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The Paediatric Committee (PDCO) and the Paediatric Investigation Plan (PIP) What Is relevant for Rare Diseases

The regulation on paediatric medicines to
stimulate useful research on medicines for
children is already in its 3rd year

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Some slides based on EMA or AEMPS sources,
gratefully acknowledged, but opinions are personal

Useful section on "Medicines for children" [http:// www.ema.europa.eu/htmls/human/paediatrics/introduction.htm](http://www.ema.europa.eu/htmls/human/paediatrics/introduction.htm)





It is generally agreed that medicines are insufficiently developed for children

The current situation (before the Paediatric Regulation)

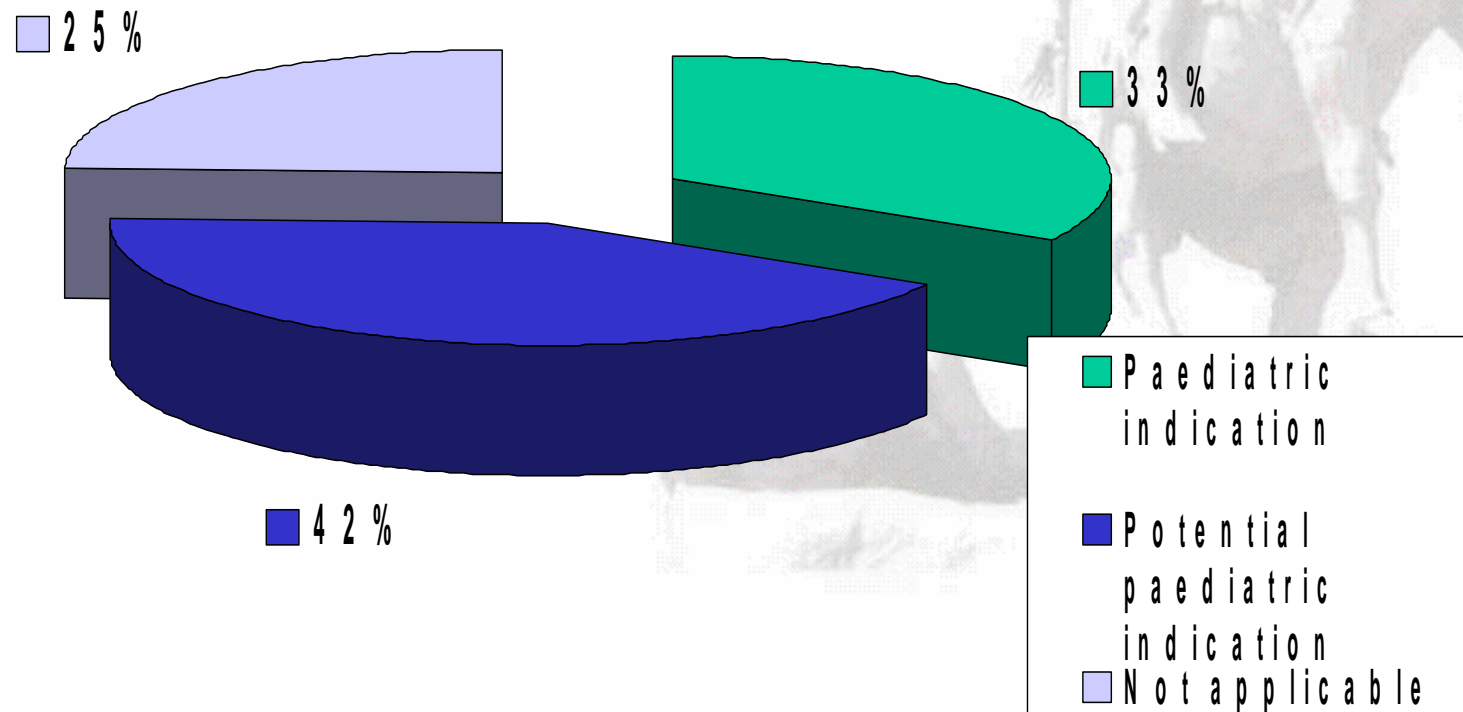
- 20% of the EU population, i.e. 100 million, is aged less than 16 years
 - ⇒ **premature neonate, term neonate, infant, child, adolescent**
- **50-90% of paediatric medicines** have not been tested and evaluated for children (used "**off label**")
- US paediatric data (BPCA) not submitted to EU Agencies


Potential risks:

- *adverse effects (overdosing)*
- *inefficacy (underdosing)*
- *improper formulation*
- *delay in access to useful medicines*

No improvement in recent past

258 Active moieties approved between 1995- January 2006) through EMA



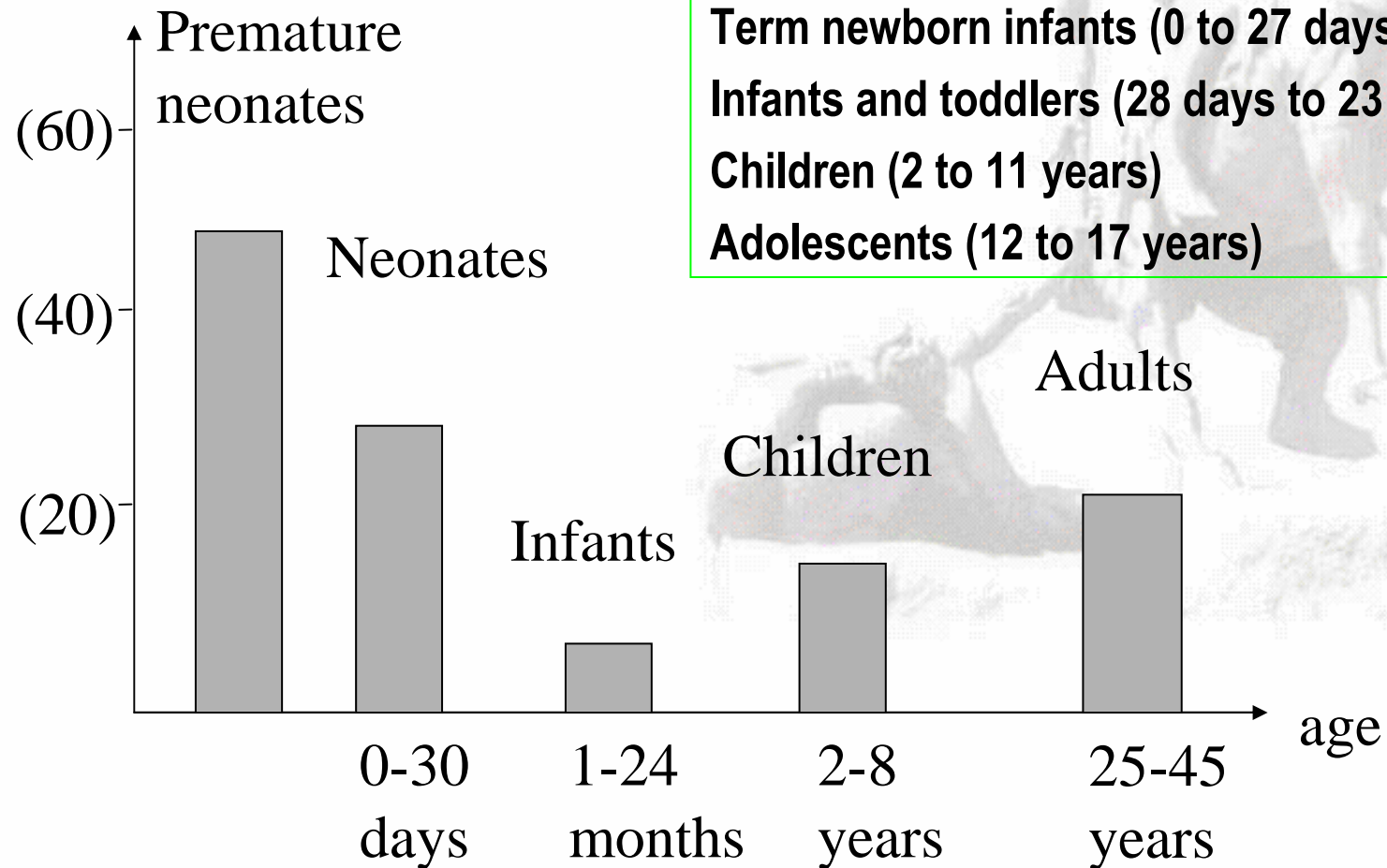


There is, then, significant lack of knowledge on many aspects of medicines for paediatric populations.

And extrapolation from adults is not a simple matter. Let us see a simple illustration...

PK does change with age in a non-linear way

Half-life of diazepam (hours)



Medicines evaluation for registration

Quality

Safety

Efficacy

In Normal Conditions Of Use, (i.e. "on label") meaning:

Summary of Product Characteristics,

Patient Leaflet

Packaging

And, if centralised as orphan medicines, **European Public Assessment Report (EPAR)** with a "summary for the public" written with input from patients' organisations via **PCWP**

Registration is made at the request of sponsors, generally drug companies. What if they do not find it worthwhile/profitable to register/develop drugs or generate data on them to meet health needs?

orphan diseases, medicines for children, diseases of poverty...

- One approach is to ensure that the required medicinal products becomes profitable to the sponsors. There are two main examples in the EU :
 - Orphan drugs (EU regulation in operation since 2000)
 - Drugs for paediatric populations (the paediatric regulation (Regulation -EC- No 1901/2006 + 1902/2006) came into force on the 26 January 2007)
- Another is for public institutions to take the initiative and do it themselves. This is also a possibility in the paediatric regulation but implementation is proving difficult

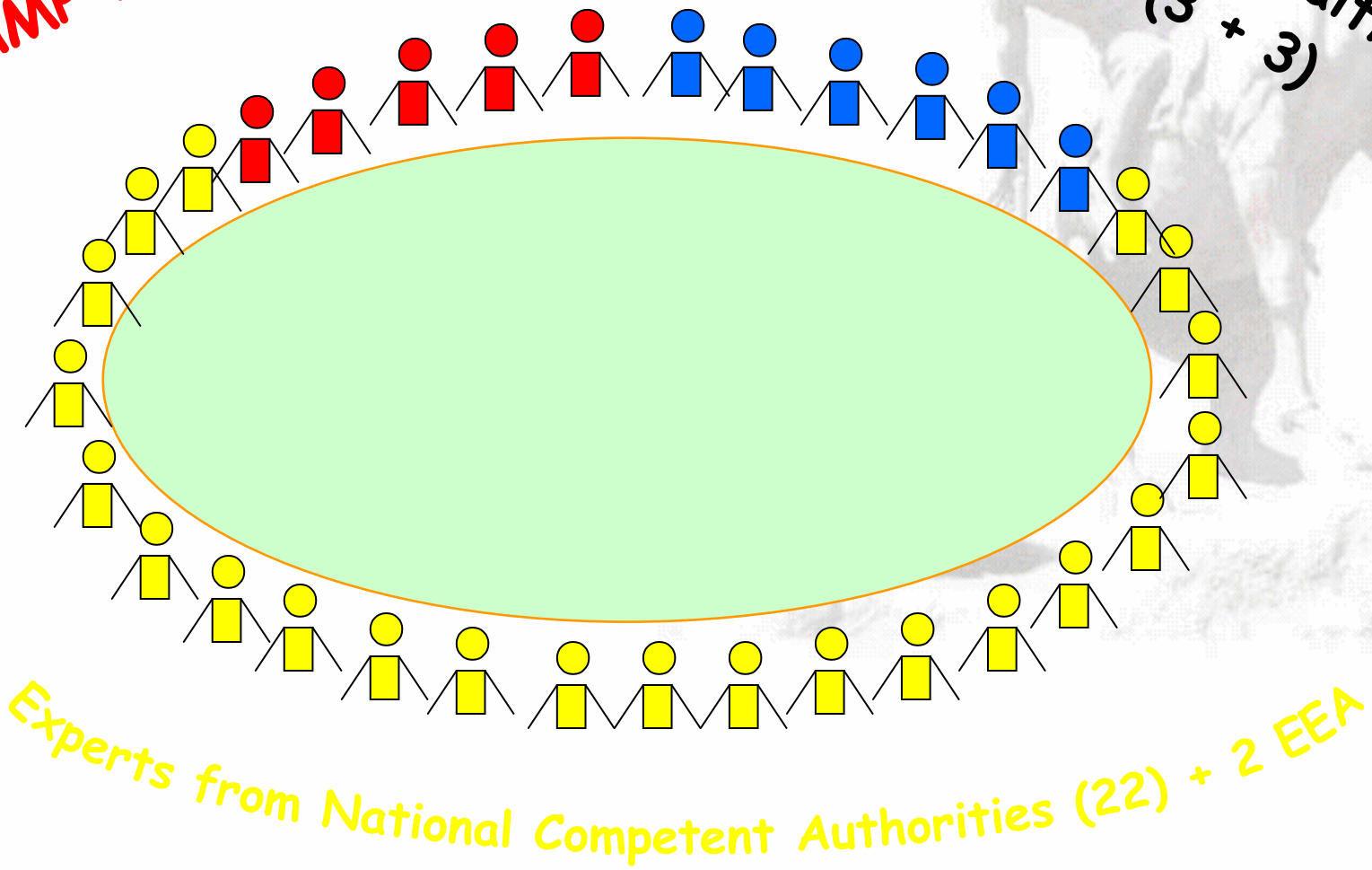
Now, we have the Regulation on paediatric Medicines (Regulation - EC- No 1901/2006 + 1902/2006) to **stimulate** needed research on them. It came into force on the 26th January 2007

(The PDCO met for the 1st time on July 2007)

The Paediatric Committee (PDCO)

CHMP members (5)

Patient/family and health professionals (3 + 3)



Experts from National Competent Authorities (22) + 2 EEA

*The Paediatric Regulation combines **obligations** and **incentives/rewards** (1)*

They depend on whether the medicine...

Is under development (art 7)

Compulsory to submit a PIP

Incentive of 6 month extension data protection

Is on the market but still under data protection (art 8)

If (usually optional) PIP submitted

Reward of 6 month extension data protection

Is on the market without protection (art 30)

If developed for children according to a PIP

paediatric use marketing authorization (PUMA) granted

Is an orphan medicine (art 37)

Compulsory, if under development, to submit a PIP


Incentive of 2 extra years of market exclusivity

*The Paediatric Regulation combines **obligations** and **incentives/rewards** (2)*

*A **Paediatric Investigation Plan (PIP)** pre-approved by the **Paediatric Committee (PDCO)** is **always** needed for the reward*

*It must be submitted to the **PDCO** early in the development for adults (end of phase I). A **deferral** of its implementation can be agreed, A **waiver** is granted in some circumstances (e.g. adult only disease, lack of expected significant benefit, etc.)*

*The reward may be obtained if the **PIP** is implemented, even in cases where the results, once obtained, do not lead to any indications.*



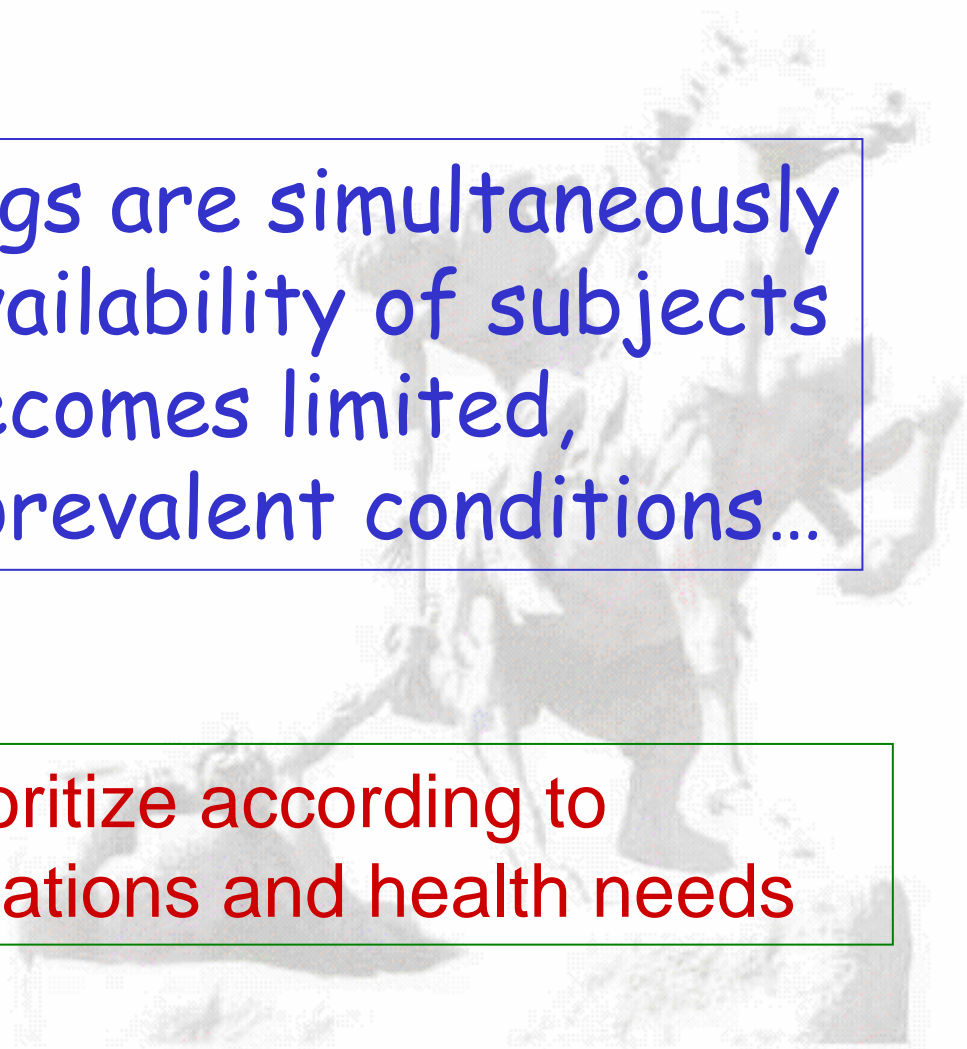
Some consequences and some
issues...

Companies cannot claim any longer that they are not interested in studying a certain indication for paediatric subjects. If the PDCO finds it of benefit for the children, they are obliged to do so

But sometimes it is not easy to distinguish between what it is an "adult only" indication or a "condition" occurring both in adults and children,

eg. a drug may be being developed in adults for an adult cancer. What if there is reason to believe that its mechanism of action would apply equally well to some paediatric cancer?

Normally, a paediatric development is, at least, "encouraged"



As so many new drugs are simultaneously investigated, the availability of subjects for clinical trials becomes limited, especially for less prevalent conditions...

The PDCO tries to prioritize according to perceived drug expectations and health needs

Agreeing on (establishing) the PIP is a (binding) responsibility of the PDCO but some directly related tasks are outside its control

The *results* of the investigation (for orphan medicines) are assessed by the CHMP.

What if the plan is not considered sufficient to grant the indication targeted?

PIPs normally include clinical trials and clinical trials are approved by NCAs

What if they are not accepted by them?

Or what if there are trials already on going in some MS (normally sponsored by the Company)?

There should be timely coordination with the rest of involved parties. This requires timely transparency, shared data bases, etc.

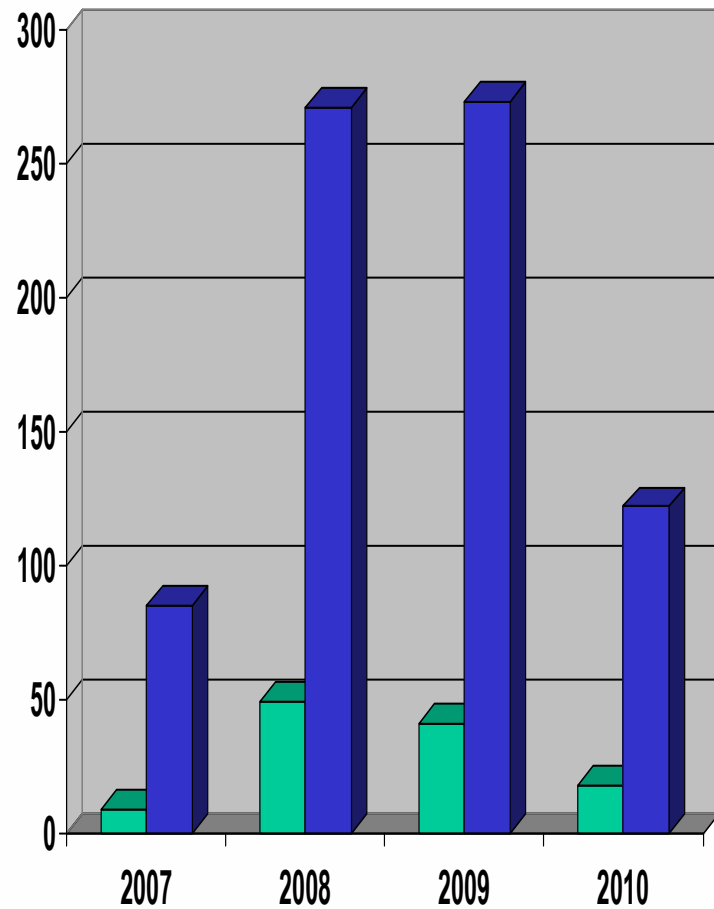
The results so far...

Up to now, April 2010, no orphan drug has been granted the 2 extra years of market exclusivity for implementing a PIP (drug development is a long process, implementing a development plan takes time)

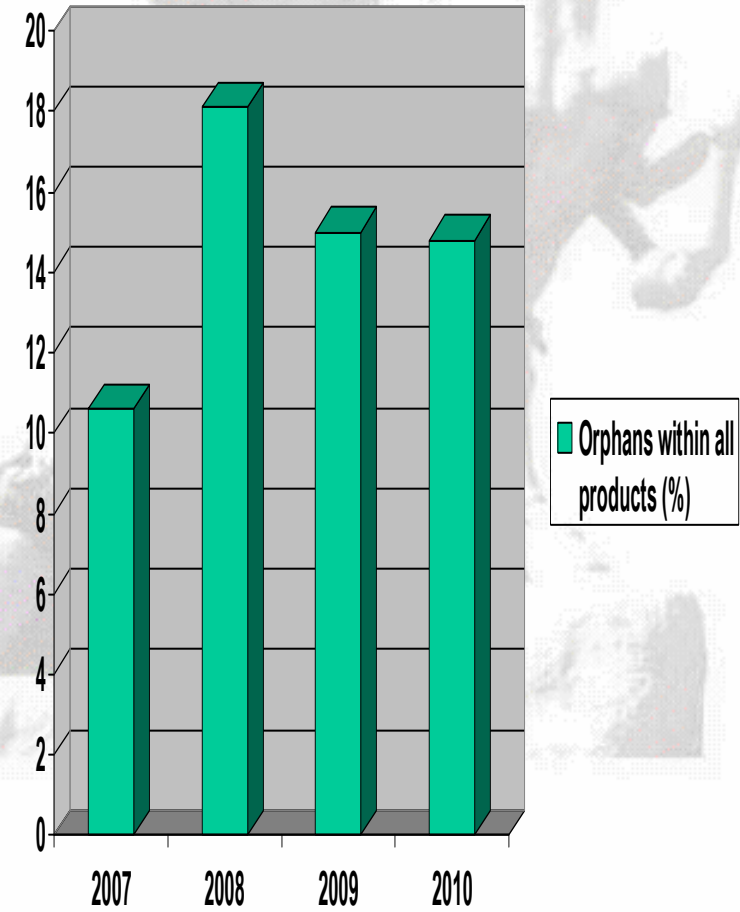
But sponsors developing orphan drugs do apply for PIPs ...

Obviously important since 15-20% of rare diseases affect only to children and 55% affect both adults and children (orphan designation data)

PIP/ Waiver applications for products with Orphan designation (2007- April 2010), (Source EMA, Preliminary)



absolute numbers



as percentage

In conclusion:

The new regulation aims to improve the situation of medicines for paediatric populations, including for orphan diseases. It will generate abundant research, bureaucracy and rewards for the industries.

That this is, in fact, efficiently translated into relevant health benefits for children is a **shared responsibility** that requires **transparency** and **good coordination between all the involved parties** and should evolve under **public scrutiny**.

But the beginnings look promising

