Medicines for children in Europe: an update

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European Academy of Paediatrics
U.E.M.S. Section of Paediatrics
Formerly CESP

What the paediatricians know
- Studies in adults not sufficient
  - Specificity disease
  - Kinetic characteristics
  - Effects on growth, development, maturation
  - Specific adverse reaction

Child... not a small adult
Infant... not a small child
Preterm...not a small newborn

What the industry knows
Explore specific needs in paediatrics?

- Paediatrics in Europe
  - 0-16 years: about 20% of total population
- Needs: 0-16 years group: specific sub-populations
  - neonates to teenagers
  - different developmental and behavioural characteristics
  - drug formulations: formulations with good acceptability
- Specific: Estimation: over 50% of medicinal products used in children
  never specifically evaluated for use in children

Dilemmas in clinical research

- Dilemma of Health Authorities:
  - In the past: protect children from clinical research
  - Now: protect children by clinical research

- Dilemma of Medical Professions:
  - Struggle with optimal drug treatment
  - Acknowledge: over-the-thumb treatments = uncontrolled trials

- Dilemma with the Public:
  - Children included in trials: science is blamed
  - Children not included: "use them as guinea pigs"
Barriers to paediatric medicine development in Europe?

- Ethical issues
- Off-label prescribing practice
- Investment
- Clinical doability

Ethical issues: The paediatric population should

- The principles:
  - not be exposed to unnecessary hazards
  - not be tested too early in drug development
  - not be tested unnecessarily in clinical trials → overprotected

- The reality:
  - do not receive new medicines: have not been tested
  - do receive off-label products
    - may get a wrong dose
    - no adequate galenical form
    - no data on safety: adverse events: rarely reported → overexposed

Situating Paediatric Clinical Trials

The Contribution of CESP
European Academy of Paediatrics

- Decision making in extreme situations involving children: Withholding or withdrawal of life supporting treatment in paediatric care. Recommendations of the Ethics WG of CESP (Kurz R et al)
  Eur J Pediatr 2001; 160: 214-216
- Ethical dilemmas in neonatology. Recommendations of the Ethics WG of CESP (Sauer PJJ et al)
- Research in children. (Sauer PJJ)
- Putting the child first: Research as a part of paediatric care. The Joseph J. Hoet Lecture on Ethics in Paediatric Research (Kurz R)
- Practical and ethical issues in paediatric clinical trials (Kurz R, Gill D)
  Applied Clinical Trials 2002; July: 60-63
- A view from Europe (Bickerstaffe R, Crawley FP, Kurz R, Seyberth HW)
  BMJ 2003; 324: 1290-1291

The Contribution of CESP
European Academy of Paediatrics

- The Clinical Trial Directive’s ethical impact on research into diseases that cause incapacity and diseases of children. Perspectives from non-commercially funded research in hospitals. (Kurz R, Crawley FP)
- Informed consent/assent in children (De Lourdes Levy M, Larcher V, Kurz R)
- Guidelines for informed consent in bio-medical research involving paediatric populations as research participants (Gill D et al)
  Eur J Pediatr 2003; 162: 455-458
- Ethical principles and operational guidelines for good clinical practice in paediatric research. Recommendations of the Ethics WG of the CESP (Gill D)
- What the paediatricians need—the launch of paediatric research in Europe
- Refugee Children: a concern for European paediatricians Mijnes S

Medicines for children in Europe: European Academy of Paediatrics
U.E.M.S. Section of Paediatrics /CESP

- Barriers to paediatric medicine development in Europe?
  - It takes at least..... 6 partners

- Challenges to European Societies
It Takes at Least.....
6 Partners

- Children / parents
- Paediatricians and allied physicians
- Academia
- Industry
- Regulatory Agencies
- Scientific Societies

Partnership?

<table>
<thead>
<tr>
<th>Paediatric Role</th>
<th>Industry Role</th>
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<tbody>
<tr>
<td>Define therapeutics needs</td>
<td>Discovery of new medicines</td>
</tr>
<tr>
<td>Develop validated end-points for</td>
<td>High throughput screening of compounds</td>
</tr>
<tr>
<td>- efficacy and safety</td>
<td>Development of new medicines</td>
</tr>
<tr>
<td>- “bridges” adult studies</td>
<td>Pre-clinical toxicology</td>
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<tr>
<td>Develop effective, efficient,</td>
<td>Human evaluation of dose, safety, efficacy</td>
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<td>ethically driven networks</td>
<td></td>
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<tr>
<td>to conduct clinical studies</td>
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<tr>
<td>Performed at all level of paediatric care</td>
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Position paper on the proposal?

European Journal of Pediatrics
May 2005
volume 164, Issue Number 5
pages: 263 - 265

Special Article
What the paediatricians need - the launch of paediatric research in Europe

The new proposals: what are they, what do they mean for us?

European Journal of Pediatrics
What the paediatricians need—the launch of paediatric research in Europe
José Ramet

Abstract
Most parents and many paediatricians are not aware that medicines for children are often not tested, labeled, or approved for their prescribed use. In 1997, the Food and Drug Administration developed incentives for pharmaceutical companies to perform paediatric research in medications. The European Commission brought out its proposal for paediatric incentives after in-depth internal reflection. Now it should be adapted quickly to boost pharmaceutical paediatric research in the EU as soon as possible.

Conclusion
The proposal must be balanced and aware that both incentives and requirements are mandatory in order to maintain and stimulate paediatric research on medicines in Europe.
Key elements of the proposal

- Paediatric Committee (PC)
- New products:
  - Paediatric Investigation Plan (PIP)
  - Reward: extension of the patent
- Established products:
  - Paediatric Use for off-patent products
  - Incentive: data exclusivity

Paediatric Committee (PC)

- Advisory body established in EMEA
- Experts in areas relevant to paediatrics (e.g. development, pharmacology, research & ethics)
- Tasks: examine & agree PIP
  - considers study methodology and expected therapeutic benefit to children
  - may request modifications
  - may grant waiver or deferral
  - gives positive or negative opinion

Medicines for children in Europe: European Academy of Paediatrics
U.E.M.S. Section of Paediatrics /CESP

Barriers to paediatric medicine development in Europe?

- It takes at least..... 6 partners

Challenges to European Societies

Six Major Objectives

- Creating European centres of excellence through collaboration
- Stimulating the creativity of “basic” research
  - at every possible level (primary - secondary- tertiary)
  - through competition between teams at European level
- Making Europe more attractive: best researchers
- Developing research infrastructure.
- Improving coordination:
  - national research programmes.
  - Also ethical

Guidelines for future European Union policy to support research

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<tr>
<th>Country</th>
<th>Number of responses</th>
<th>% of total responses</th>
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<tr>
<td>TOTAL</td>
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<td>100%</td>
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The globalisation of clinical trials

‘Nearly 40% of all clinical trials are now conducted in poorer countries such as Russia and India, where costs are lower and patients more vulnerable. And that’s raising questions about ethics and oversight.’
Challenges
What could EAP’s-UEMS Paediatrics contribution be to paediatric research?

- be able to respond to increased research needs
- define “centers” of excellence
- organize a “research task distribution” in Europe
- be present at EMEA & related advisory groups
- develop scientific excellence
- stimulate gifted medical students: consider careers in paediatric research
- act on research, education, higher education, lifelong learning
- support major international research projects
- act on education, training, research stimulation

Objectives
1. Increase high quality research into medicines for children
2. Increase availability of authorised medicinal products for children
3. Improve the information available

Achieve objectives without
- unnecessary studies on children
- delaying authorisation for adults

For older drugs: Paediatric-Use Marketing Authorisation (PUMA)

- for authorised off-patent products developed specifically for paediatric use
- according to an agreed PIP
- can use existing name (brand recognition)
- amended data requirements

Incentive – Data exclusivity

12 years data protection

Future?

Children / parents
- Paediatricians at all levels
- No research exclusivity

Academia
- Industry
- Regulatory Agencies
- Societies

“It is difficult to make predictions... especially about the future”

Y. Berra

Key measures for patented medicines

Requirement at the time of applications for new medicines for
- data in children (as agreed by paediatric committee) or
- a waiver from the requirement or
- a deferral of the timing of the studies

Reward for studies conducted
- 6-months extension of the supplementary protection certificate (in-effect, a patent extension)
- for orphan medicines, 2-years additional market exclusivity (10+2)
Barriers to paediatric medicine development in Europe?

- Ethical issues
- Off-label prescribing practice
- Investment
- Clinical doability