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Fundació Doctor Robert
UAB

The Paediatric Committee (PDCO)

Fernando de Andres-Trelles
(UCM, PDCO, AEMPS)

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Some of the slides based on EMA sources, gratefully acknowledged* but opinions are personal

* Comprehensive and helpful section on “Medicines for children” at the EMA website http://www.ema.europa.eu/htms/human/paediatrics/introduction.htm

MEDICINES ARE COMPLEX

In general, **medicines** are therapeutic, preventive or diagnostic tools of chemical, biological “recombinant” or “cell” type and of industrial origin, available on the market (with a price often intervened) after having being authorised (“registered”) by specific “agencies” generally at the initiative of the industry and on the basis of data (evidence) submitted and usually generated by it and not always easily available. They are normally prescribed and dispensed before being used by the patient (“consumer”) who generally does not pay directly for them. In the EU, public institutions are the main reimbursing bodies; Pricing and reimbursement are not related to the EMA

MEDICINES ARE REGISTERED AS SUCH

Medicines evaluation for registration

Quality

Safety

Efficacy

In Normal Conditions of Use, meaning:

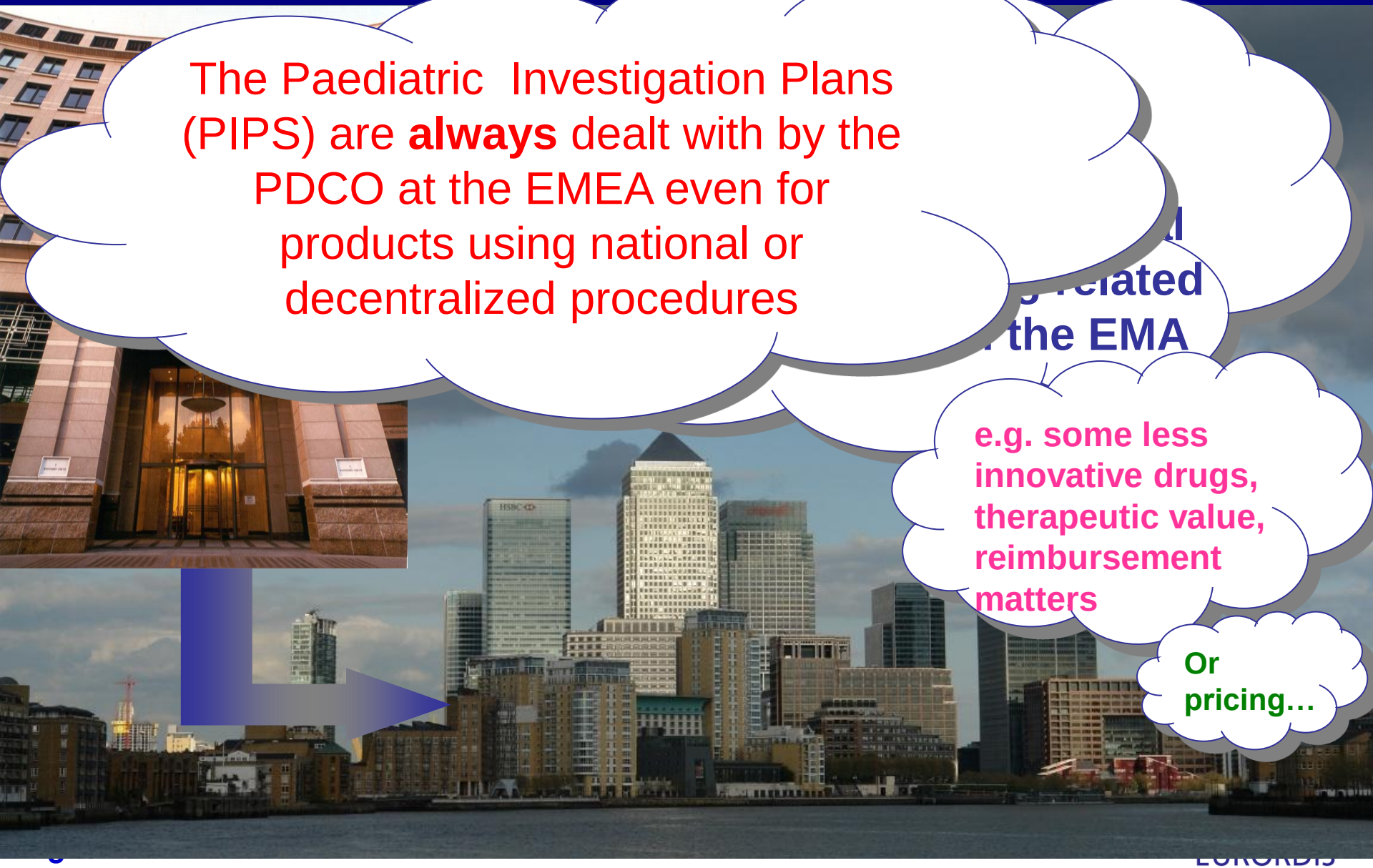
Summary of Product Characteristics (SPC)

Patient Leaflet (PL)

Packaging

And, if centralised, European Public Assessment Report (EPAR)

European Medicines Agency (EMA). Established 1995



The Paediatric Investigation Plans (PIPS) are **always** dealt with by the PDCO at the EMEA even for products using national or decentralized procedures

…related

…the EMA

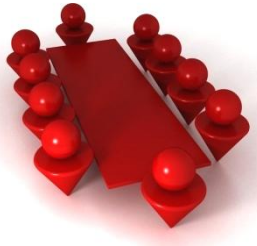
e.g. some less innovative drugs, therapeutic value, reimbursement matters

Or pricing…

The Regulatory process in the EU now incorporates a specific step to consider paediatric plans on time

Clinical development

Pharm → Non-clinical → I → II → III → Post-mkt



PIP
(PDCO prospectively decides what to inves-tigate for children CASE BY CASE). Compulsory request. Binding decision

(CHMP) Approves ALL centralized hu-man medicines

Binding decision

Orphan Drug Designation (COMP)
(Optional request)

Scientific Advice/Protocol Assistance (SAWP). Optional prospective case by case request. Not binding advice. Free of charge for paediatric plans and for orphan drugs

EMA "human" committees basically nominated by National Agencies (in chronological order) and one working party of the CHMP –the SAWP (scientific advice working party)-

With input from PDCO and COMP

SAWP

CHMP
(Committee for Human Medicinal Products)

COMP
(Committee for Orphan Medicinal Products)

HMPC
(Committee for Herbal Medicinal Products)

PDCO
(Paediatric Committee)
Chair: D. Brasseur - Vice-Chair: D. Mentzer
29 members nominated by NA
and 3+3 patients and health profesionals representatives

CAT
(Committee for Advanced Therapy Medicinal Products)

PRAC
(Pharmacovigilance Risk Assessment Committee)

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The situation before the Regulation

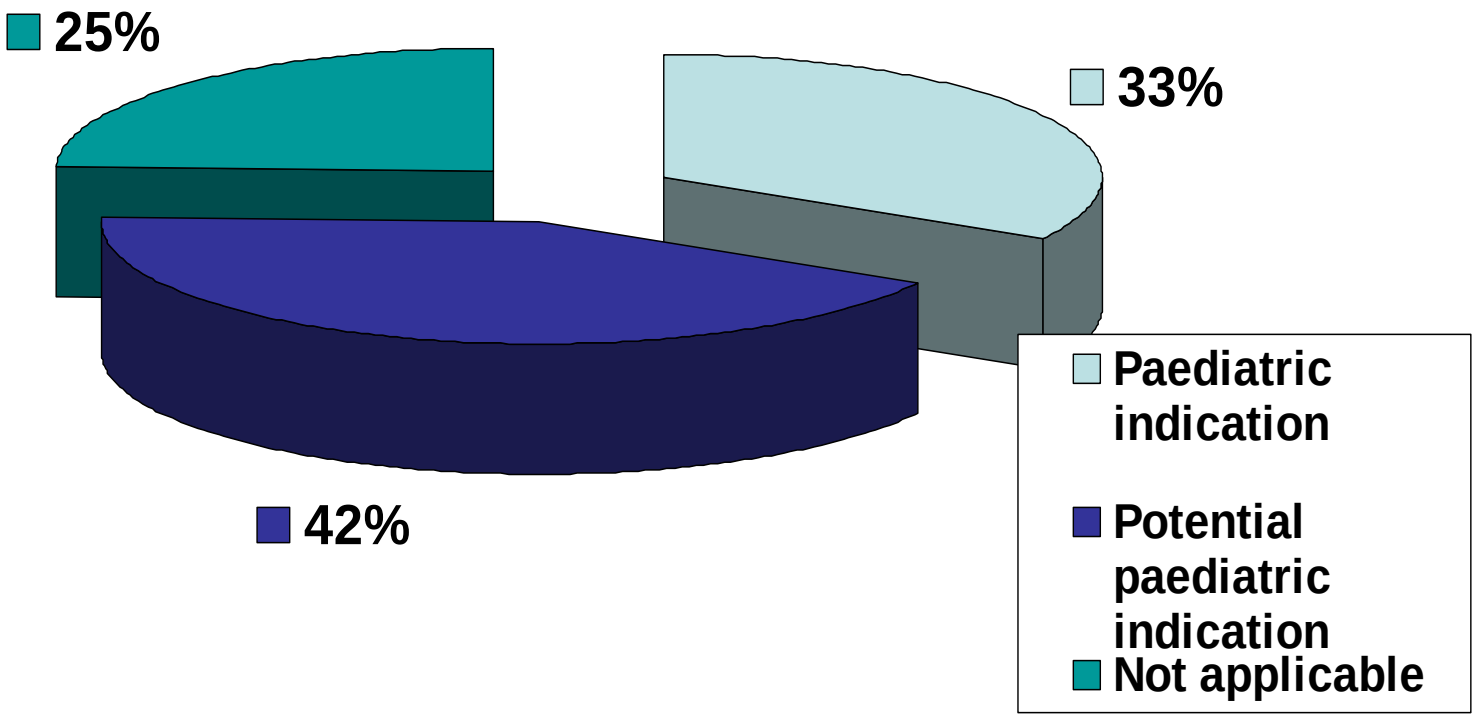
- 20% of the EU population, i.e. 100 million, is aged less than 16 years
  - premature neonate, term neonate, infant, child, adolescent
- 50-90% of paediatric medicines have not been tested and evaluated
- US paediatric data (BPCA) not submitted to EU Agencies

Potential Risks:

- adverse effects (overdosing)
- inefficacy (under-dosing)
- improper formulation
- delay in access to innovative medicines

No much improvement in the first 12 years of the European Medicines Agency

258 active moieties approved (1995- January 2006) through EMA



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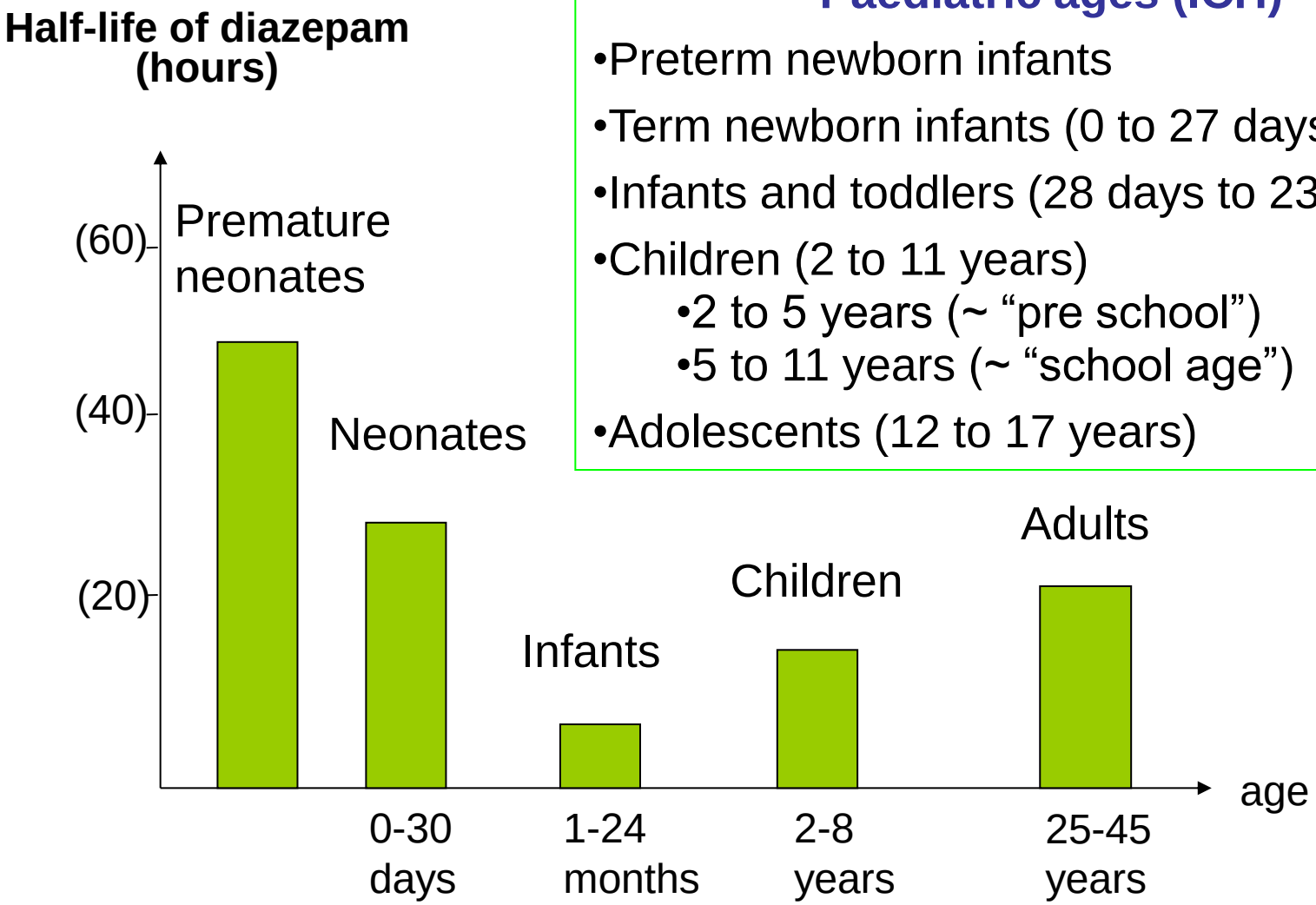
MEDICINES FOR CHILDREN

There is significant lack of knowledge on many aspects of medicines for pediatric populations that cannot be easily extrapolated from adult data. A simple illustration…

Pharmacokinetics (PK) change with age in a non-linear way



Paediatric ages (ICH)

- Preterm newborn infants
- Term newborn infants (0 to 27 days)
- Infants and toddlers (28 days to 23 months)
- Children (2 to 11 years)
  - 2 to 5 years (~ “pre school”)
  - 5 to 11 years (~ “school age”)
- Adolescents (12 to 17 years)

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Two examples from the Summary of Product Characteristics of medicines developed prior to the Paediatric Regulation, one used for multiple sclerosis (MS) and the other for hemophilia

SPC of a drug for Multiple Sclerosis “standard ” in paediatric therapeutics: interferon beta-1a (**) (1)

4.1 Therapeutic indications

** is indicated for the treatment of

- Patients diagnosed with relapsing multiple sclerosis (MS). In clinical trials, this was characterised by two or more acute exacerbations (relapses) in the previous three years without evidence of continuous progression between relapses; ** slows the progression of disability and decreases the frequency of relapses.

- Patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis (see section 5.1). ** should be discontinued in patients who develop progressive MS.

No mention of paediatric patients

SPC of a drug for Multiple Sclerosis “standard ” in paediatric therapeutics: interferon beta-1a (**) (2)

4.2 Posology and method of administration

……

Adults: The recommended dosage for the treatment of relapsing MS is 30 micrograms (1 ml solution), administered by intramuscular (IM) injection once a week (see section 6.6). No additional benefit has been shown by administering a higher dose (60 micrograms) once a week.

Paediatric population: The safety and efficacy of ** in adolescents aged 12 to 16 years have not yet been established. Currently available data are described in section 4.8 and 5.1 but no recommendation on a posology can be made. The safety and efficacy of ** in children below 12 years of age have not yet been established. No data are available

SPC of a drug for Multiple Sclerosis “standard ” in paediatric therapeutics: interferon beta-1a (**) (3)

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Interferons, ATC code: L03 AB07. Interferons are a family of naturally occurring proteins …..,

Paediatric population: Limited data of the efficacy/safety of ** 15 micrograms IM once per week (n=8) as compared to no treatment (n=8) with follow up for 4 years showed results in line to those seen in adults, although the EDSS scores increased in the treated group over the 4 year follow-up thus indicating disease progression. No direct comparison with the dose currently recommended in adults is available.

SPC of a drug for Multiple Sclerosis “standard ” in paediatric therapeutics: interferon beta-1a (**) (4)

4.8 Undesirable effects

…….

…….

…….

Paediatric population: Limited published data suggest that the safety profile in adolescents from 12 to 16 years of age receiving ** 30 micrograms IM once per week is similar to that seen in adults.

Current Summary of the Product Characteristics of a factor IX (***): Use in children hardly mentioned:

4.1 Therapeutic indications

…….

Paediatric population

The safety and efficacy of *** in children less than 6 years of age has not been established. There are insufficient data to recommend the use of *** in children less than 6 years of age.

…….

5.1 Pharmacodynamic properties

There are insufficient data to recommend the use of *** in children less than 6 years of age

……..

Registration: What if it is not profitable to register/develop drugs or generate data to meet health needs?

orphan diseases, medicines for children, diseases of poverty…

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

The Regulation on Paediatric Medicines (Regulation -EC- No 1901/2006 + 1902/2006), to stimulate much-needed research, came into force on January 26, 2007.

A new EMA committee (PDCO) met for the first time on July 2007.

The PDCO meets monthly at the EMA and is responsible for coordinating/implementing all aspects of the Regulation

The 1000th PIP was submitted in October 2010

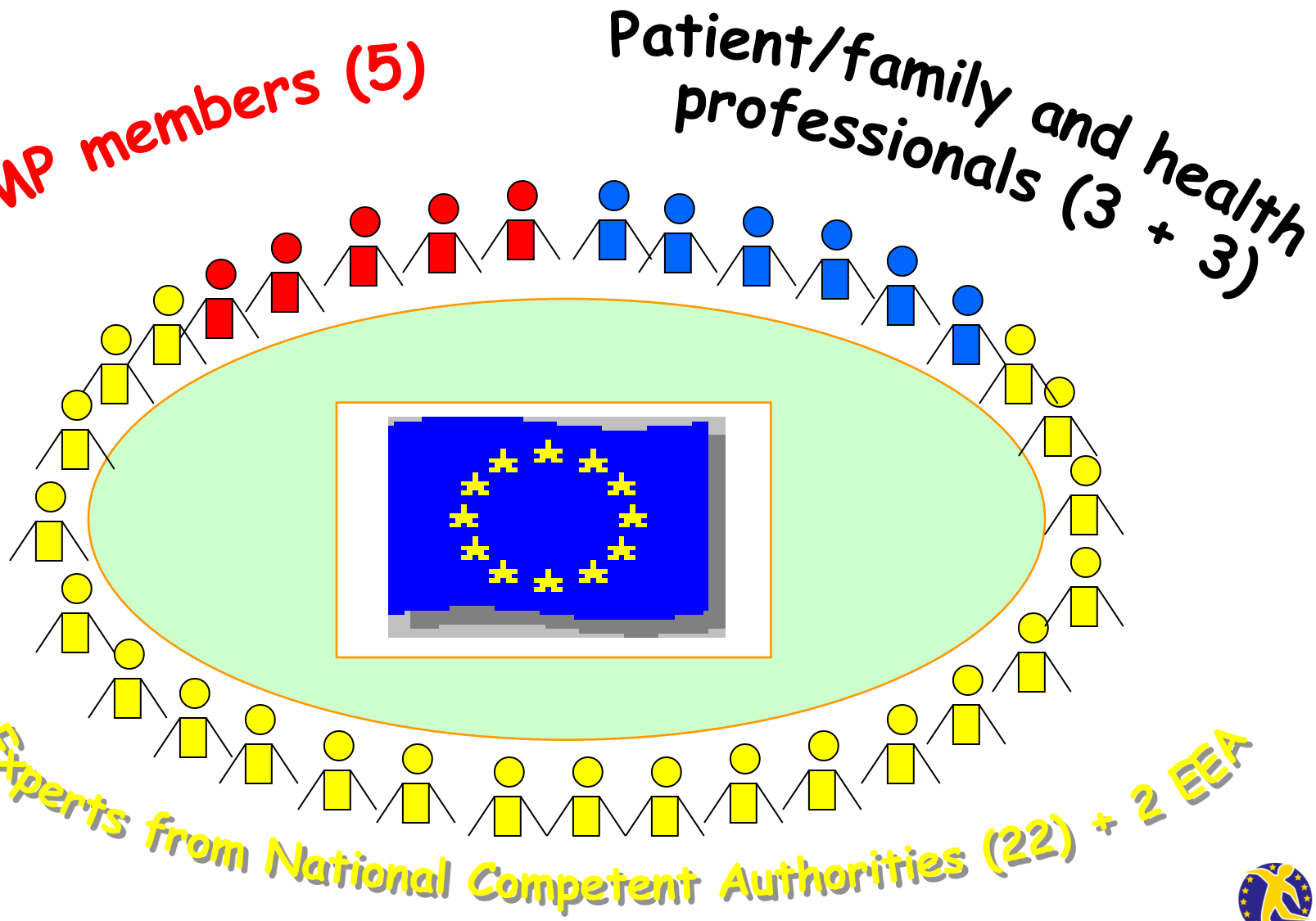
The stated objectives of the Regulation

- **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 authorisation for adults

The main tools to achieve these objectives

- **An expert committee:**
  Paediatric Committee (PDCO)
- **A binding (agreed, evolving) paediatric development: the Paediatric Investigation Plan (PIP)**
- **A set of rewards and incentives**
  - For new and on-patent products
  - For off-patent products
- **A series of other tools for information, transparency, and stimulation of research**

The Pediatric Committee (PDCO)



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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 Authorisation (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, possibly, in cases where the results, once obtained, do not lead to any indications.

The Pediatric Investigation Plan (PIP):

- Is the basis for the development and authorisation of a medicinal product for the paediatric population subsets
- Includes details of the timing and the measures proposed to demonstrate:
  - **Quality**
  - **Safety**
  - **Efficacy**

  Marketing Authorisation criteria
  - As well as **prospective pharmacovigilance measures** (e.g. risk management plans including for long-term effects)
- Is to be agreed upon and/or amended by the Paediatric Committee (PDCO)
- Is binding! on Company

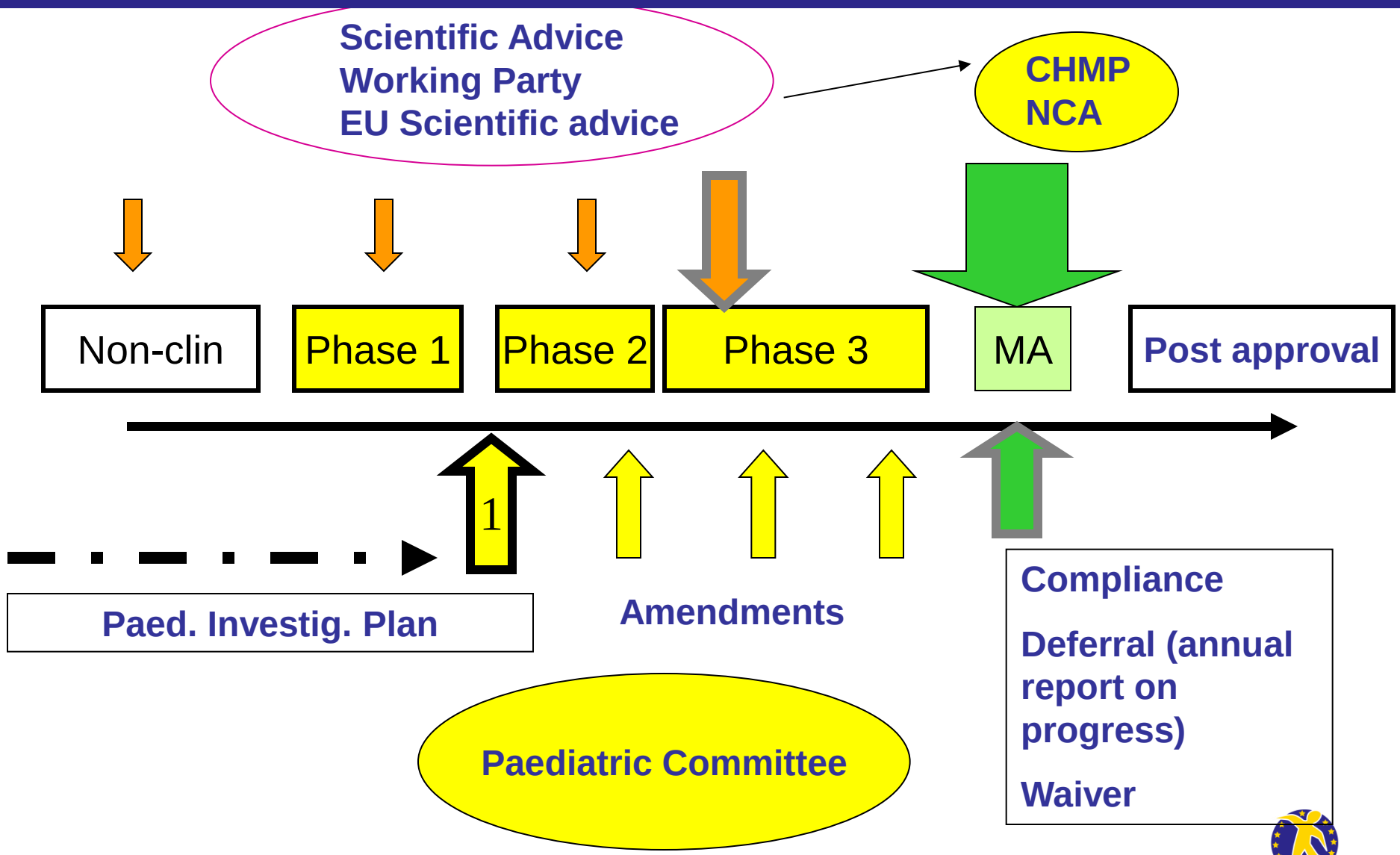
Paediatric clinical development (when?)

- **Mainly or exclusively paediatric diseases**: Complete development in children. Initial tolerability/ safety in adults.

- **Serious diseases with limited therapeutic options both in adults and children**: early development in children.

- **Other diseases**: development in children only when development in adults well advanced. Even, for safety reasons, post-marketing of the adult medicine.

Submission of the PIP (when?)



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Other measures established by the Regulation (normally with input/ coordination by the PDCO)

- Inventory of paediatric needs, based on survey of existing uses by Member States (MS).
  - EU funding available for research, esp. for off patent products identified as priority
- Critical assessment of available results of paediatric studies, to be submitted by Companies to Member States or the EMA (arts 45 and 46)
- Improved communication and transparency of paediatric information e.g.
  - SPC to refer to children studies even if results negative.
  - Paediatric clinical trials to be published in EUCTR (EU Clinical Trials Register)
  - Approved PIPs are accessible on the EMA webpage
- European network of paediatric research to be coordinated by the EMA-PDCO.

Some consequences and 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 children, they are obliged to do so

- Without unnecessary studies in children
- Without delaying authorization in adults

And this often requires performing clinical studies in children . . .

Obviously, ethics is a major issue for paediatric clinical trials

There is guidance/ legislation on the matter ….

- International ethics principles: Declaration of Helsinki (Endorsed generally by European countries, but not fully by the U.S. FDA - mainly on placebo related issues-), etc.
- EU Directive on Clinical Trials: 2001/20/EC
- Commission Directive on Good Clinical Practice: 2005/28/EC
- EU Ethical Considerations on clinical trials with children (recommendation by an ad hoc group chaired by the European Commission. Final: 2008)

…. But there is a lack of full harmonization even within the European Union,

e.g. some Member States do not allow conducting any paediatric clinical trials without potential direct clinical benefit for the participants

Some consequences and issues…

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 exclusively paediatric cancers?

When felt useful, a paediatric development is, at least, "encouraged"

Some consequences and issues…

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

How many 13-15 y.o. schizophrenia patients can feasibly be enrolled in a c.t.?

In a placebo controlled c.t.?

According to ethical principles?

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

Wider use should be done of alternative methods of generating evidence

What about PIPs for new medicines for our previous example: Multiple Sclerosis (MS)?

Data as for January 2012

Since 2007, **17 applications for PIP/ Waiver** for products related to Multiple Sclerosis submitted:

Art. 7: 14

Art. 8: 2

Art.30 (PUMA): 1

11 with published Decisions:

8 agreed PIPs

3 full waivers

But still no related new paediatric indication for MS granted

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.

At least the beginning looks promising

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