assessment and recommended changes	Years	Member States reporting variation implementing recommendations
us				
Diclofenac	Sections 4.2, 4.3 & 4.8	Paediatric information clarified	2011	Belgium, Finland, Italy, Romania, Slovenia, Spain, Sweden, United Kingdom
Ethosuximide	Syrup formulation Sections 4.2 & 5.1 Capsule formulation Sections 4.2 & 5.1	Paediatric information clarified	2011	Belgium, United Kingdom
Famciclovir	See outcome of Art.30 Procedure in April 2010	Paediatric information clarified	2011	Cyprus, Finland, Italy, United Kingdom
Felis domesticus	Section 4.2	Paediatric information clarified	2010	United Kingdom
Felodipine	Sections 5.1 & 5.2	New study data	2010-2011	Belgium, Cyprus, Finland, Spain, Sweden, United Kingdom
Fentanyl	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	Paediatric information clarified	2009-2011	Austria, Finland, Italy, Spain, Sweden, United Kingdom
Flumazenil	Sections 4.1, 4.2 & 5.2	New indication	2011	Finland, Spain, United Kingdom

Active substance (INN)	Recommended changes to product information	Outcome of assessment and recommended changes	Years	Member States reporting variation implementing recommendations
Gentamicin	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	New safety information	2010-2011	Belgium, Finland, Sweden, United Kingdom
Glucosamine	Sections 4.2 and 4.4	Paediatric information clarified	2010	Belgium, Finland, Italy, United Kingdom
Isradipine	Section 4.2	Paediatric information clarified		None
Itraconazole	Sections 4.2, 4.8, 5.1 & 5.2	Paediatric information clarified	2011	Belgium, Finland, United Kingdom
Levothyroxine	Section 4.2	Paediatric information clarified	2009-2011	Belgium, Cyprus, Finland, Romania, Sweden, United Kingdom
Lisinopril	Sections 4.2, 4.8, 5.1 & 5.2	New indication	2009-2011	Cyprus,Finland, Sweden, United Kingdom
Mepivacaine	Section 4.2 & 4.3	Paediatric information clarified	2010-2011	Belgium, Finland, Romania, Sweden, United Kingdom
Mesalazine	Section 4.2	Paediatric information clarified	2010-2011	Belgium, Cyprus, Finland, Slovenia, Sweden, United Kingdom
Metoclopramide	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	New safety information	2008, 2011, 2012	Belgium, France, Spain, Sweden, United Kingdom
Metronidazole,	Sections 4.1, 4.2 & 4.8	Paediatric information	2010-2011	Belgium, Cyprus, Finland, Italy, Sweden, United Kingdom

Active substance (INN)	Recommended changes to product information	Outcome of assessment and recommended changes	Years	Member States reporting variation implementing recommendations
Metronidazole / Spiramycin		clarified		
Milrinone	Sections 4.1, 4.2 4.4, 4.8, 5.1, 5.2 & 5.3	New indication	2011	Belgium, Sweden, United Kingdom
Mirtazapine	Sections 4.2, 4.8 & 5.1	New study data	2010-2011	Austria, Finland, Romania, Sweden, United Kingdom
Neridronic acid	Sections 4.1 & 4.2	Paediatric information clarified		Italy
Oxazepam	Section 4.4	New safety information	2010	Sweden, United Kingdom
Oxybutynin	Section 4.1 & 4.4	Paediatric information clarified	2010-2011	Belgium, Spain, Sweden, United Kingdom
Paclitaxel	Section 4.2	Paediatric information clarified	2010-2011	Finland, Italy, Slovenia, Spain, Sweden, United Kingdom
Phleum pratense / Modified, adsorbed grass pollen	Section 4.2	Paediatric information clarified	2010	Portugal, Spain, United Kingdom
Propofol	Sections 4.4 & 5.2	Paediatric information clarified	2010-2011	Belgium, Finland, Sweden, United Kingdom
Propranolol	Sections 4.2 & 4.8	New indication	2011	Belgium, Spain, Sweden, United Kingdom
Quinapril	Sections 5.1 & 5.2	New study data	2011-2012	Belgium, Romania, United Kingdom
Remifentanil	Sections 4.1, 4.2, 4.4 & 5.1	Paediatric information clarified	2010-2011	Finland, Romania, Slovenia, Spain, Sweden, United Kingdom
Rifaximin	Sections 4.1, 4.2 & 5.1	New study data	2010	Spain
Risedronic acid[2]	Sections 4.2 & 5.1	New study data	2010-2011	Austria, Finland, Italy, Romania, Spain, Sweden, United Kingdom
Simvastatin	Sections 4.2, 4.4, 4.8, 5.1 & 5.2	New study data	2009-2010	Belgium, Finland, Italy, Slovenia, Sweden, United Kingdom
Timolol	Sections 4.2,	Paediatric	2011	Belgium

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

Active substance (INN)	Recommended changes to product information	Outcome of assessment and recommended changes	Years	Member States reporting variation implementing recommendations
	4.4, 5.1 & 5.2	information clarified		
Topiramate	Sections 4.4, 4.8 & 5.1	New study data	2010-2011	Finland, Slovenia, Sweden, United Kingdom
Tranexamic acid	Section 4.2, 4.3, 4.4, 4.8, 5.1 & 5.2	New study data	2010-2011	Belgium, United Kingdom
Triptorelin	Sections 4.2, 4.4 and 4.8	Paediatric information clarified	2010-2011	Slovenia, Spain, United Kingdom
Vespula spp. / Lyophilised wasp venom	Sections 4.1, 4.2, 4,3 & 4.4	Paediatric information clarified	2010	United Kingdom

8.2. Article 46

8.2.1. Centrally authorised medicines

Summary:

- For centrally authorised products, 108 procedures ("FUM", follow-up measures) of evaluation of studies submitted through this Article have been finalised by 2011. This figure may cover the same study(ies) submitted for more than one product and for more than one procedure. In 2 of them, the data have submitted directly through a variation procedure.
- In total, 55 active substances were addressed by 105 submitted studies. Subsequent to these 108 procedures, the CHMP recommended 15 changes to the product information for 13 active substances.
- In total, the various sections of SmPCs were recommended to be changed: for 1 active substance in section 4.1 (indication), for 8 active substances in 4.2 (posology and administration), for 2 active substances in 4.4 (warnings), for 3 active substances in section 4.8 (undesirable effects), for 10 active substances in section 5.1 (pharmacodynamics) and for 6 active substances in section 5.2 (pharmacokinetics).

Table 24: List of Article 46 CAP outcomes resulting in SmPC changes

Year	Number of procedures	Active substance(s)	Trade name	Marketing authorisation holder	Outcome of assessment, recommended SmPC change(s)
2009	1	Cinacalcet	Mimpara	Amgen Europe B.V	Section 5.2
2009	1	Telithromycin	Ketek	Aventis Pharma S.A.	Section 4.2 and 5.2
2010	1	Aripiprazole	Abilify	Otsuka	Sections 4.2 and

Year	Number of procedures	Active substance(s)	Trade name	Marketing authorisation holder	Outcome of assessment, recommended SmPC change(s)
				Pharmaceutical Europe Ltd.	5.1
2010	1	Palonosetron hydrochloride	Aloxi	Helsinn Birex Pharmaceuticals Ltd.	Sections 4.2, 5.1 and 5.2
2010	1	Pramipexole dihydrochloride monohydrate	Mirapexin/ Sifrol	Boehringer Ingelheim International GmbH	Section 5.3
2010	1	Pramipexole dihydrochloride monohydrate	Mirapexin/ Sifrol	Boehringer Ingelheim International GmbH	Sections 4.2 and 5.1
2010	1	Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)	Prevenar	Wyeth Lederle Vaccines S.A.	Section 5.1
2010	1	Fondaparinux sodium	Arixtra	Glaxo Group Ltd.	Sections 5.1, 5.2
2010	1	Nitric oxide	INOmax	INO Therapeutics AB	Sections 4.2 and 5.1
2011	1	Virus, live attenuated, measles, virus, live attenuated, mumps, virus, live attenuated, rubella, virus, live attenuated, varicella*	Proquad	Sanofi Pasteur MSD, SNC	Section 4.8
2011	1	Adalimumab	Humira	Abbott Laboratories Ltd.	Sections 1, 4.1, 4.2, 5.1, 5.2, 6.3, 6.5
2011	1	Tenofovir disoproxil fumarate	Viread	Gilead Sciences International Ltd.	Sections 4.2, 4.4, 4.6, 4.8 5.1, 5.2 and 5.3
2011	2	Rufinamide	Inovelon	Eisai Ltd.	Section 4.8
2011	1	Adefovir dipivoxil	Hepsera	Gilead Sciences International Ltd.	Sections 4.2 and 5.1
2011	1	Tenofovir disoproxil fumarate	Viread	Gilead Sciences International Ltd.	Sections 4.4, 5.1

* One or more procedures still ongoing

8.2.2. Medicinal products authorised through national/mutual recognition/decentralised procedure

Summary:

- In 2009, studies have been received for 70 nationally authorised medicinal products and those authorised through mutual recognition, or decentralised procedures, for assessment under Article 46 of the Paediatric Regulation.
- In 2010, a total of 56 studies were submitted in respect of nationally authorised medicinal products and those authorised through mutual recognition, or decentralised procedures, for assessment under Article 46 of the Paediatric Regulation. The assessment was finalised for 19 products and the assessment report was published for 13 of these studies, recommending to change the SmPCs of the medicinal products corresponding to 6 active substances.
- In 2011, a total of 45 studies were submitted in respect of nationally authorised medicinal products and those authorised through mutual recognition, or decentralised procedures, for assessment under Article 46 of the Paediatric Regulation. The assessment was finalised for 20 procedures and the assessment was published for 17 of these studies, recommending for 4 of them to amend the SPCs.
- The data provided by the Member States included entries for active substances, for which assessments under Article 45 and / or 46 are scheduled but have not yet been started or completed; these entries are not listed below.
- The assessment reports are being made public by the CMD(h) here: http://www.hma.eu/291.html.
- The following table lists the completed assessments of studies submitted under Article 46 of the Paediatric Regulation and, where necessary, the implementation by the Member States reporting variations. In total, for 20 active substances, 25 assessments were completed, out of which 6 recommended changes to the SmPC of the concerned medicinal products, mostly in the sections 4.2 (posology) and 5.2 (pharmacokinetics).

Table 25: Article 46 non-CAP

Year	Active substance (INN)	Medicinal product	Pharmaceutical form(s)	Recommended changes to Product information	Outcome of assessment and recommended changes	Member States reporting variation implementing recommendations
2011	Alfuzosin	Xatral	Film-coated tablet, prolonged-release tablet	Section 4.2, 5.1	New study data	Belgium, Cyprus, Sweden
2009, 2011	Atomoxetine	Strattera (2 procedures)	Capsules	None	No change necessary	None
2010	Donepezil	Aricept	Film-coated tablets, oral solution	None	No change necessary	None
2010 - 2011	Esomeprazole	Nexium	gastro-resistant granules for oral suspension/	Sections 4.2 and 5.1	New study data	Spain, Sweden

Year	Active substance (INN)	Medicinal product	Pharmaceutical form(s)	Recommended changes to Product information	Outcome of assessment and recommended changes	Member States reporting variation implementing recommendations
			sachet			
2010 - 2011	Famciclovir	Famvir and associated names (2 procedures)	Film-coated tablets	Sections 4.2, 5.1 and 5.2	Paediatric information clarified (in conjunction with Article 45)	Cyprus, Finland, Italy
2011	Gabapentin	Neurontin	Oral solution, film-coated tablet	None	No change necessary	None
2010	Granisetron	Kytril	Ampoules, Tablets	Sections 4.4, 4.5 and 4.8	Safety information added	Portugal
2011	Glimepiride	Amaryl	Tablets	None	No change necessary	None
2011	Human coagulation factor XIII	Fibrogammin P	Powder and solvent for intravenous injection	None	No change necessary	None
2011	Influenza vaccine	Afluria/Enzira	Suspension for injection in a pre-filled syringe	None	No change necessary	None
2010 - 2011	Lansoprazole	Agopton	Capsule, oro-dispersible tablet	Section 4.2	Paediatric information clarified	Austria, Finland, Italy, Romania
2010 - 2011	Montelukast	Singulair (2 procedures)	Chewable tablets	None	No change necessary	None
2010	Pimecrolimus	Elidel (3 procedures)	Cream	None	No change necessary	None
2011	Inactivated poliomyelitis vaccine	Poliorix	Solution for injection	None	No change necessary	None
2010 - 2011	Ropinirole	Adartrel	Film-coated tablets	Section 5.2	New study data	Finland, Spain, Romania
2010	Salmeterol xinafoate / Fluticasone propionate	Seretide Diskus/ Seretide Eudraler	Powder for inhalation, Pressurised suspension	Sections 4.2 and 5.2	New study data	Finland, Slovenia, Spain, Sweden, Romania

Year	Active substance (INN)	Medicinal product	Pharmaceutical form(s)	Recommended changes to Product information	Outcome of assessment and recommended changes	Member States reporting variation implementing recommendations
		and associated names	for inhalation			
2010	Somatropin	Genotropin and associated names	Powder and solvent for solution for injection	None	No change necessary	None
2010	Tacrolimus	Prograf	Hard capsules	None	No change necessary	None
2011	DTP-Polio vaccine	Tetravac and associated names	Suspension for injection	None	No change necessary	None
2010	Valproate sodium	Depakin and associated names	Modified release granules	None	No change necessary	None

9. Questionnaires and annual surveys

9.1. Overview of received data

Table 26: Member States having provided any data from National Competent Authorities (NCA) and from National Competent Authorities (NPO). The data provided did not cover all questions for some Member States.

Member State	2007-2009 NCA	2007-2009 NPO	2010 NCA	2010 NPO	2011 NCA	2011 NPO
Austria	X		X	X	X	X
Belgium	X	X	X	X	X	
Bulgaria	X	X		X		X
Cyprus	X	X	X	X	X	
Czech Republic	X	X	X	X	X	X
Denmark	X	X	X	X	X	X
Estonia	X		X	X	X	X
Finland	X		X	X	X	X
France	X	X		X	X	
Germany	X	X	X	X	X	X
Greece			X	X		
Hungary	X		X	X	X	X
Ireland	X	X	X	X	X	X
Italy	X	X	X	X	X	X

Member State	2007-2009 NCA	2007-2009 NPO	2010 NCA	2010 NPO	2011 NCA	2011 NPO
Latvia	X		X		X	
Lithuania	X	X		X	X	X
Luxembourg	X	X		X		X
Malta	X	X	X	X	X	X
The Netherlands	x		X	X	X	X
Poland			X	X	X	X
Portugal	X		X	X	X	X
Romania	X			X	X	X
Slovakia	X			X		X
Slovenia	X	X		X	X	X
Spain				X	X	
Sweden	X		X	X	X	X
United Kingdom	X	X	X	X	X	X

9.2. Questionnaire to Member States (annual survey)

L:\NCAannual.doc

9.3. Questionnaire to National Patent Offices (annual survey)

L:\NPO.doc

9.4. Questionnaire to Member States (survey 2007-2011)

L:\NCA5year.doc

厚生労働科学研究費補助金（医薬品・医療機器等レギュラトリーサイエンス総合研究事業）
分担研究報告書

小児医薬品開発における倫理的配慮に関する研究

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研究要旨

日本における小児を対象とする臨床試験・臨床研究における倫理的配慮の在り方について検討するために、本年度は先行する欧米（英語圏）でのガイドラインの現状について情報収取を行うとともに、詳細な検討が必要と判断された主要ガイドラインについては邦訳を行った。2000 年以前より、ある程度のまとまった議論に基づいてガイダンスを出していたのは、米国の大統領委員会及び小児科学会（AAP）、並びに英国小児科学会（RCPCH）であった。AAP と RCPCH のガイドラインでは、小児臨床試験・臨床研究における倫理的配慮として取り上げるべき事項の幾つかが共有されていた。しかし一方では、それぞれ当時の国内における研究規制と社会的関心事を強く反映したものとなっており、ガイドラインにおいて言及される事項と内容に相違が見られる部分もあった。日本でのガイドラインを今後作成していくにあたっては、こうした先行ガイドラインの比較検証とともに、論点についての俯瞰的な見取り図を作成する必要がある。

A．研究目的

日本国内における小児科領域の臨床試験・臨床研究の環境整備を進めるための方法論・方策の検討を行うにあたり、倫理的観点からは「社会的弱者」とされる小児を対象とする臨床試験・臨床研究における倫理的配慮の在り方について検討することが、本分担研究の目的である。研究初年度である平成 25 年度は、欧米（英語圏）での現状について情報収集を行うことを目的とした。

B．研究方法

欧米で先行する小児臨床試験・臨床研究における倫理的配慮に関するガイドラインについて情報収集を行った。一つには、PubMed 等を用いた文献検索から、その他には小児臨床試験・臨床研究における倫理的配慮について研究を行っている第一級の研究倫理専門家から、あらかじめ検討すべき主要ガイドラインについての情報を得た。

（倫理面への配慮）

当分担研究は直接に人を対象とする研究は実施しないため、非該当。

C．研究結果

欧米（英語圏）においてこれまで公表された小児臨床試験・臨床研究に関連する倫理ガイドラインとして、主要なものでは下記に示す 19 編が存在することを把握し、其々の文書を入手した。各文書について精読し、其々

が示す倫理的配慮のポイントについて検討した。

下記文書のうち、特に次年度以降に実施予定の比較整理のうえで重要と判断されたもの（④、⑤、⑩：下線部）については、邦訳を行った（なお、⑤、⑩の邦訳を付録１．及び付録２．として文末付記）。

【米国】

① Department of Health, Education, and Welfare. National Institutes of Health. Protection of Human Subjects, Policies and Procedures. *Federal Register,* Vol. 38, No. 221, Part II, November 16.（1973 年）

② The U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Research Involving Children: Report and Recommendations.（1977 年）

③ The U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Research Involving Children: Appendix to Report and Recommendations.（1977 年）

④ Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations（American Academy of Pediatrics: Committee on Drugs, 1977 年）

⑤ Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations（American Academy of Pediatrics: Committee on Drugs, 1995 年）

⑥ Informed Consent, Parental Permission, and Assent in Pediatric Practice（American Academy of Pediatrics: Committee on Bioethics, 1995 年）

⑦ Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations（American Academy of Pediatrics: Shaddy RE, Denne SC, and the Committee on Drugs and Committee on Pediatric Research, 2010 年）

⑧ Department of Health and Human Services: Food and Drug Administration. 21 CFR Parts 50 and 56. Additional Safeguards for Children in Clinical Investigations of Food and Drug Administration-Regulated Products. *Federal Register*, Vol. 78, No. 38, February 26.（2013 年）

【英国】

⑨ Guidelines to aid ethical committees considering research involving children（The British Paediatric Association: Working Party on Ethics of Research in Children, 1980 年）

⑩ Guidelines for the ethical conduct of medical research involving children（Royal College of Paediatrics and Child Health: Ethics Advisory Committee, 2000 年）

⑪ Guidelines For Research.（National Children's Bureau, 2003 年）

⑫ Medical Research Council. MRC Ethics Guide: Medical research involving children.（2004 年）

⑬ Guidelines for Research with Children and Young People.（The NCB Research Center, National Children's

Bureau, 2011年）

【その他】

⑭ The Ethics Working Group of the Confederation of European Specialists in Paediatrics (CESP). Guidelines for informed consent in biomedical research involving paediatric populations as research participants（2003年）. *Eur J Pediatr*, 162: 455-8.

⑮ The Ethics Working Group of the Confederation of European Specialists in Paediatrics (CESP). Informed consent/assent in children. Statement of the Ethics Working Group of the Confederation of European Specialists in Paediatrics (CESP).（2003年）*Eur J Pediatr*, 162: 629-33.

⑯ The Ethics Working Group of the Confederation of European Specialists in Paediatrics (CESP). Ethical principles and operational guidelines for good clinical practice in paediatric research. Recommendations of the Ethics Working Group of the Confederation of European Specialists in Paediatrics (CESP).（2004年）*Eur J Pediatr*, 163: 53-7.

⑰ Trinity College Dublin Children's Research Centre. Ethical Guidelines.（2006年）

⑱ The Royal Australasian College of Physicians Paediatric & Child Health Division. Ethics of Research in Children.（2008年）

⑲ Ethical Considerations for Clinical Trials on Medical Products conducted with the Paediatric Population: Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use.（2008年）

D．考察

日本ではこれまで、小児を研究対象とする場合に特有の、もしくはそこで顕著に立ち現れてくる倫理的課題についてほとんど分析・検討がなされてきておらず、従って議論の蓄積が極めて乏しい現状にある。そのため、日本でのガイドラインを作成するためには、英米で先行するガイドラインでの議論の過程と結論について詳細な分析を加える必要がある。

小児臨床試験・臨床研究における倫理的配慮について、2000年以前より、ある程度のまとまった議論に基づいてガイダンスを出しているのは、米国の大統領委員会及び小児科学会（AAP）、並びに英国小児科学会（RCPCH）であった。

AAPとRCPCHのガイドラインは、小児臨床試験・臨床研究における倫理的配慮として取り上げるべき事項の幾つかを共有していた。その中でもとりわけ、「研究デザイン」、「利益」、「リスク」、「同意（アセント・代諾者の問題を含む）」、「倫理審査委員会」については、いずれのガイドラインでも相当な重きが置かれた言及がなされていた。一方で、米国、英国のガイドラインは、それぞれ当時の国内における研究規制と社会的関心事を強く反映したものとなっていることも窺えた。そのため、例えば両者に共通して言及されている"minimal risk"（最小限のリスク）であっても、その定義・内容には少なからぬ差異が見受けられている。

このことから、日本における小児臨床試験・臨床研究での倫理的配慮の在り方を検討するためには、幾つかの主要な先行ガイドラインに