Medicines for children in Europe: an update

José Ramet
Secretary-general
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

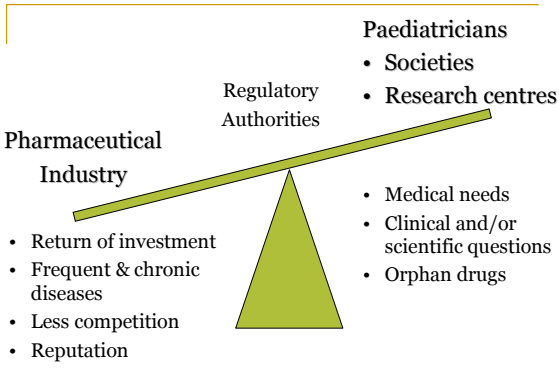
Child… not a small adult
Infant… not a small child
Preterm…not a small newborn

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



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

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

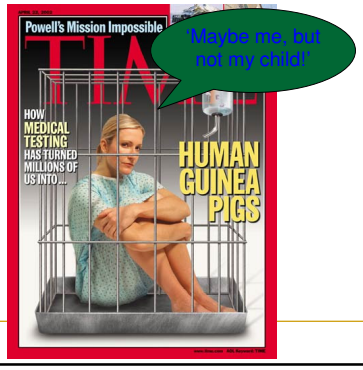
Ethical issues: The paediatric population should

- 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) Eur J Pediatr 2001;160:364-368
- Research in children. (Sauer PJJ) Eur J Pediatr 2002; 161: 1-5
- Putting the child first: Research as a part of paediatric care. The Joseph J. Hoet Lecture on Ethics in Paediatric Resarch (Kurz R) Int J Pharm Med 2002; 16: 11-13
- 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) Int J Pharm Med 2003; 17: 7-9
- Informed consent/assent in children (De Lourdes Levy M, Larcher V, Kurz R Eur J Pediatr 2003; 162: 629-633
- 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
- Testing medications in children (reply) (Crawley FP, Kurz R, Nakamura H N Engl J Med 2003; 348: 763-4.
- Ethical principles and operational guidelines for good clinical practice in paediatric research. Recommendations of the Ethics WG of the CESP (Gill D Eur J Pediatr 2004; 163: 53-57
- What the paediatricians need—the launch of paediatric research in Europe Eur J Pediatrics 2005 Ramet J 164; 5 :263 – 5
- Refugee Children - a concern for European paediatricians Mjönes S Eur J Pediatr 2005; 164: 535-8

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?

Paediatric Role

- Define therapeutics needs
- Develop validated end-points for
  - efficacy and safety
  - "bridges" adult studies
- Develop effective, efficient, ethically driven networks to conduct clinical studies
- Performed at all level of paediatric care

Industry Role

- Discovery of new medicines
  - High throughput screening of compounds
- Development of new medicines
  - Pre-clinical toxicology
  - Human evaluation of dose, safety, efficacy

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

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.

It Takes at Least..... 6 Partners

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

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


COMMISSION OF THE EUROPEAN COMMUNITIES

Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

(presented by the Commission)

EN EN

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

Interactive Policy Making
Online consultations

Guidelines for future European Union policy to support research

1727 responses received

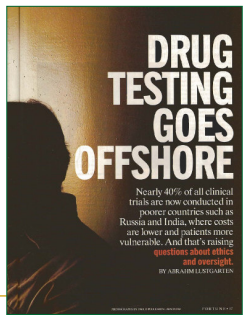
Country	Number of responses	% of total responses	Country	Number of responses	% of total responses
DE - Germany	258	14.9%	CH - Switzerland	25	1.4%
UK - United Kingdom	157	9.1%	FI - Finland	22	1.3%
IT - Italy	147	8.5%	LT - Lithuania	22	1.3%
BE - Belgium	142	8.2%	IL - Israel	17	1.0%
FR - France	132	7.6%	PL - Poland	16	0.9%
ES - Spain	123	7.1%	CY - Cyprus	12	0.7%
NL - Netherlands	89	5.2%	CZ - Czech Republic	10	0.6%
PT - Portugal	81	4.7%	EE - Estonia	10	0.6%
EL - Greece	80	4.6%	HU - Hungary	10	0.6%
AT - Austria	79	4.6%	BG - Bulgaria	8	0.5%
SV - Sweden	68	3.9%	SK - Slovak Republic	7	0.4%
TR - Turkey	44	2.5%	SL - Slovenia	6	0.3%
IE - Ireland	33	1.9%	MT - Malta	5	0.3%
NO - Norway	31	1.8%	LV - Latvia	4	0.2%
Other country	30	1.7%	LU - Luxembourg	1	0.1%
RO - Romania	29	1.7%	IS - Iceland	1	0.1%
DK - Denmark	28	1.6%	*TOTAL*	*1727*	*100%*

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**

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?

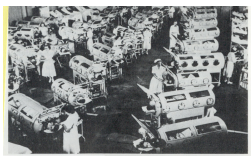
- be able to respond to increased resear
- define
  - "centers"
  - organize a "research task distri
- be present at EMEA & related advis
- develop scientific excellence
  - stimulate gifted medical students: conside paediatric research
  - act on research, education, higher educatio
  - support major international research projec
  - act on education , training , research stimulation

From private practice to research centre

From clinical to fundamental

Major advantage of paediatrics

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

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)

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**
+2 years data protection

Medicines for children: Key measures

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