EU Regulatory Network

Challenges and Opportunities for Croatia

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The Role of the Paediatric Committee (PDCO)

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THE CONTEXT THE PDCO WAS CREATED

Paediatric needs

- Medicines that are used in children were not studied and assessed (50 to 90% in EU)

  - Studies take longer, are more expensive
  - Children 'protected' from research, when ethical need to prescribe based on evidence

- The US initiative showed that the situation could be changed

Paediatric Regulation

- 'Regulation' is the highest legal text in EU
- Entry into force January 2007

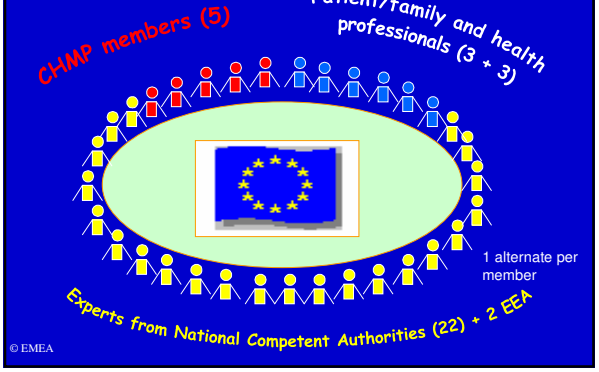
- Improve the health of children
  - Increase high quality, ethical research into medicines for children
  - Increase availability of authorised medicines for children
  - Increase information on medicines
- Achieve the above
  - Without unnecessary studies in children
  - Without delaying authorisation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

THE PDCO WAS CREATED AS PART OF THE PAEDIATRIC REGULATION

Main Pillars of the Regulation

- Paediatric Committee
- OBLIGATIONS
- REWARDS
- Paediatric Investigation Plan
- Transparency measures
- Other measures

Paediatric Committee (PDCO)



Paediatric Committee

1 Chair
1 Vice-Chair

27 Member States

3 Patients/families representatives

3 Health Professionals representatives

- Neonatology, paediatric cardiovascular diseases, immunology, transplantation, respiratory, ICU, vaccines, pharmacology, PK, haematology, oncology, endocrinology and diabetes, adolescent medicine, pharmacovigilance, anaesthesiology, infectious diseases, gastroenterology and nutrition, general paediatrics,
- Formulations (plus permanent external experts)
- Adult internal medicine, non-clinical toxicology
- Additional methodologist

THE ROLE THE PDCO :

WITHIN THE FRAME OF THE EU REGULATION

Main Pillars of the Regulation[2]

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New products

- **Unauthorised products**
  - Obligation to submit <u>results</u> compliant with agreed Paediatric Investigation Plan (PIP) before validation of marketing authorisation application, *or Deferral of studies, or Waiver* (or invalid application)
  - **Reward**: 6-month extension of the patent protection
  - Conditions: Compliance with Plan, Authorisation in all 27 Member States, and Information in "Product Information"

Authorised products

- **Authorised products on patent**
  - Obligation to submit <u>results</u> compliant with agreed Paediatric Investigation Plan (PIP) at time of validation of new indication, new route of administration, or new formulation (or invalid application), *or Deferral of studies, or Waiver*
  - **Rewards**: 6-month extension of the patent protection

Conditions: Compliance with Plan, Authorisation in all Member States, and Information in "Product Information"

Orphan drugs

- 15-20% of rare diseases affect children only, and 55% affect both adult and children (*orphan designation data*)
- Additional 2 years of market exclusivity to EU reward for orphan drugs: 10years
- Conditions: Compliance with plan, Authorisation in all 27 Member States, and Information in Product information

'Off-patent' products

Optional Procedure

- For off-patent products only
- Paediatric Use Marketing Authorisation (PUMA)
  - Covers Paediatric indication and Formulation
  - Need for Compliance with the Paediatric Investigation Plan
- **Reward**: 10 years data protection

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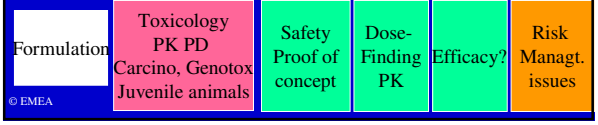
Paediatric Investigation Plans

- Intended to support an indication in all subsets of the paediatric population
- Data on efficacy, safety and formulation
- Timelines
- In practice, discussion per indication of the development and formulation for each age group



Paediatric Investigation Plans

Application:

- Rationale for development
- Outline of paediatric development
- Proposal for age-appropriate formulation
- Outline of each trial
- Binding decision on company

Ensuring the PIP is appropriate

- Involvement of external experts
- Involvement of learned societies to work out 'standard PIPs'.
- Asking different questions to different companies developing me-too products

Protecting children in research

Paediatric Investigation Plans include:

- DSMB as standard requirement
- Measures to minimise pain, distress and fear
- Advocating sparse sampling where possible
- Modelling and simulation whenever possible
- Innovative (non conventional) methodology for design and analysis, if this allows limiting the number of children while maximising information

Paediatric Committee

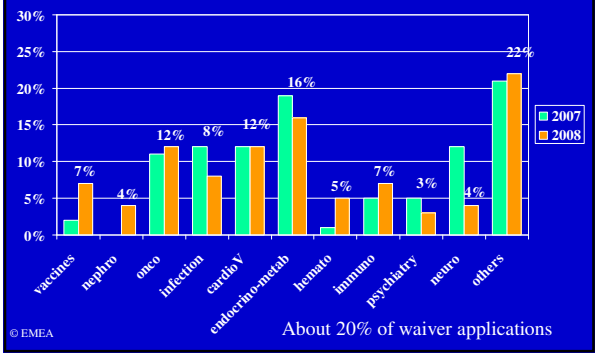
- PIP and Waivers requests:

	2007 (Aug-Dec)	2008 (Jan-October)	Total
Indications	202	333	**535**
Applications	85	225	310*

** About 20% of waiver requests*

- Committee has worked on other topics than PIPs.

Therapeutic areas PIP/waivers



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Public Access to paediatric trials

- European database of clinical trials (EUDRACT)
  - Protocol and results-related information
  - *New expanded database under construction (pilot mid 2009)*
- Existing paediatric studies (*collection of all existing studies, 12,000 answers) to be assessed and published*
  - About 1000 products with 5 studies per product
- Access to reports from Eudravigilance (Adverse reactions database pre and post authorisation)
- EMEA decisions with summary of PIP content
- Mandatory inclusion of paediatric information in Summary of Product Characteristics

Pharmacovigilance in chidren

Adults are not a good model, and children should not be the other option

- Risk prevention rather than risk management
- Better use of non-clinical models

- Need for academic work in prospective, modern **long-term** pharmacovigilance and pharmacoepidemiology

Post-authorisation activities

- Safety measures proposed in the **PIP**

Normal measures are strengthened:

- Obligation to include long-term follow-up of adverse drug reactions, specifically for children
- Obligation to include long-term follow-up of efficacy
- Post-marketing data – pharmacovigilance
  - Risk Management Plan
- Periodic safety update reports (every 6 months, then 2 years)

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Other measures (1)

- Inventory of all existing paediatric uses of medicines by Member States
  - The Paediatric Committee has drawn up and adopted on 26 October 2007 a Guidance on the content and format of data to be collected by the Member States on **all existing uses of medicinal products in the paediatric population**
  - The Paediatric Committee will establish the **inventory of paediatric needs**, based on the information obtained from the survey

Other measures (1)

- EMEA network of paediatric research networks

(*strategy adopted, implementation in 2009*)

- Inventory of existing networks
- Accreditation of networks in 2009

Other measures (2)

- Workshops
  - EMEA Workshop on **Modelling** in Paediatric Medicines (14-15 April 2008, EMEA, London, UK)
  - EMEA Workshop on **FP7 & off-patent medicines developped in children** (6 June 2007, EMEA)
  - EMEA Workshop on **Neonates** (11 October 2006, EMEA)
  - EMEA Workshop on **Paediatric pain** (28 October 2004, EMEA)

Other measures (3)

- Inventory of off-patent products for which studies are required
  - In order to ensure that funds are directed into research of medicinal products with the highest need in the paediatric population, the PDCO has revised and, after public consultation, adopted a priority list of off-patent products for which studies are required.

Other measures (3)

- Expertise provided by PDCO throughout the review of the guidelines relevant to the development of medicines for children drawn up by the CHMP and aimed at helping applicants to prepare marketing-authorisation applications for medicinal products for children use

The titles of scientific guidelines, reflection papers and concept papers relevant to the development of medicines for children are listed on EMEA website

Conclusions

- PDCO : Strong arm of the EU Regulation to change dramatically the way medicines are developed for children
- High Workload for EMEA, and industry
- Global cooperation on paediatric development
- Major opportunity for methodological innovations and for changes in the approaches in development
- Transparency of trials as a major change
- Need for more and better quality, ethical research (protection of children involved in research)

Major tool for Better Medicines for children!

Abbreviations

- DSMB: Data and Safety Monitoring Board
- EU: European Union
- EUDRACT: European Database of Clinical Trials (CT)
- EUDRAVIGILANCE: European Database of Adverse Reactions (Clinical trials and post authorisation)
- NC: non clinical safety
- PD: pharmacodynamics
- PDCO: Paediatric Committee
- PIP: Paediatric Investigation Plan
- PK: pharmacokinetics
- PUMA: Paediatric Use Marketing Authorisation
- SmPC: Summary of Product Characteristics
- W: Waiver