EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Paediatric regulation: an update on submissions of paediatric investigation plans

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The EU Paediatric Regulation

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

Pillars of the Paediatric Regulation

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

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

PIPs

Why do we need PIPs?

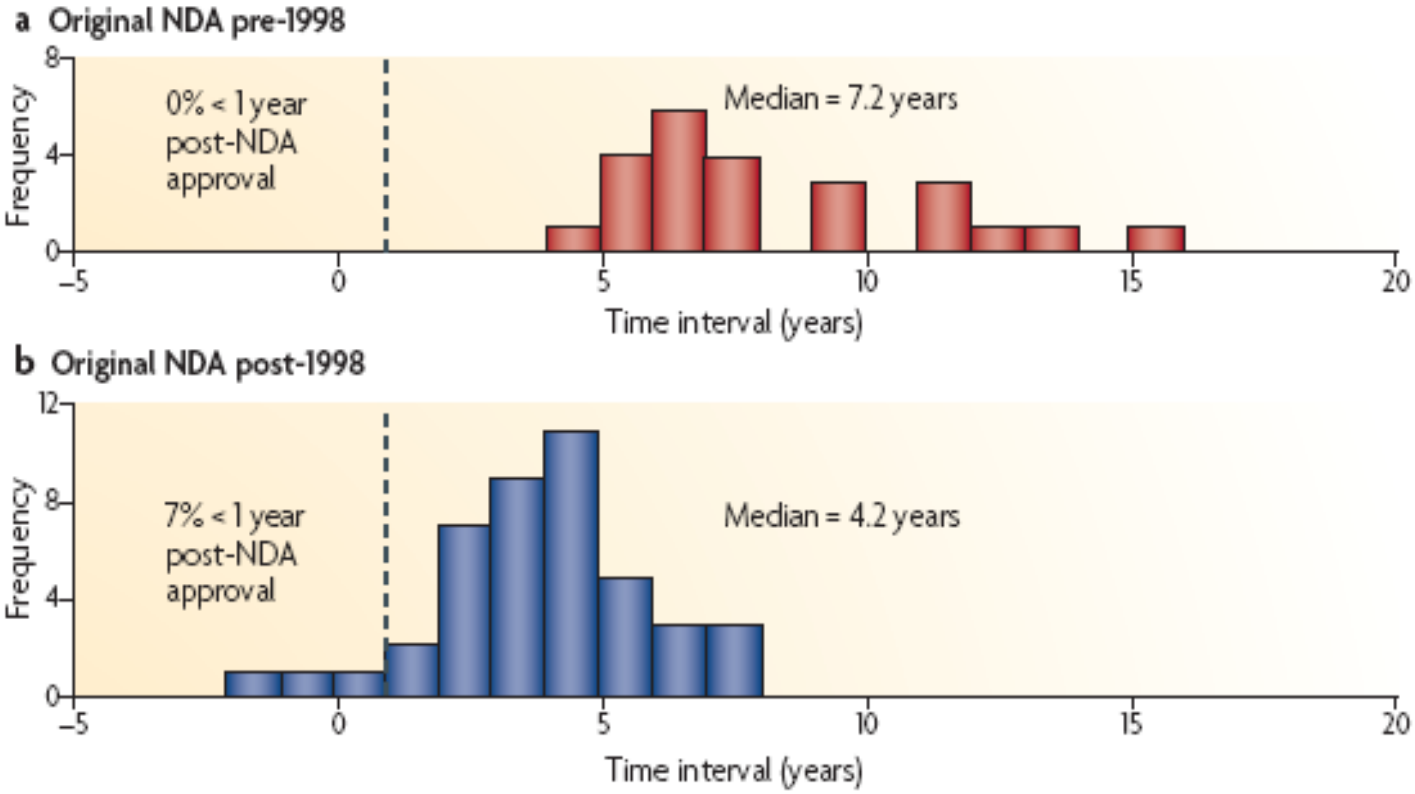


Figure 1 | **Impact of legislation on the timeliness of supplemental paediatric NDA submissions.** Distributions of original New Drug Application (NDA)-to-supplemental NDA time

Impact on MA timelines
(Nature Reviews, June 2007)

When can a medicinal product be authorised?

3 elements:

- Quality
- Safety
- Efficacy

In one or more specific therapeutic indications

To establish:

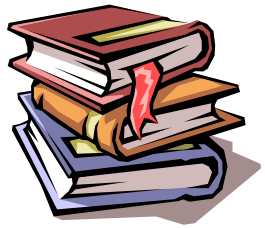
- benefit/risk ratio (to be positive!)

What is a PIP?

"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



When do applicants need to submit a PIP?

Paediatric regulation:

"not later than upon completion of the human pharmacokinetic studies in adults specified in Section 5.2.3 of Part I of Annex I to Directive 2001/83/EC"

Where do applicants submit the PIP?

To the European Medicines Agency

(both for centralised and national/DCP/MRP products)

However, validation and (possibly) compliance check of regulatory procedures attracting a PIP may occur at national level

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), but there is a PIP!
- **Class waiver:** for a class of products in a condition, or for all products aimed at a condition

Legal grounds:

- *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 be deferred, but initiation may not be!
- **Completion dates established**

Structure of the PIP

- Section A: Regulatory with condition/indication
- Section B : Targeted conditions / indications and needs
  - **General pharmacology**
  - Clinical need by age groups/subsets (with prevalence)
  - Benefit of the product versus alternatives
- Section C : Waiver request
- Section D: Summary of existing data and Development plan
  - **Quality**
  - Non-clinical
  - Clinical (±Risk management Plan)
- Section E: Timelines, deferral request

Pharmaceutical form / formulation

Quality: main points

- **Chemical / Biological :**
  - Summary of quality aspects
  - Specificites related to paediatric-specific route of administration:
    - parenteral/ transcutaneoous/ nasal spray …

→ Toxicity of the constituents / excipients *(e.g. ethanol/PEG/preservatives)* / colours in children

→ Development of an age-appropriate formulation

- number of strengths available
- size of tablets or concentration / volume
- taste/smelling → acceptability
- Convenience of administration

Quality: some issues

- Minimal dosage frequency:
  - Pharmacology of extended vs immediate formulations
  - Impact of the number of pills/ taste on treatment adherence in children/ adolescents
- Size:
  - Limitations for children < 6 years for large size tablets
  - New formulations: microtablets/ spray etc.
- Convenient, easy and reliable administration:
  - Role of Fixed Dose Combination - debated
  - SC Administration without needle

Validation / Compliance check of a regulatory procedure (MA/ variation/line extension application)

Validation

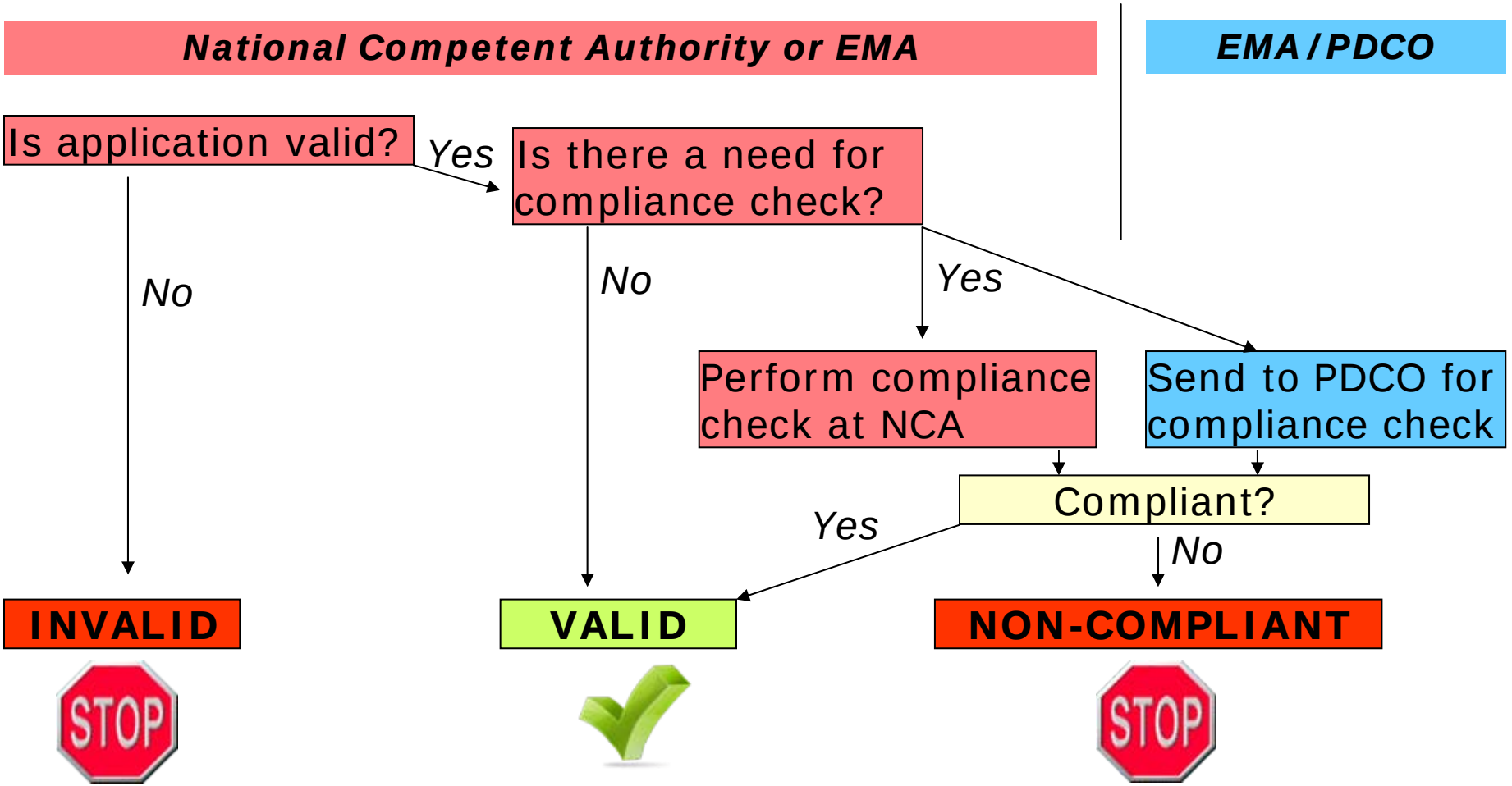
- Performed by either European Medicines Agency (centralised procedure) **or National Competent Authority (national/MRP/DCP)**
- **NCAs cannot delegate validation to EMA**
- Validation always necessary, compliance check not always needed
- Several checks:
  - ✓ Condition/indication, **pharm. form** and route must correspond to agreed PIP/waiver/class waiver
  - ✓ Documents attached (full study reports, OR PIP with deferral, OR waiver [product-specific or class])
  - ✓ Need for compliance check? Y/N

Which documents for pharmaceutical form?

Compliance Check

- Can be performed by:
  - National Competent Authority (can delegate to PDCO)
  - European Medicines Agency (PDCO)
- Compliance check will determine:
  - Validation of application for MA (or variation/extension)
  - Access to reward (after FINAL compliance check; both positive and negative study results grant reward, provided other conditions met)

Possible outcome of validation / compliance check procedure:



Compliance check for new pharmaceutical forms: documents required

- Appropriate sections of the **Quality Overall Summary (Module 2):**
  - **Section 2.3.P.1** Description and composition of the drug product
  - **Section 2.3.P.2** Pharmaceutical Development
  - **Section 2.3.P.3** Manufacture
  - **Section 2.3.P.5** Control of drug product (including specifications)
  - **Section 2.3.P.7** Container Closure System
  - **Section 2.3.P.8** Stability
- Not necessary to go to the details of the module 3.

Compliance check: principles

Based on:

- full study report for clinical studies (EU Commission Guideline)
- Specific documents for quality
- opinion's key binding elements

Compliance check ***≠ assessment***

Judged as 'yes' or 'no' on key binding elements.

- One « no » = noncompliance!
- NO negotiation,
- NO clock-stop,
- NO re-examination

Results so far

EMA decisions @ 30 Apr 2010

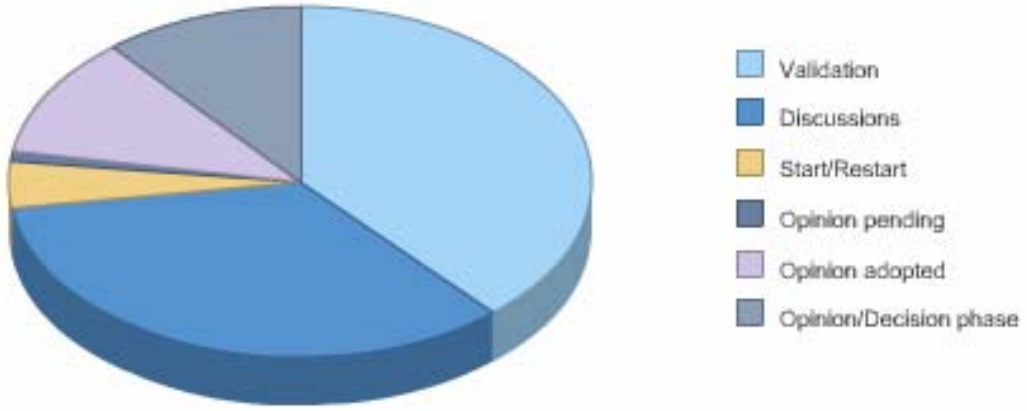
Year	Number of Modifications	Total Number of Applications
2007	0	3
2008	4	125
2009	49	253
2010	24	51
Grand Total	77	432

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**

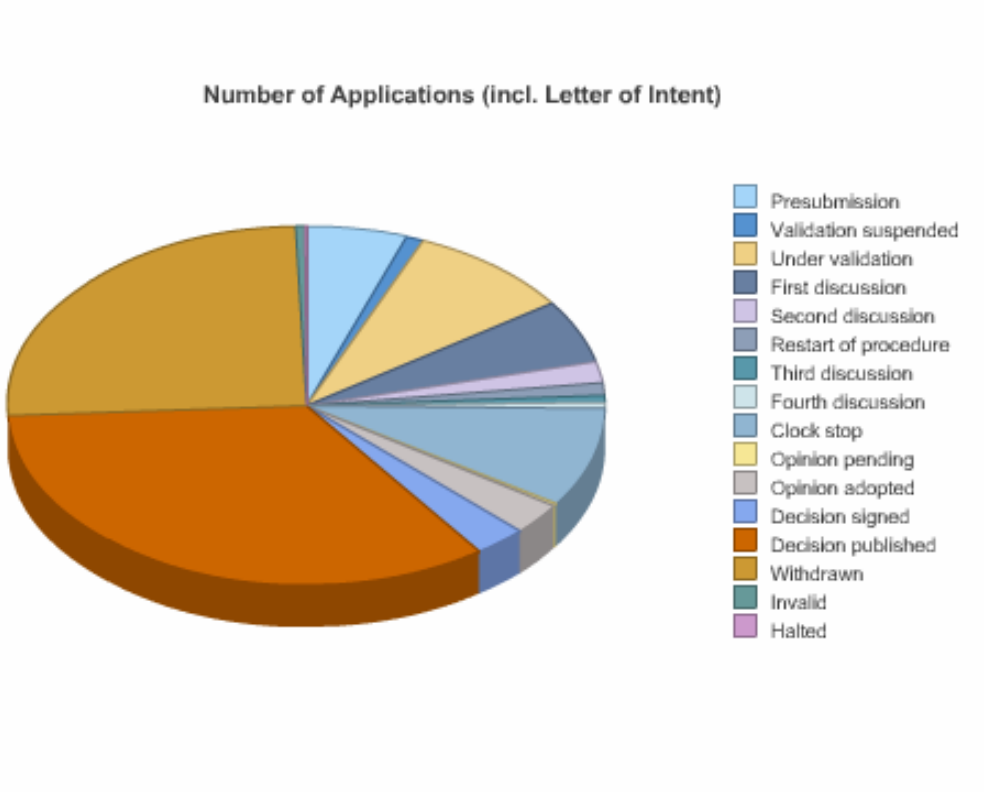


High workload for EMA and PDCO

Total procedures (including LoI and modifications)

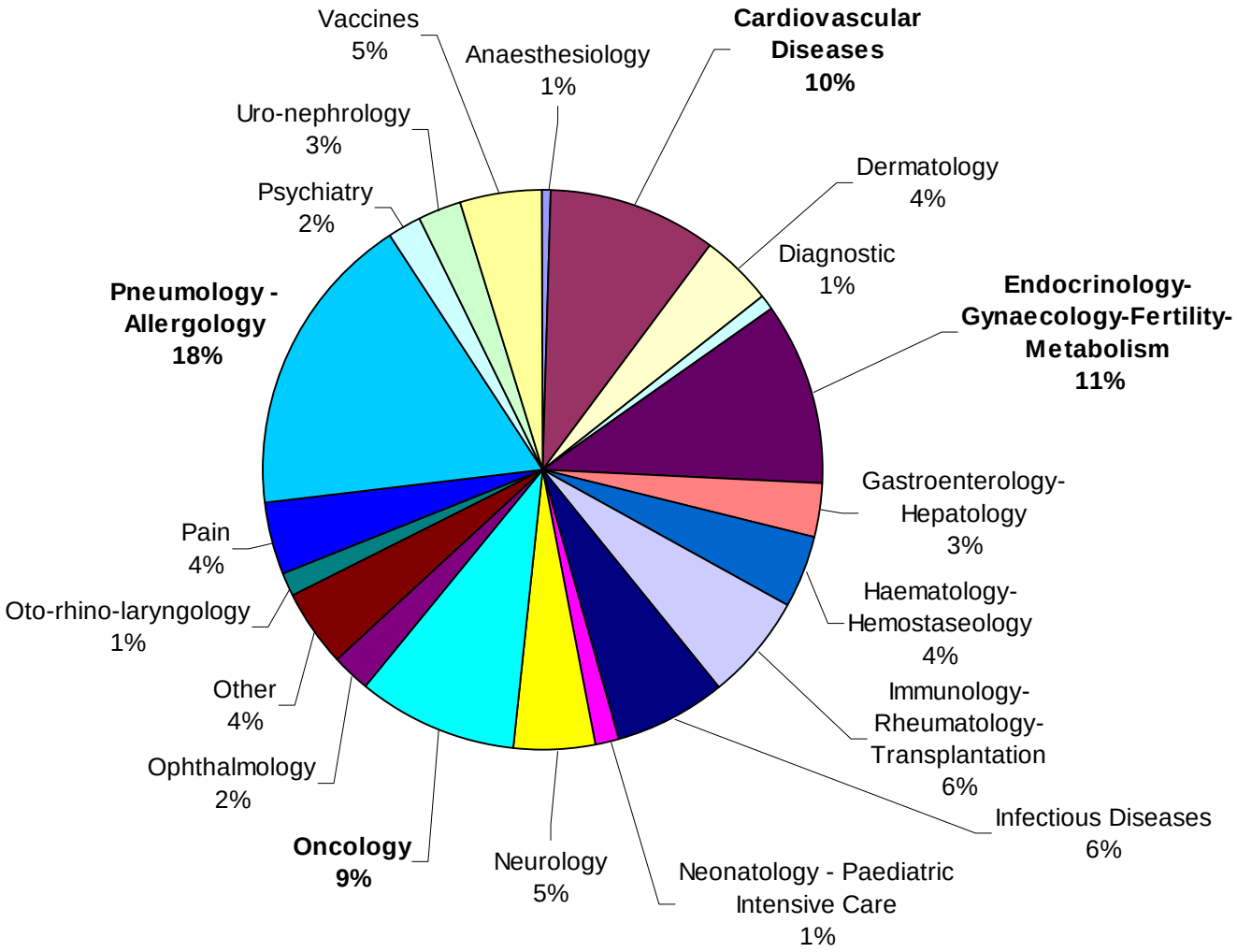
(July 2007 - 30 April 2010)

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**

APP010 Number of Applications with Orphan designation

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

	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	122	751[1]
Applications submitted for a product not yet authorised *(Article 7[2])*	186	191	104	520 *(69%)*
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	16	208 *(28%)*
Applications submitted for an off-patent product developed specifically for children with an age-appropriate formulation *(Article 30[2])*	10	10	2	23 *(3%)*
PIPs and full waiver indications covered by these applications	395	395	150	1111

PDCO opinions

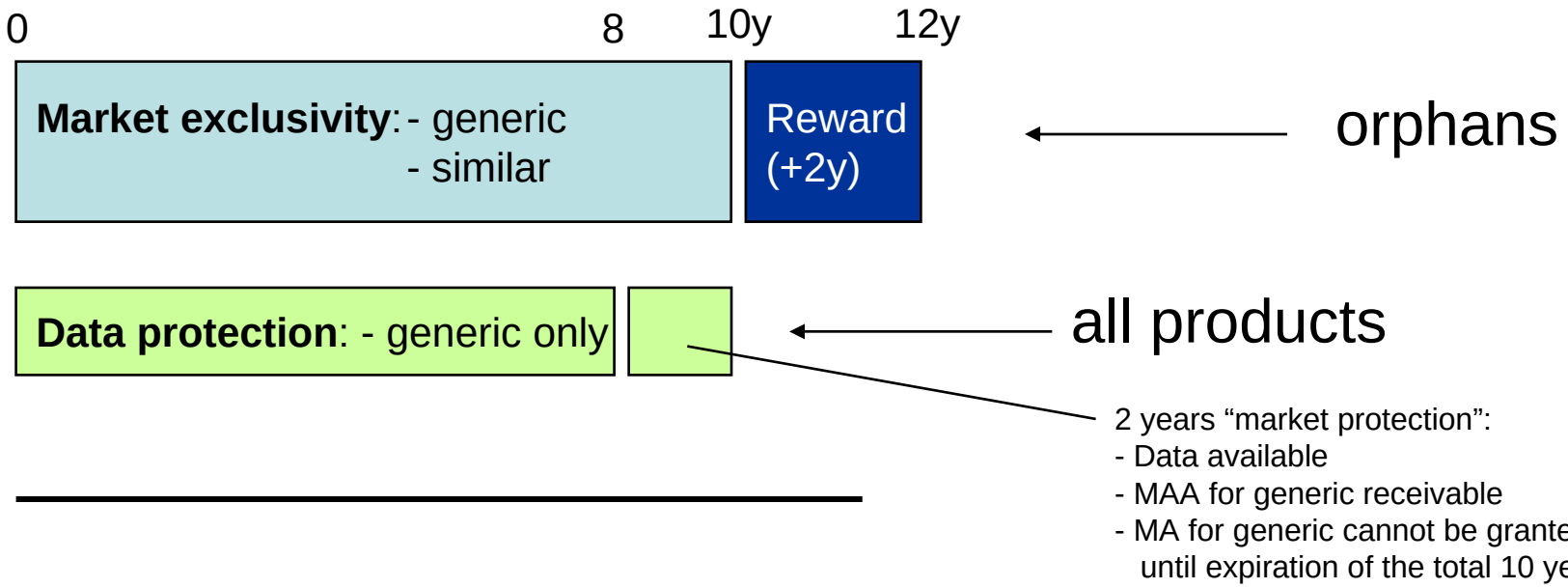
Number of Paediatric Committee (PDCO) opinions	2008	2009	2010	Cumulative total
Positive on full waiver	48	67	13	138
Positive on PIP, including potential deferral	81	122	34	239
Negative opinions adopted	4	13	3	20
Positive opinions adopted on modification of a PIP	8	51	36	95
Positive opinions on compliance with a PIP	5	8	3	16
Negative opinions on compliance check with a PIP	0	1	0	1

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**

Thank You

Data protection, patent, SPC and paediatric reward



Paediatric reward for patented MP:

There has to be a SPC (SPC is prolonged, not patent