Paediatric Medicines
The New European Legislation

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Presentation Outline

- The current situation and the Need for a Regulation
- Legislative process of the Regulation
- Objectives and main pillars of the Regulation
- The Paediatric Committee
- Measures
- Paediatric Investigation Plan
- Waivers and deferrals
- Post authorisation requirements
- The PEG
- Inventories of therapeutic needs

The current situation

- 20% of the EU population, i.e. 100 million is aged less than 18 years
- Children are not one single population
- Includes preterm and term newborn infants, infants and toddlers, children and adolescents) (ICH E11)
- Developmental, physiological and psychological differences between age groups and compared to adults
- 50-90% of paediatric medicines have not been tested and evaluated in children

The current situation

Risks:

- Appropriate dose?
- Increased risk of adverse effects (overdosing)
- Ineffective treatment (underdosing)
- Use of improper formulations
- Delay in access to innovative medicines

Why do we need a legislation?

- A child is not a small adult
- Clinical trials in children are more complex:
  - Refusal from parents
  - Take longer
  - Small populations
  - Cost more
  - 'Unethical' (Guinea pigs, placebo)
- Children require specific formulations

Why do we need a legislation?

- Paediatric indications are not profitable, as incidence of most illnesses is smaller
- Liability of use in children
- The US example: incentives stimulate research (but: US data not submitted)

Studies of medicinal products are performed by industry mostly in young adults, but not in children

Legislative Process

- European Commission round table, EMEA in December 1997
- Council Resolution in December 2000 (recognising the success of the US initiative)
- Debates, extensive consultations with Member States between 2001-2004
- Extended impact assessment 2003/4

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First proposal

adopted by the Commission in September 2004

Legislative process

- First reading by Council of Ministers started November 2004
- First reading by European Parliament in April 2005
- Political Agreement in December 2005

Legislative process

- Second readings in EP and Council, started in March 2006
- Adoption end 2006?
- No transition phase until implementation
- Implementing Guidelines?
- Staggered implementation

The European Regulatory Framework

Directive 2001/83/EC, as amended
Framework for the regulation of medicinal products

Regulation (EC) No 726/2004
Establishing the EMEA and 'creating' the centralised procedure

Directive 2001/20/EC
Framework for the regulation and conduct of clinical trials

Regulation (EC) No 141/2000
Establishing a Community system for orphan designation

Council Regulation (EEC) No 1768/92
Creating the Supplementary Protection Certificate

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 use of medicines in children
- Achieve the above
  - Without unnecessary studies in children
  - Without delaying authorisation for adults

Objectives of the Regulation

- Development of medicines for children should be an integral part of the development of medicinal product
- Integrated into the development program for adults

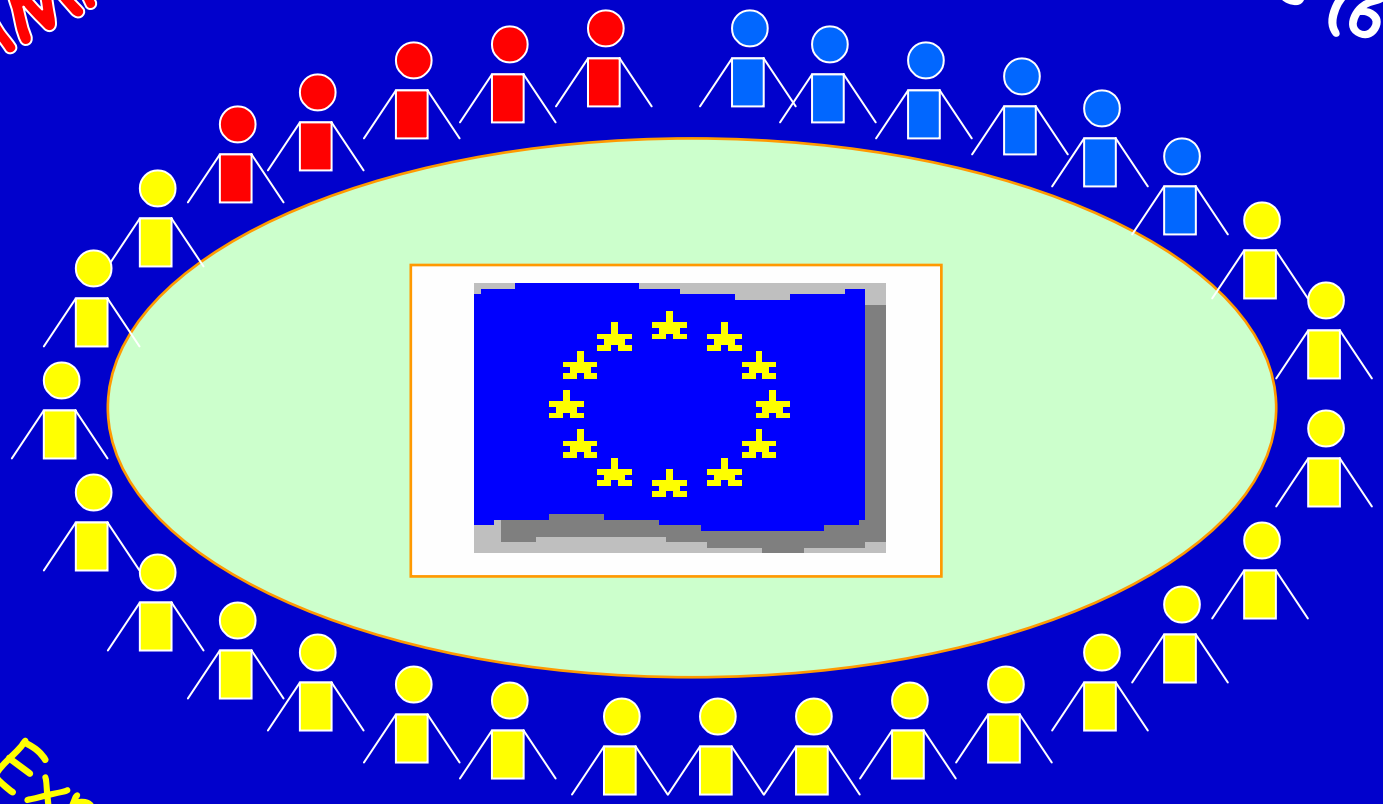
Main pillars

- Creation of a Paediatric Committee at EMEA
- Measures for patented medicinal products
- Measures for off-patent medicinal products
- Paediatric Investigation Plans (PIP)
- Other measures

Paediatric Committee

CHMP members (5)

Patient/family and health-care professionals (6-10)



Experts from National Competent Authorities (20)

Paediatric Committee

- Expertise in all aspects related to medicines for children (paediatric research, pharmacology, ethics, paediatric medicine and research…..)
- Will consider the potential therapeutic benefit of studies in children
- Avoid unnecessary studies in children
- Avoid any delay in the authorisation of medicines for other populations

Paediatric Committee

Assessment of:

- Paediatric Investigation Plans (PIP)
- Requests for waivers and deferrals
- Compliance with PIP
- Data for Safety, Efficacy and Quality at the request of CHMP or NCA

Paediatric Committee

- Support the various measures proposed in the Regulation, e.g.:
  - Survey of use
  - Definition of paediatric needs
  - Support and advice on the European Paediatric Network
  - Scientific contribution to documents and provide advice on paediatric medicines

Rewards, Incentives and Requirements

Dependent on the current status of the product

- Patent protected new products
- ‘Old’ products without patent protection
- Orphan drugs

Rewards, Incentives and Requirements

- Rewards will be granted even if results fail to lead to the authorisation of a paediatric indication
- Include study results in the SmPC and, if appropriate, in the package leaflet
- Authorisation in all Member States mandatory

New products

Patent-protected products

- Obligation to submit results of agreed Paediatric Investigation Plan (PIP) at time of marketing authorisation or variation

- **Reward**:

  - 6-month extension of the Supplementary Protection Certificate (= patent protection)

New products (2)

- **No results of agreed PIP, no waiver?**
  = Invalid application for MA

- Paediatric study results can be submitted either with Marketing Authorisation Application (MAA) for adults, or later (deferral of initiation or completion of studies in children as defined by the Paediatric Committee)

‘Old’ products

Off-patent products not covered by a patent or supplementary protection certificate

- Paediatric Use Marketing Authorisation (PUMA) ***New type of MA!***

Old products (2)

Incentive:

- 10 years data protection/exclusivity: (*as for new products*)
- Use of existing brand name (brand recognition)
- Superscript of a symbol

Orphan drugs

- 15-20 % of rare diseases only affect children, 55 % affect adults and children

- **Reward:**

  2 years extra market exclusivity added to existing 10 years

Free scientific advice

- Free scientific advice to applicants:
- On the design and conduct of studies to demonstrate quality, safety and efficacy
- On pharmacovigilance and risk management systems post authorisation

Free scientific advice

- Collaboration Paediatric Committee / Scientific Advice
- 5 CHMP members in the Paediatric Committee
- Paediatric Committee responsible for Paediatric Investigation Plan
- Divergent positions SA / PC?
- Establish working procedures to avoid divergences
- Arbitration process as last resort

Paediatric Investigation Plan (Articles 15-19)

- Document upon which the development and authorisation of a medicinal product for the paediatric population should be based
- Include details of the timing and the measures proposed to demonstrate:
  - Quality
  - Safety
  - Efficacy

} MA conditions

Paediatric Investigation Plan

- Research and development programme to ensure availability of data in the paediatric population
- Describes any measures to adapt formulation for different subsets of the paediatric population so as to make the use of the medicinal product more acceptable, easier, safer or more effective (for different subsets)
- To be agreed by the Paediatric Committee
- Binding to receive reward
- Can be amended

Paediatric Investigation Plans

- Scope includes formulations, preclinical safety, clinical efficacy, and pharmacovigilance / risk management (long term safety)
- Precise description of the development
- Timing of studies: beginning, duration and end with respect to submission of Marketing Authorisation applications
- Justification for waivers and deferrals (with timelines)

Paediatric Investigation Plans

Reference ICH E11

- 5 Sub-populations
- Timing
  - Seriousness of the disease to be treated
  - Availability of (authorised) treatment
- Type of data to be submitted
  - Efficacy, Proof of concept for serious diseases
  - Dose and PK, PK/PD
  - Safety
  - Extrapolation of adult data (when to perform in relation to adult development)
- Minimizing Risk and Distress

Waivers

- Product likely to be ineffective or unsafe in all or part of the paediatric population
- Disease occurs only in adults
- No significant therapeutic benefit over existing treatments for children
- For one or more subsets of the paediatric population
- For one or more specified indications

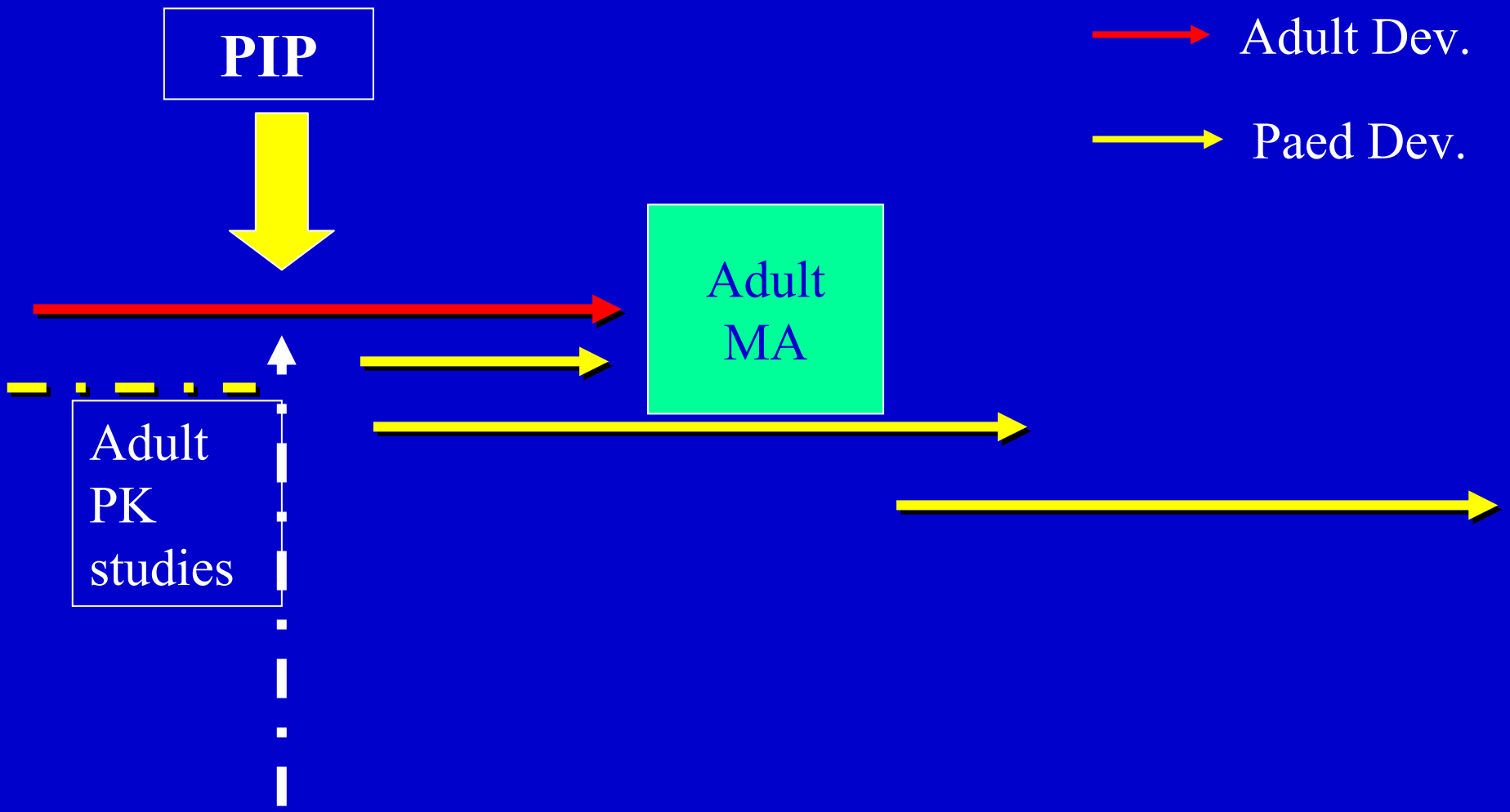
Waivers

- Granted waiver may be reviewed and changed
- If a waiver is removed from the list the requirements to submit the data according to an agreed PIP will not apply for 36 months
- List of waivers will be published by the EMEA
- Regular revisions

Deferrals

- Request to defer initiation or completion of some or all the measures set out in the PIP
- Request on initiative from applicant or Committee
- For part or all paediatric subpopulations
- Annual report to monitor deferred studies
- To ensure that studies in children are safe and do not delay the authorisation for adults.

Timing (new products)



Other measures

Inventory of use in children

- Member States to collect available data on all existing uses of medicinal products in children within 2 years
- Assessment by the Paediatric Committee

Inventory of therapeutic needs

- Identifying research priorities
- To be made public within 3 years
- Taking into account prevalence and seriousness of the condition, available treatments, safety issues

Other measures

European paediatric research network

- To link together existing networks, investigators and clinical trial centres
- Build up competences at a European level
- To coordinate and facilitate the conduct of studies at a European level
- Avoid duplication of studies

Other measures

Database of clinical trials and authorised products:

- Public access to information on paediatric clinical trials from the European database of Clinical Trials (modified EUDRACT)
- Transparency of EUDRACT (derogation from Art 11 of Directive 2001/20/EC)

Added to Regulation by the EP

- **Community funding for studies into off-patent medicinal products**
  - From Framework Programmes (FP7)
  - Amount?
  - Link with identified Needs
- **Transfer of Marketing Authorisation or access to data, if product is withdrawn from the market**
  - After having benefited from incentives/rewards
  - 6 months before discontinuation
  - Public

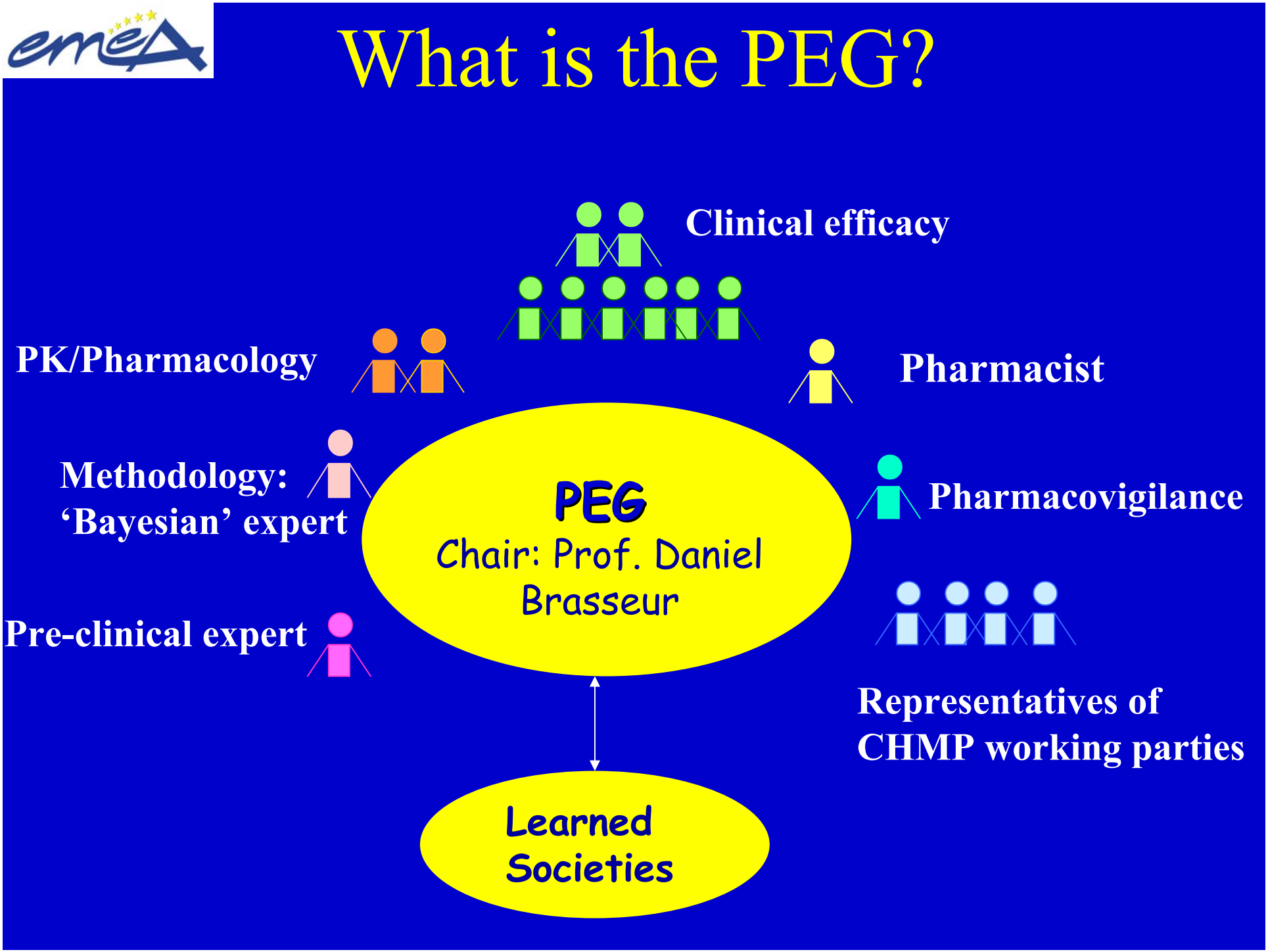
Post-authorisation requirements

- Place the product on the market within two years (taking into account the paediatric indication)
- Obligation to ensure the follow-up of efficacy and adverse drug reactions
- In cases of particular cause of concern
  - Risk management system
  - Post-authorisation studies

In the meantime . . .

Creation of the Paediatric Working Party (PEG) by the CHMP

What is the PEG?



PEG role and mandate

- Advice on the use and development of medicinal products in children to the EMEA and scientific committees
- Assessment of paediatric needs
- Recommendations and contributions to Guidelines:
  - Development of medicinal products for neonates
  - Formulations of choice for children
  - Conduct of Pharmacovigilance in children
  - Guideline on PK in children

PEG role and mandate

- Commenting on the new Regulation
- The PEG will be replaced by the Paediatric Committee

Inventory of Needs

- Identify the needs in different therapeutic areas where there should be research and development (either “old” or “new” products)
- Based on a public health perspective and supported by evidenced-based medicine
- Methodology based on work carried out by the French Medicines Agency (AFSSAPS)
- No prioritisation
- Assessment of current and potential use, legal status, available formulations

Inventory of Needs

- Gastroenterology / Hepatology
- HIV
- Pain
- Rheumatology
- Cardiovascular
- Epilepsy
- Chemotherapy I
- Immunology
- Diabetes (under preparation)
- Migraine (under preparation)

Inventory of Needs

Limits of the methodology:

- Not all information available on existing MA
- Snapshot of a dynamic process
- Products in the pipeline not included
- No identification of priorities

Conclusions

- Slow regulatory process (> 7 years)
- Challenge for all stakeholders involved, **but**
- Fundamental progress towards better medicines for children
- Stimulation of innovation and research

Websites

- **EMEA**: www.emea.eu.int
- **European Union**: www.europa.eu.int
- **DG Enterprise**: http://pharmacos.eudra.org (Regulation proposal and explanatory texts)
- **DG Research**: www.cordis.lu

Abbreviations

CHMP	Committee for Human Medicinal Products
EP	European Parliament
EUDRACT	European Database on Clinical Trials
FP7	7th Framework Programme
ICH	International Conference on Harmonisation
NCA	National competent authorities
MA	Marketing authorisation
MS	Member States
PEG	Paediatric Expert Group/Working Party
PIP	Paediatric Investigation Plan
PUMA	Paediatric Use Marketing Authorisation
SmPC	Summary of Product Characteristics