Encouraging development of paediatric medicines: the experience in the European Union.

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Towards EU Accession – Belgrade 29-30 November 2010

Part 0

The EU

EU: 27 member states

EEA: 27 EU MS + Norway, Iceland, Liechtenstein

7 Institutions of the EU:

The European Council

The Council (of the EU)

European Parliament

EU Commission

EU Court of Justice

EU Court of Auditors

EU Central Bank

Part 1

Adult medicines in paediatric use
(a.k.a. off-label use of medicinal products in children)

Off-label use of medicinal products in children

- Use in children despite a relative lack of information on how to prescribe safely.
- The (EU) Paediatric Regulation aims to improve the information available to prescribers and families and therefore to reduce off-label use.
- Studies have shown that off-label use is associated with more adverse reactions to drugs for children; adverse reactions in children may be more severe or different from what is known in adults.

European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

October 2004
EMEA/126327/2004

Evidence of harm from off-label or unlicensed medicines in children
EMEA

http://www.ema.europa.eu/pdfs/human/paediatrics/12632704en.pdf

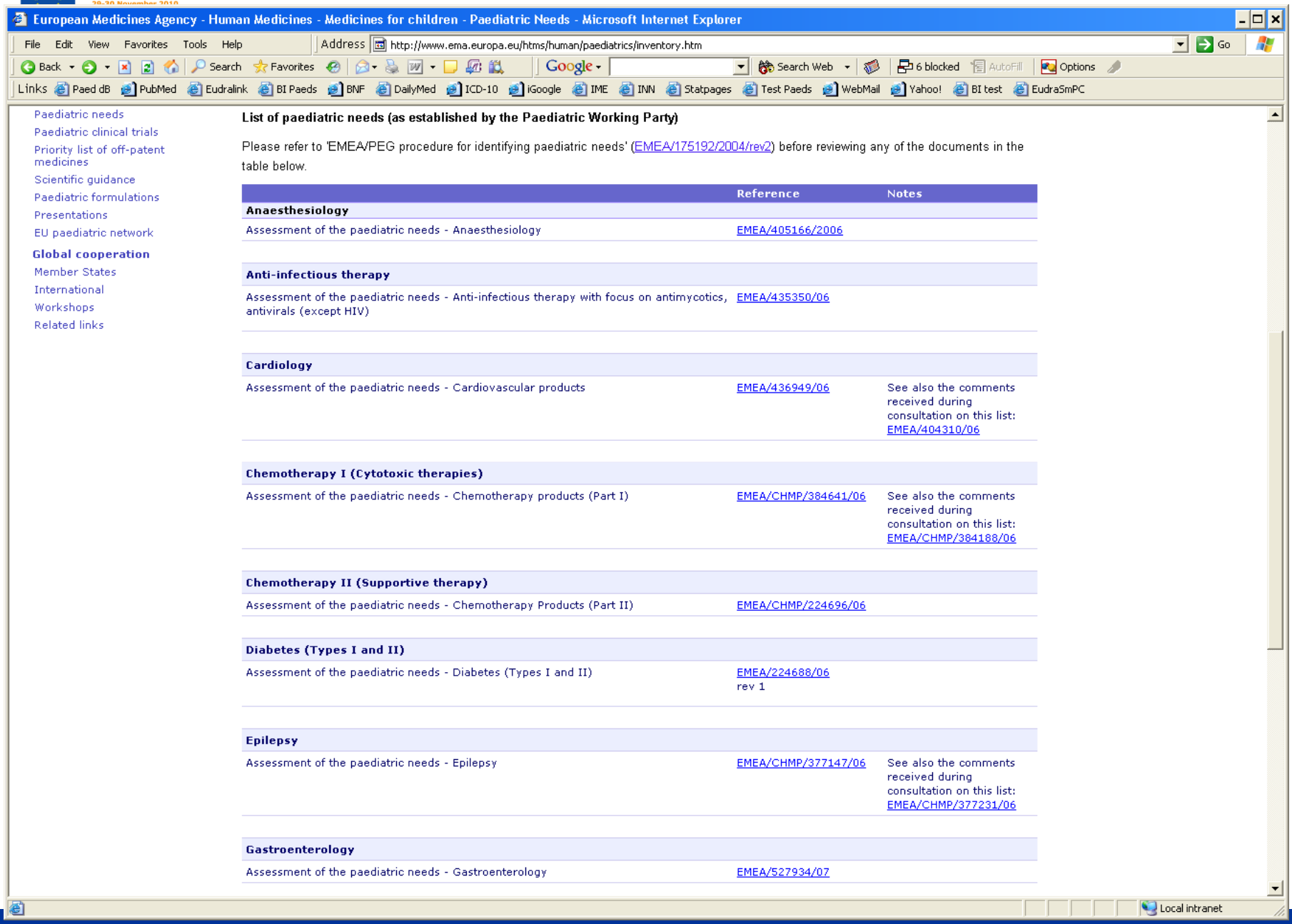
Executive Summary

This document has been prepared by the EMEA on the basis of limited available evidence, following a request from the European Commission. It focuses on evidence of harm from off label or unlicensed medicines in children from both a review of literature and a search of the EMEA Eudravigilance database.

Very few publications specifically address the issue of off label and/or unlicensed medicines.
Underreporting is the case for paediatric adverse drug reactions (ADR's) as for adults, but may be even more common for unlicensed, off-label medicines. In contrast to spontaneous reporting, prospective monitoring of ADR's indicates higher incidence and in particular shows up to double incidence when including both clinical and laboratory parameters detection.
In a large specific study of children admitted to a paediatric hospital, ADR's were associated with 112 (3.9%) of the 2881 licensed drug prescriptions and 95 (6%) of the 1574 unlicensed or off-label drug prescriptions (35% of all prescriptions). In another large prospective study of community paediatricians, off-label drug use was significantly associated with adverse drug reactions (relative risk 3.44; 95% CI 1.26, 9.38).
The profile of ADR's in children is dominated by anti-infective, anti-asthmatic, and gastrointestinal adverse reactions, which may only reflect the most common diseases observed in children, but central nervous system adverse reactions are equally common. Reporting from various sources provides different profiles of ADR's and for example, parents seem more aware of central nervous system effects. In all cases the publications did not address long-term consequences of medicines' use.
The use of off -label and unlicensed medicines also implies that there were no proper labelling and dosing recommendations. As a consequence, medications errors including dosing errors, more common in children than in adults, should be taken into consideration as additional

Off-label use of medicinal products in children: first answer

- List of Paediatric Needs by EMA's Paediatric Expert Group (2006)
- Aim: to identify the needs in the different therapeutic areas where there should be research and development of medicinal products, either old (i.e. off patent) or new ones.
- Consultation of EU member states, learned societies.
- To be updated soon by EMA's PDCO (Q1 2011)



Paediatric needs
Paediatric clinical trials
Priority list of off-patent medicines
Scientific guidance
Paediatric formulations
Presentations
EU paediatric network
Global cooperation
Member States
International
Workshops
Related links

List of paediatric needs (as established by the Paediatric Working Party)

Please refer to 'EMEA/PEG procedure for identifying paediatric needs' (EMEA/175192/2004/rev2) before reviewing any of the documents in the table below.

	Reference	Notes
Anaesthesiology		
Assessment of the paediatric needs - Anaesthesiology	EMEA/405166/2006	
Anti-infectious therapy		
Assessment of the paediatric needs - Anti-infectious therapy with focus on antimycotics, antivirals (except HIV)	EMEA/435350/06	
Cardiology		
Assessment of the paediatric needs - Cardiovascular products	EMEA/436949/06	See also the comments received during consultation on this list: EMEA/404310/06
Chemotherapy I (Cytotoxic therapies)		
Assessment of the paediatric needs - Chemotherapy products (Part I)	EMEA/CHMP/384641/06	See also the comments received during consultation on this list: EMEA/CHMP/384188/06
Chemotherapy II (Supportive therapy)		
Assessment of the paediatric needs - Chemotherapy Products (Part II)	EMEA/CHMP/224696/06	
Diabetes (Types I and II)		
Assessment of the paediatric needs - Diabetes (Types I and II)	EMEA/224688/06 rev 1	
Epilepsy		
Assessment of the paediatric needs - Epilepsy	EMEA/CHMP/377147/06	See also the comments received during consultation on this list: EMEA/CHMP/377231/06
Gastroenterology		
Assessment of the paediatric needs - Gastroenterology	EMEA/527934/07	

Refer to list of paediatric needs Cardiovascular products	
HYDROCHLOROTHIAZIDE	
Authorised indication	Oedema and hypertension
Authorised age group	No age limit specified
Authorised dose	12.5 - 25 mg daily
Authorised formulation	Tablets 25 mg
Needs	Define lower age limit and investigate where needed Data on PK, efficacy and safety in indication tubulopathies in children < 18 years Age-appropriate formulation
METOLAZONE	
Authorised indication	Oedema and hypertension
Authorised age group	Adults
Authorised dose	-
Authorised formulation	-
Needs	Data on PK, efficacy and safety < 18 years Age-appropriate formulation
POTASSIUM SPARING DIURETICS	
AMILORIDE	
Authorised indication	Adjunct to thiazide and loop diuretics in oedema (not available as monosubstance in all Member States)
Authorised age group	Adults
Authorised dose	-
Authorised formulation	-
Needs	Data on PK, safety and efficacy in children > 3 months Availabililty of monosubstance in all Member States Data on PK, efficacy and safety in indication monotherapy in congenital tubulopathies *(e.g. nephrogenic diabetes insipidus, primary hypomagnesemia with secondary hypocalcemia (TRPM-defect), thiazide-like salt losing tubulopathies (Bartter-Gitelman syndromes), Liddle-*

Separate lists by therapeutic area, arranged in tabular format

Priority List of off-patent medicinal products

- Funding of studies for off-patent medicinal products provided by Paediatric Regulation through the EU Framework Program 7 (FP7)
- List of priorities revised annually by EMA. Shared with FDA/NIH to avoid overlap or duplication of efforts, and facilitate multinational trials where necessary
- The list is adopted after public consultation and is not ranked
- Used by EU Commission to assign FP7 funds to projects

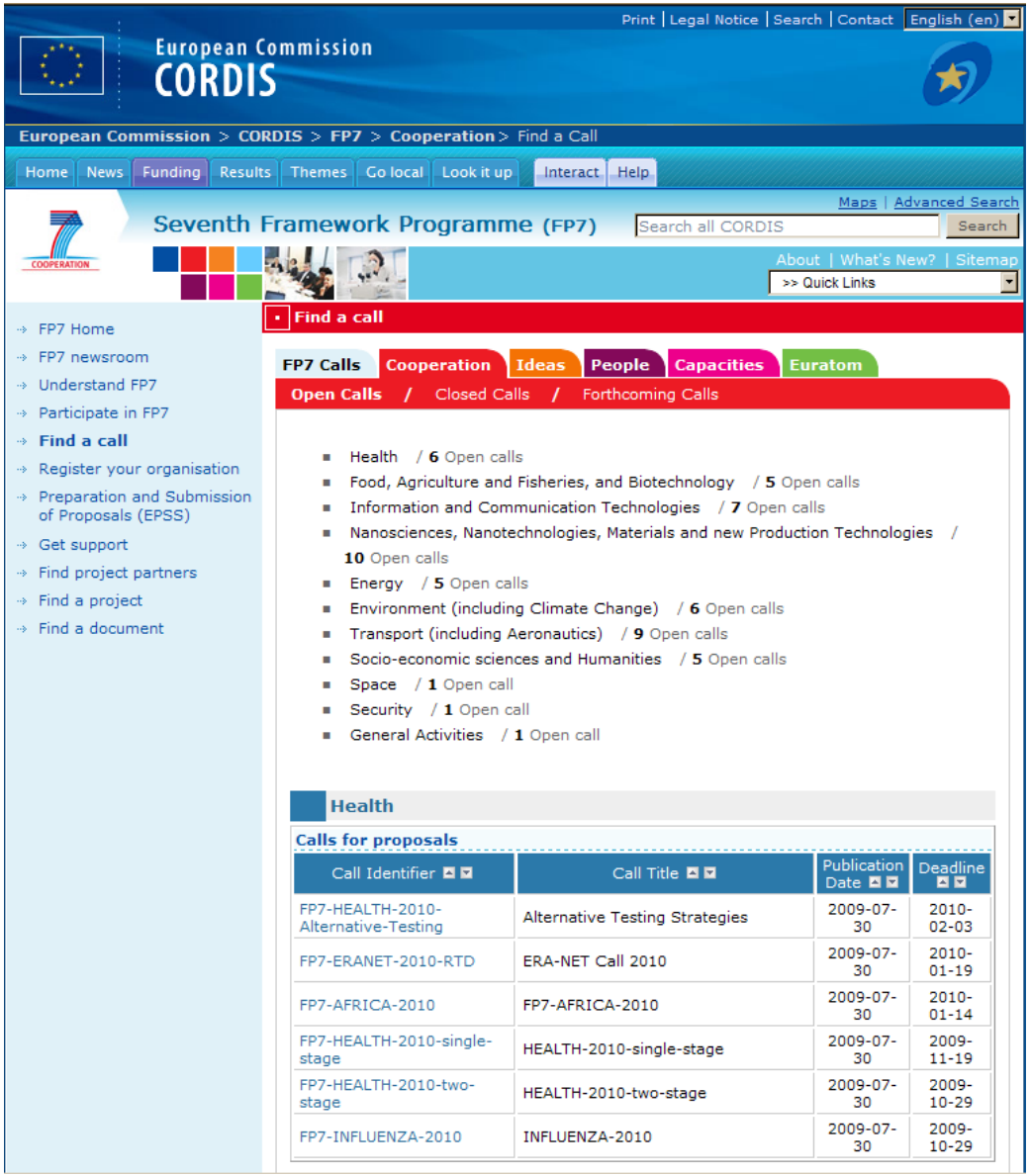
Priority List of off-patent medicinal products

The products are listed according to their therapeutic field and condition(s) in alphabetical order.
Age-appropriate formulations (even if not stated explicitly for a product) and data in neonates (except for oncology) are considered to be of high priority.

Therapeutic field	Product	Condition(s)	Specific needs
Cardiology	(refer also to 'nephrology')		
	adrenaline	Shock, cardiac failure	Data on efficacy in neonates.*
	amiodarone	Supraventricular and ventricular arrhythmia	Data on long-term safety.
	dobutamine	Shock, cardiac failure	Data on efficacy in neonates.*
	dopamine	Shock, cardiac failure	Data on efficacy in neonates.*
	milrinone	Cardiac failure	Data on PK, efficacy and safety.*
	propranolol	Hypertension, supraventricular tachycardia	Data on PK, efficacy and safety.
* Please note that there is a need for international consensus on the definition of 'shock' in neonates, and any medicine development should take this into consideration.			

FP7 website

http://cordis.europa.eu



Part 2

Overview of the EU Paediatric Regulation

Why is there a EU Paediatric Regulation?

for

=

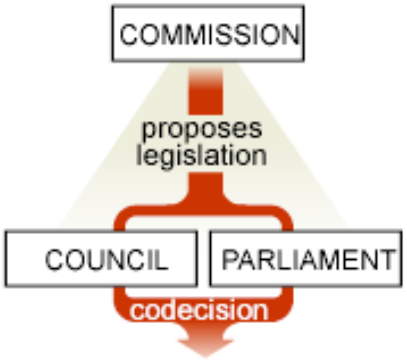
Objectives of the EU Paediatric Regulation

- Improve the health of children:
  - Increase high quality, ethical **research** into medicines for children
  - Increase **availability** of authorised medicines for children
  - Increase **information** on medicines
- Achieve the above:
  - Without unnecessary studies in children
  - Without delaying authorization for adults

Milestones in the development of the Paediatric regulation

- **1997:** US BPCA approved
- **December 1999**: first draft document to Council of EU Health Ministers):
  - Mandatory system *(neonates!)*
  - Identification of paediatric needs
  - Pharmacovigilance not included initially
- EU Orphan regulation **(1999)** used as example
- **December 2000:** EU Health Ministers urge the EU Commission to draft Paediatric legislation
- **2004:** First draft prepared, → regulation (most powerful EU legislation as directly applicable)

Milestones in the development of the Paediatric regulation



- **Dec 2004-Jun2006:** regulation wri
  - length not due to complexity: development less difficult than expected
  - Mandatory scope not challenged
  - Guideline on studies in small populations in parallel
  - Parliament added public funding of studies and transparency
  - Duration of reward debated (Industry refused to provide data on cost of paediatric trials)
  - Patient's organisations involved
  - Paediatricians invited to lobby members of the EU Parliament
  - Problem of penalties

Milestones in the development of the Paediatric Regulation

- **26 January 2007:** entry into force of the Paediatric Regulation
  - Free EMA "paediatric" scientific advice
- **4 July 2007** (6 months from entry into force):
  - Paediatric Committee (PDCO) first meeting
- **26 July 2008** (18 months from entry into force):
  - **Applications for MA (<u>new products</u>) should contain results of studies conducted in compliance with agreed PIP (unless: waiver or deferral)**
- **26 January 2009** (24 months from entry into force):
  - **Same obligation extended to applications for new indication, new route of administration or new pharmaceutical form for <u>authorised "patented" products</u>**

Pillars of the Paediatric Regulation

- Paediatric Committee
- Paediatric Investigation Plan
- A system of OBLIGATIONS and REWARDS
- TRANSPARENCY MEASURES
- OTHER MEASURES

EMA Staff vs. PDCO

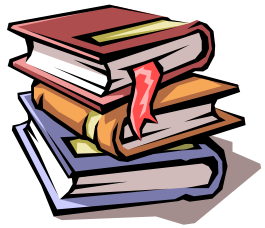
- EMA Staff:
  - Section Paediatric Medicines
  - Currently 30 staff: 20 Scientific Administrators (physicians, pharmacists, biologists…) + 10 Assistants (secretaries, database administrator…)
  - Scientific and Secretariat (legal, regulatory) support to PDCO
  - Based in London, at EMA
- PDCO:
  - >60 members/alternates (see later)
  - Not EMA staff! (hospitals, national agencies…)
  - Scientific discussions and opinions
  - Based in EU member states

Paediatric Investigation Plans

Details of timing and measures proposed (i.e studies, trials and pharmaceutical development) necessary to obtain a paediatric indication with an age appropriate formulation in all paediatric subsets affected by the condition

- Quality
- Safety
- Efficacy

Marketing Authorisation criteria



EU Paediatric Regulation: obligations versus incentives

Type of MP	**Obligation**	**Incentive**	**Comments**
New# Medicinal product	Paediatric Investigation Plan or Waiver	6 months extension of SPC (patent) *	Necessary for **validation** of application
On Patent and authorized Medicine	Paediatric Investigation Plan or Waiver	6 months extension of SPC (patent)*	When new indication or new route or new pharmaceutical form: necessary for **validation**
Orphan Medicine	Paediatric Investigation Plan or Waiver	2 additional years of market exclusivity*	In addition to 10 years
Off patent Medicine	None (voluntary PIP possible for PUMA)	10 years of data protection	Research funds Paed. Use MA (PUMA)

**if compliance with PIP, information, approval EU-wide*
#according to GMA concept

Rewards

Reward is given for all PIPs correctly completed, but PIPs are "always" required (cfr. US PREA, where: obligation but no reward)

-> if development is compliant with agreed PIP (compliance statement in MA);

-> if results of studies included in Summary of PC + patient's leaflet;

-> if product is authorised in all MSs (except for PUMA):

- **Non-orphan products: 6-month extension of SPC (patent protection)** *[not when MAH applied for +1 market protection]*
- **Orphan medicinal products: + 2 additional years of market exclusivity**
- **PUMA: 8+2 years of data+market protection**

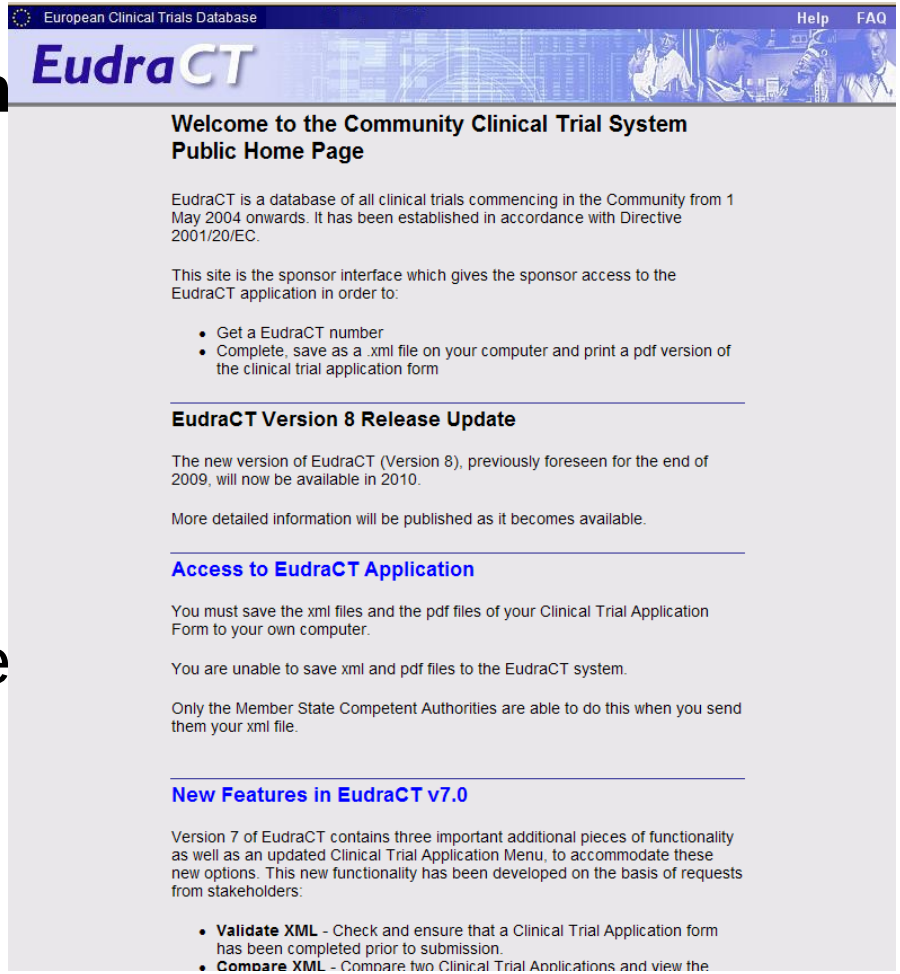
- *Product-specific or class waiver does **NOT** trigger the reward*
- *« negative » PIP results do allow reward*
- *Inconclusive studies in PIP do **NOT** trigger the reward*

Provision of Information

Paediatric clinical trials in EUDRACT:

- To include results of all clinical trials and of other trials 'submitted to NCAs'
- To include third countries trials linked to a PIP
- Paediatric information to be made public
- Expected to be implemented: Q1 2011

Public access to


European Clinical Trials Database Help FAQ

EudraCT

Welcome to the Community Clinical Trial System Public Home Page

EudraCT is a database of all clinical trials commencing in the Community from 1 May 2004 onwards. It has been established in accordance with Directive 2001/20/EC.

This site is the sponsor interface which gives the sponsor access to the EudraCT application in order to:

- Get a EudraCT number
- Complete, save as a .xml file on your computer and print a pdf version of the clinical trial application form

EudraCT Version 8 Release Update

The new version of EudraCT (Version 8), previously foreseen for the end of 2009, will now be available in 2010.

More detailed information will be published as it becomes available.

Access to EudraCT Application

You must save the xml files and the pdf files of your Clinical Trial Application Form to your own computer.

You are unable to save xml and pdf files to the EudraCT system.

Only the Member State Competent Authorities are able to do this when you send them your xml file.

New Features in EudraCT v7.0

Version 7 of EudraCT contains three important additional pieces of functionality as well as an updated Clinical Trial Application Menu, to accommodate these new options. This new functionality has been developed on the basis of requests from stakeholders:

- **Validate XML** - Check and ensure that a Clinical Trial Application form has been completed prior to submission.
- **Compare XML** - Compare two Clinical Trial Applications and view the

Art. 45 and 46 **(completed studies for authorized products)**

- Art. 45: all **existing** paediatric studies to be communicated to EMEA/NCAs (deadline 26/1/2008) → approx. 10,000 emails received
- Art. 46: results of all **new** paediatric studies, sponsored by applicant, to be submitted to EMEA/NCA within 6 months of completion (LPLV), whether part of a PIP or not.

Part 3

Results so far

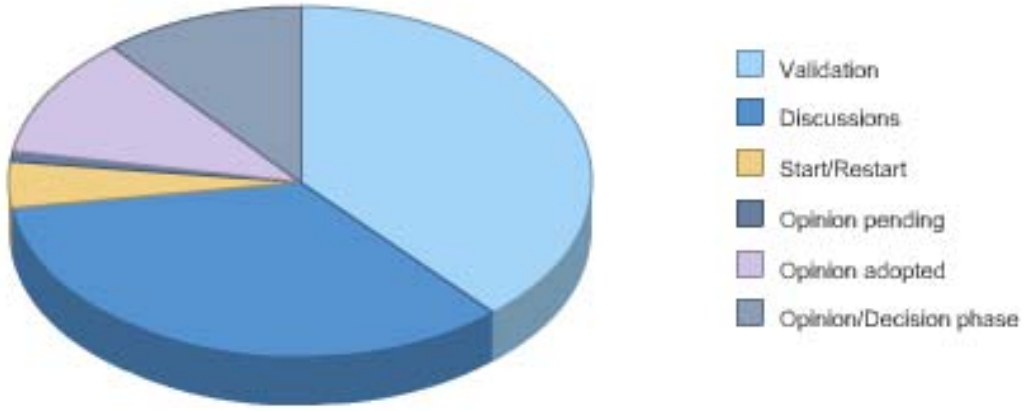
EMA decisions @ 30 Apr 2010

Year	Number of Modifications	Total Number of Applications
2007	0	3
2008	4	125
2009	49	253
2010	24	51
Grand Total	77	432

High workload for EMA and PDCO

Current number of active (open) applications
(30 April 2010)

Aggregated Status	Number of Applications
Validation	118
Discussions	105
Start/Restart	13
Opinion pending	3
Opinion adopted	34
Opinion/Decision phase	34
Grand Total	**307**

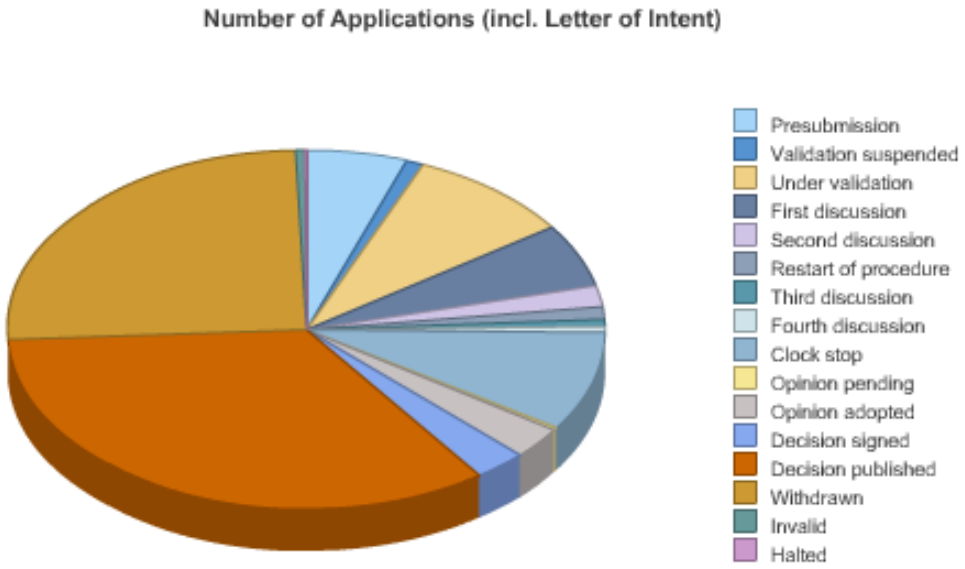


High workload for EMA and PDCO

Total procedures (including LoI and modifications)

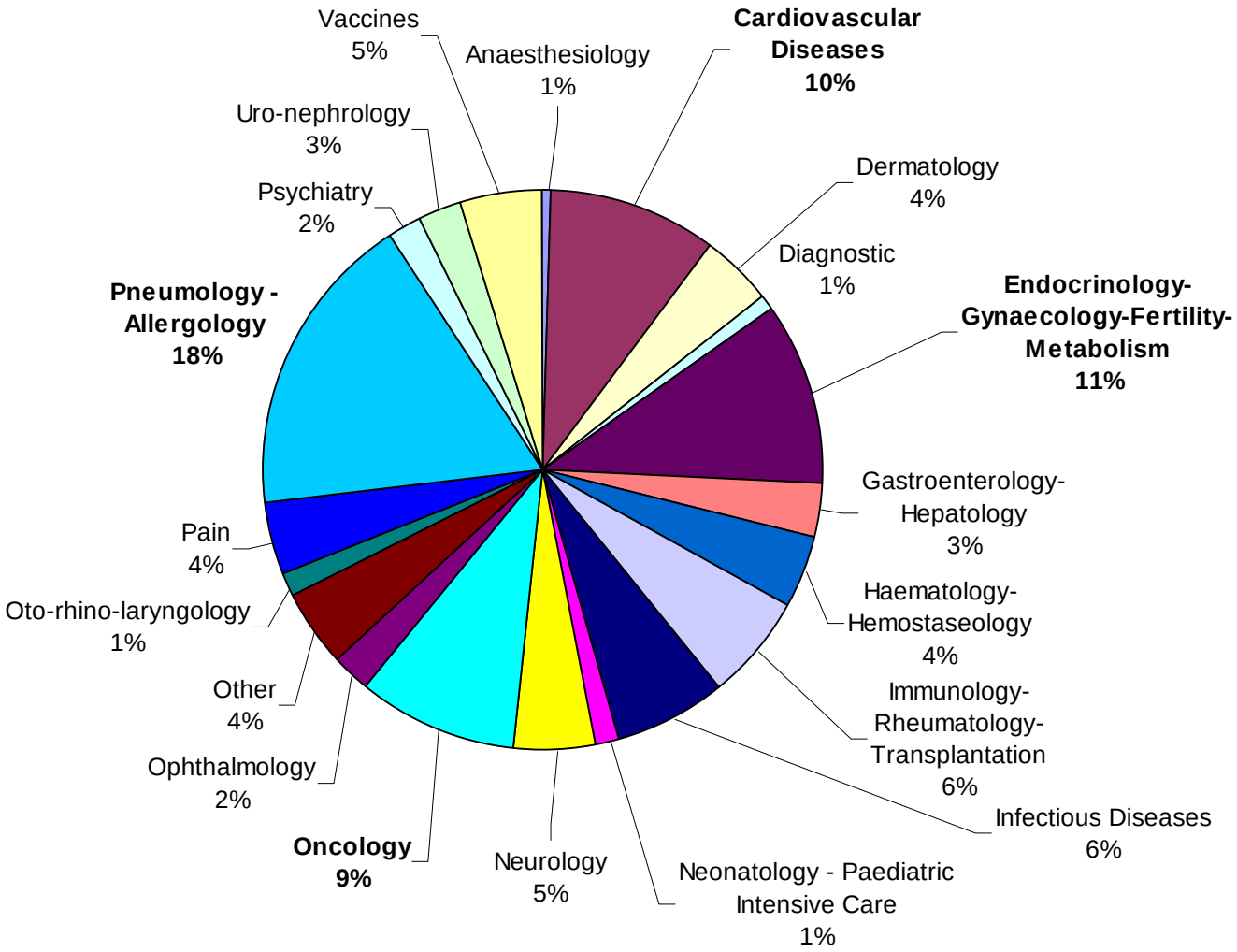
(July 2007 - 30 April 2010)

Name	Number of Applications
Presubmission	65
Validation suspended	11
Under validation	107
First discussion	68
Second discussion	23
Restart of procedure	13
Third discussion	8
Fourth discussion	6
Clock stop	107
Opinion pending	3
Opinion adopted	34
Decision signed	34
Decision published	405
Withdrawn	302
Invalid	6
Halted	1
Grand Total	**1193**



Number of Applications
(excluding modifications)

N=817
30 Apr 2010



Withdrawn applications / Orphan MP

APP008 Number of Withdrawn LOIs and Applications

Type	Started	After Opinion	Number of Applications
Letter of Intent	No	No	58
Letter of Intent Total			**58**
Application	No	No	25
	Yes	No	139
		Yes	12
Application Total			**176**

Submitted in	PIP/Waiver	Number of Modifications	Total Number of Applications
2007	Full Waiver	0	9
	PIP	0	30
	2007 Total	**0**	**39**
2008	Full Waiver	0	30
	PIP	0	71
	2008 Total	**0**	**101**
2009	Full Waiver	1	21
	PIP	18	58
	2009 Total	**19**	**79**
2010	PIP	0	1
	2010 Total	**0**	**1**

APP010 Number of Applications with Orphan designation

Year	Number of Applications
2007	9
2008	49
2009	41
2010	18
	17

Updated April 2010

Updated 20/11/2010

Annex of the November 2010 PDCO meeting report

	2008 (January to December)	2009 (January to December)	2010 (January to current month)	Cumulative total (2007 to 2010)
Total number of validated PIP/waiver applications	271	273	311	941[1]
Applications submitted for a product not yet authorised *(Article 7[2])*	186	191	269	685 *(73%)*
Applications submitted for a product already authorised and still under patent, in view of a submission of a variation/extension for a new indication, pharmaceutical form or route of administration *(Article 8[2])*	75	72	40	232 *(25%)*
Applications submitted for an off-patent product developed specifically for children with an age-appropriate formulation *(Article 30[2])*	10	10	3	24 *(2%)*
PIPs and full waiver indications covered by these applications	395	395	373	1334

PDCO opinions

Updated 20/11/2010

Number of Paediatric Committee (PDCO) opinions	2008	2009	2010	Cumulative total
Positive on full waiver	48	67	49	173
Positive on PIP, including potential deferral	81	122	191	396
Negative opinions adopted	4	13	6	23
Positive opinions adopted on modification of a PIP	8	51	96	155
Negative opinions adopted on modification of a PIP	0	0	4	4
Positive opinions on compliance with a PIP	5	8	8	21
Negative opinions on compliance check with a PIP	0	1	0	1
Opinions adopted under Art 14.2	0	0	2	2

Free paediatric Scientific Advice / Protocol Assistance

	Year 2007	Year 2008	Year 2009
Total SA requests	***213***	***264***	***311***
Total PA requests	***68***	***56***	***77***
Paediatric scientific advice	14	13	14
Paediatric follow-up SA	4	5	9
Paediatric protocol assistance	-	5	4
Paediatric follow-up PA	3	-	3
Total paediatric SA+PA	**21**	**23**	**30**

Updated Feb 2010

Collaborations
(national health authorities, other EU institutions, etc.)

- FDA: paediatric cluster with FDA (Staff exchanges, Monthly TCs [now with PMDA/Japan], FDA participation to NCWG, FWG, experts meetings)
- Health Canada (confidentiality Agreement 2007)
- WHO ("Making Medicines Child Size", 2008; Network of Regulatory Agencies on Paediatric Medicines)
- ICH → guidelines on paediatrics :
  - Paediatric formulations
  - ICH E11
  - Juvenile animal studies?
  - PK for modelling, etc.

  (not on the agenda for the time being)
- EU Commission: Industry → Health Directorate; Research Dir.)

Reporting – Performance Indicators – Survey of paediatric use

- **Annual report** to the European Commission (ongoing) on companies benefiting of, or infringing the Regulation (first report published)
- **Performance indicators** are tracked for report at 6 (and 10) years
- **Survey of paed use** (ongoing)
  - 10 MS provided data (very heterogeneous) – larger states missing!
  - Analysis ongoing
  - Results presented to PDCO November 2010

FP7 funding - Health area 4.2 results (2007-2010)

Off-patent medicines for paediatric use

Call	Response	Support	EU contribution	Success Rate
2nd	15 proposals	6 projects	~ 22 mio	40%
3rd	12 proposals	3 projects	~ 18 mio	25%
4th	10 proposals	3 projects	~ 16 mio	30%
Total	37 proposals	12 projects	~ 56 mio	32%

Conclusions on impact of EU Paediatric legislation

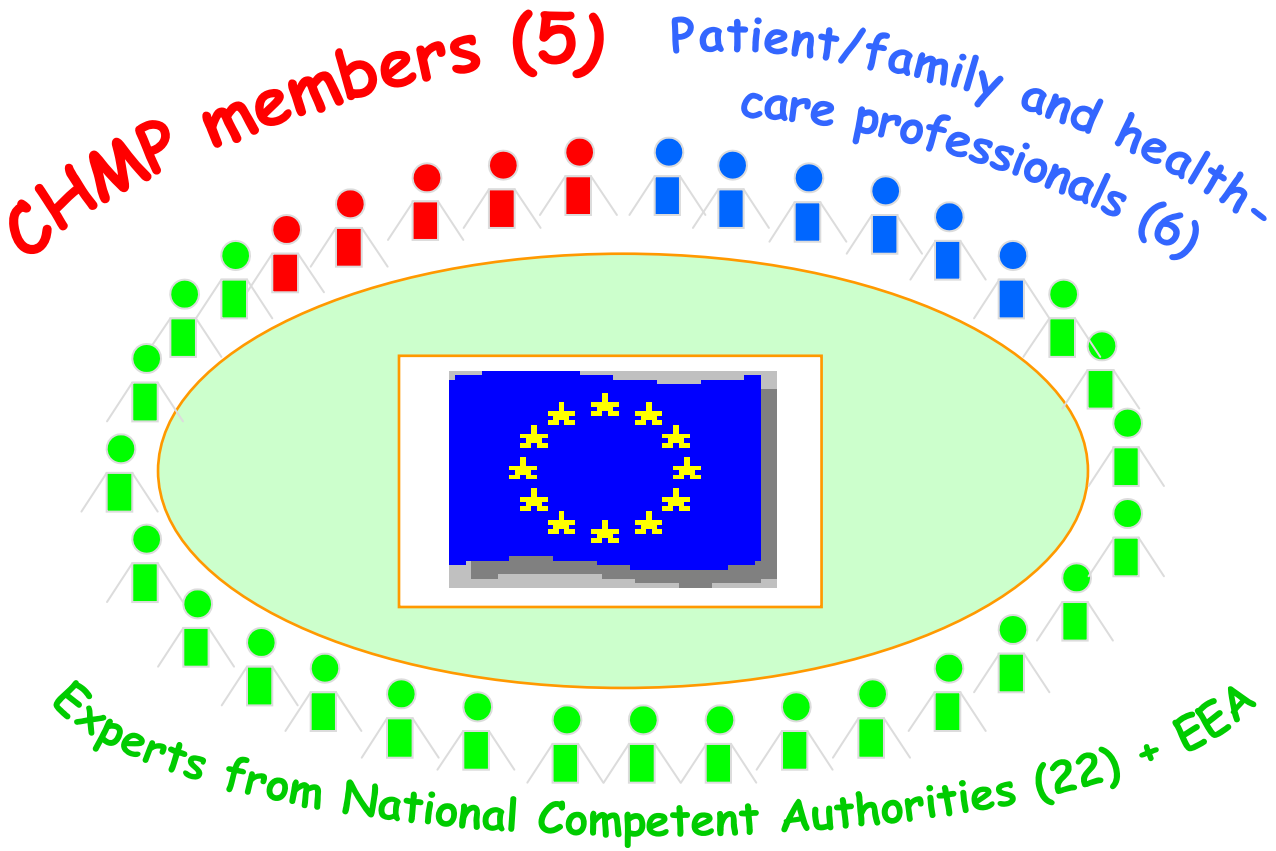
Impact on workload and resources at EMA is high (not just on EMA)

- Most legal deadlines have been met with success, thanks to preparation and motivation of staff and Committee
- Public funding assigned through FP7
- No evidence yet of an increase in clinical trials
- Active and positive collaboration within the Agency
- Product information changes already visible
- Delayed publication in EudraCT: Q3 2010

Part 4

PDCO responsabilities and organisation

Paediatric Committee (PDCO)



+ alternates

Composition of PDCO

- 27 members, 1 from each EU member state
  - ✓ 5 nominated by CHMP (members of both committees)
  - ✓ The remaining 22 are nominated by the remaining 22 member states
- 6 representatives nominated by EU Commission:
  - ✓ 3 representatives of Healthcare professionals
  - ✓ 3 representatives of Patients' and Parents' organizations
- 2 representatives of EEA MS (Norway, Iceland): no right to vote

Each member has an alternate

Functioning of PDCO

- Chair and vice-chair nominated among its members (not alternates). Can be renewed once.
- Members, chair and vice-chair have 3-year terms.
- Meets 12 times a year, for 2.5-3 days, in London at EMA
- 1-2 informal meetings per year (1.5 days) in rotating EU countries

"Main" roles of PDCO

- To adopt opinions on PIP/waivers (decision signed by EMA Executive Director, not by EU Commission)
- To provide advice on any question relating to paediatric medicines (at the request of the Agency's Executive Director or the European Commission)
- To assess data generated in accordance with agreed PIP, to adopt opinions on the quality, safety or efficacy of any medicine for use in the paediatric population (at the request of the CHMP or a national competent authority)

"Other" roles of PDCO

- To advise Member States on the content and format of data to be collected for a survey on all existing uses of medicinal products in the paediatric population
- To establish and regularly update an inventory of paediatric medicinal product needs
- To advise and support the EMA on the creation of a European network of persons and bodies with specific expertise in the performance of studies in the paediatric population
- To advise the EMA and the EU Commission on the communication of arrangements available for conducting research into paediatric medicines.

Waivers:

Three types:

- **"total" (product-specific) waiver** → for all conditions/indications being applied for a product
- **partial waiver:** one and more subset(s), indication(s), <u>but there is a PIP!</u>
- **Class waiver:** for a class of products in a condition, or for all products aimed at a condition

<u>Legal grounds:</u>

- *Lack of efficacy and safety*
- *Disease or condition occurring only in adults population*
- *Lack of significant therapeutic benefit*

Deferral(s):

Instrument to avoid delaying marketing authorisation in adults

"Deferred" means Marketing Authorisation Application for adults is possible before initiation / completion of one or more measures in the PIP

- **Given by study / measure** (cfr US PREA: "total" deferral)
- **For initiation and / or completion of study / measure:** completion of a clinical trial may

Part 5

ENPREMA

European Network of Paediatric Research at EMA

ENPREMA

Key operational goals

- To link together existing networks
- To provide expertise and access to infrastructure for industry to conduct studies in children
- To define consistent and transparent quality standards
- To harmonise clinical trial procedures
- To define strategies for resolving major challenges
- To communicate with external stakeholders

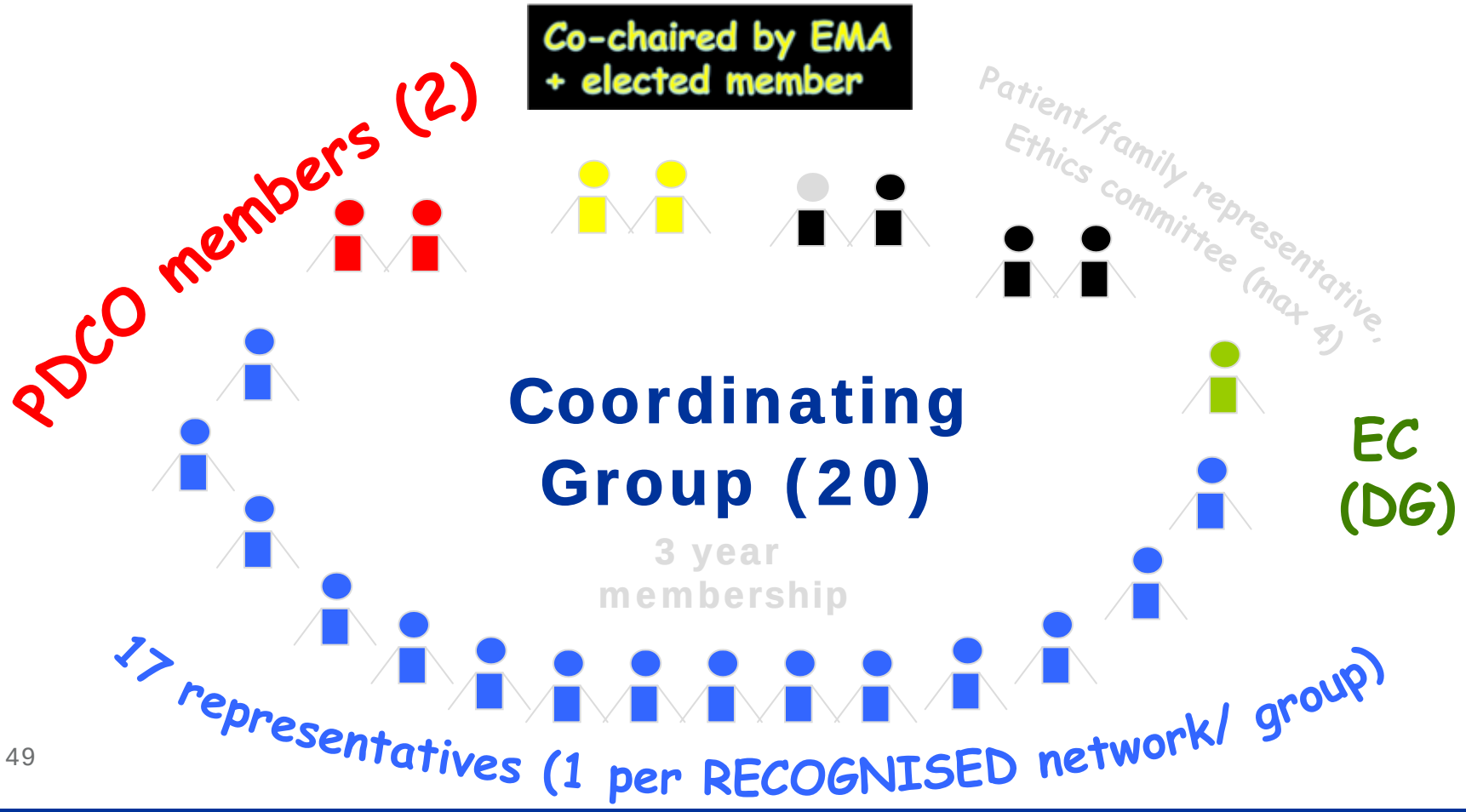
ENPREMA

What has been achieved so far ?

- Implementation strategy adopted by EMA Management Board (Jan 2008)
- Identification of existing networks
  - List published on EMA webpage (2009)
- First workshop with existing networks (Feb 2009)
- 2 working groups:
  - **WG 1:** structure and operational model
  - **WG 2:** definition of recognition criteria (Criteria published on the EMA web-page for public consultation, Feb 2010)
- Definition of structure and coordination group (2010)

Proposed Structure Coordinating Group

ENPREMA



ENPREMA

Coordinating Group

- Max 20 members, for a maximum of 3 years
- 2 Members of the Paediatric Committee
- 1 Member of the European Commission
- 17 representatives of networks / groups of networks
- No industry in the group but obvious stakeholder

ENPREMA

Role of EMA

- to provide secretarial support to the activities of the network
- to organize and host meetings of the network
- to coordinate exchange of information between network partners
- to provide information to external partners and stakeholders

The EMA does not decide on recognition

ENPREMA

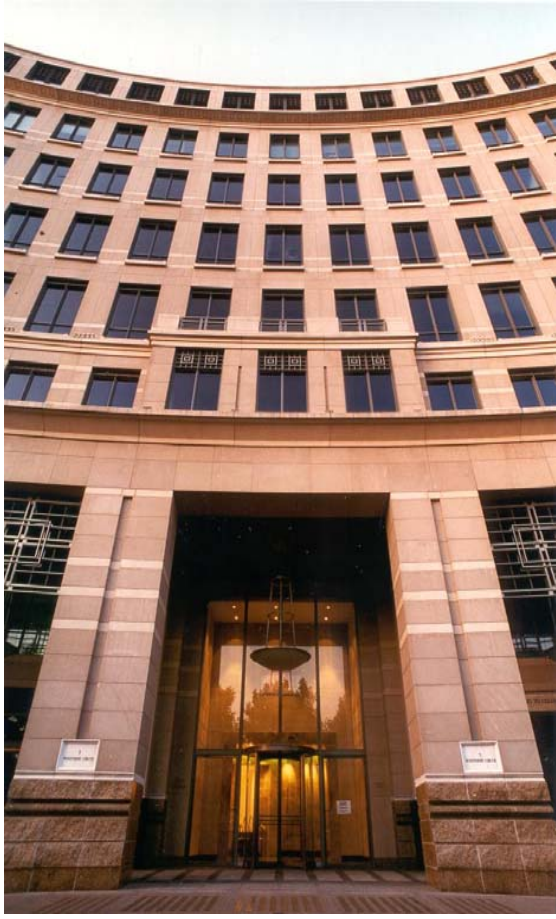
Next Steps

- 3-month period for networks to do self-assessment and publish results
- All networks fulfilling recognition criteria automatically member of ENPREMA
- Implementation of coordinating group by end of 2010
- Election of Chair of coordinating group during first official ENPREMA meeting scheduled for 10/11 March 2011 (2 days, one with industry)

ENPREMA

More information

http://www.ema.europa.eu/htms/human/paediatrics/network.htm



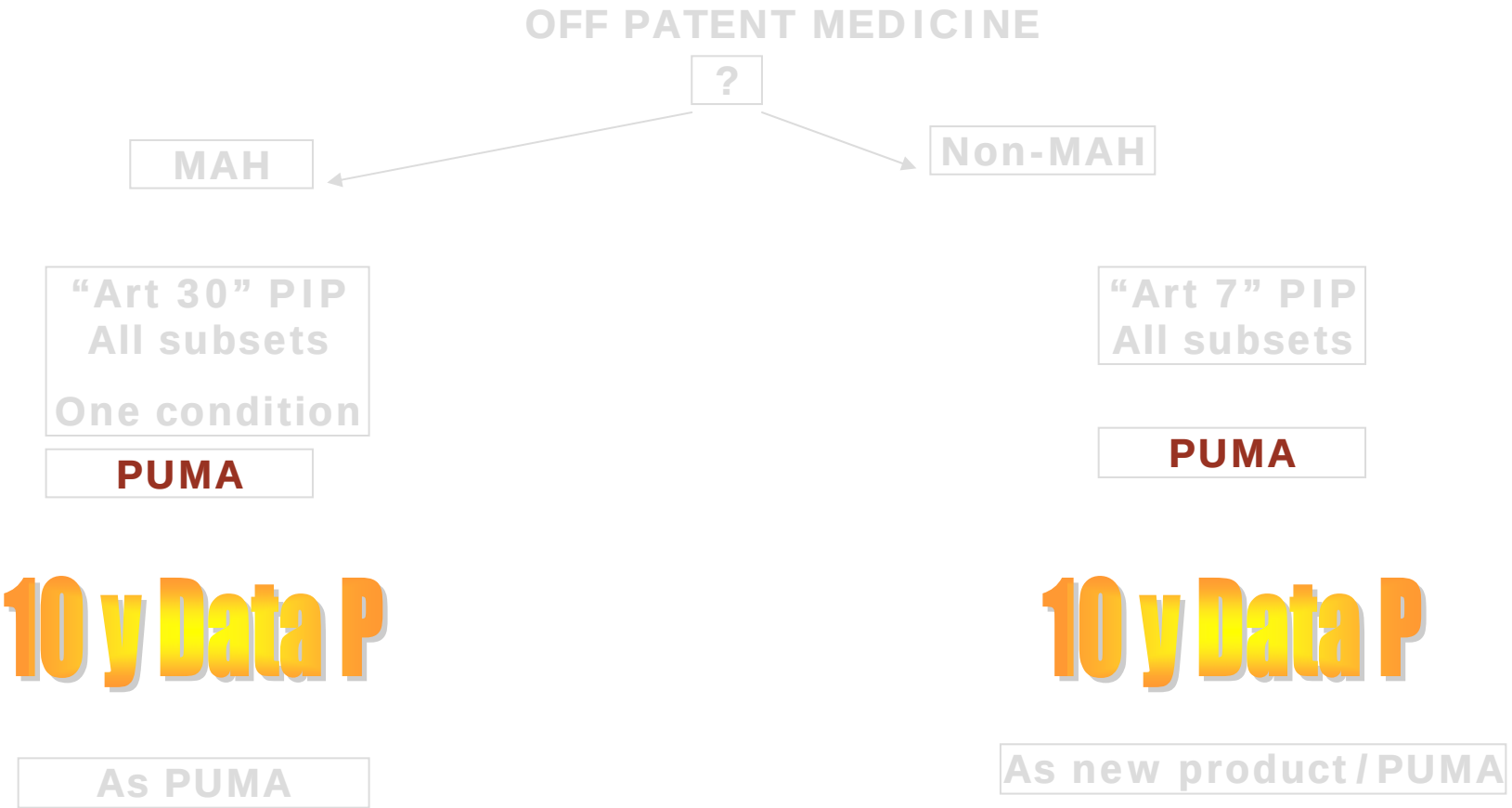
Part 6

PUMA
Paediatric Use Marketing Authorisation

PUMA

- New dedicated type of Marketing Authorisation application (MAA) for exclusive paediatric use
- Intended for off-patent medicinal products:
  - Authorised: PIP is voluntary (art 8 does not apply, as there is no patent/SPC)
  - Not authorised: PIP is compulsory (as art. 7 will apply at MAA even if not a new active substance), only possible reward is PUMA reward (as no patent/SPC)
- Incentives:
  - 10 year marketing protection (compliance with agreed PIP necessary) on data contained in the PUMA (8+2+[1])
  - Fee reduction for MA/postauthorisation
- Projects funded from FP7 in the priority list of off-patent products should aim at a PUMA

PUMA proposal



PUMA

- Results so far rather disappointing
- 24 to 30 PIP applications for possible PUMA

  (difficult to say as PIP application for new product + possible PUMA not identifiable)
- 2 PUMA applications so far
- Incentive is weak (data protection + market protection) and limited to the paediatric data

Conclusion

Implications of paediatric regulation for national agencies

(national competent authorities)

- Nomination of representatives in PDCO
- Paediatric regulation applies also to “national” products, not only centralised ones:
  - Validation of each “new medicinal product” triggers art. 7 → need for PIP + results or deferral / waiver
  - Existing, on-patent products trigger art. 8 for new indications, routes and ph. Forms
  - Paediatric validation” task of the national agency. Possible stop at validation!
  - Compliance check: for completed studies/measures, can be either done by national agency or delegated to PDCO

Thank You

and thanks to Agnes Saint-Raymond and the Paediatric team for analyses, data and graphs

PDCO celebration for 1000th application