Challenges and Opportunities of Developing Paediatric Medicine

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GRIP has received research funding from the European Union

In this presentation I will discuss

- Children's access to medicines compared to adults
- Consequences of lack of approved paediatric medicines
- The recent paediatric initiatives
- Suggested causes of lack of paediatric medicines
- Some measures to build capacity in Europe for development of paediatric medicines

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Medicines for children – A global challenge

Medicines needed to treat children which fulfil the criteria of Quality, Safety and Efficacy are not available to the same extent as are medicines needed to treat adults - ***anywhere in the world!***

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Consequences of the lack of approved medicines for children

- Paediatric formulations commonly not available
- Paediatric data commonly not available
- Unlicensed and off-label use in children
- Children do not benefit or benefit late from innovative drug development

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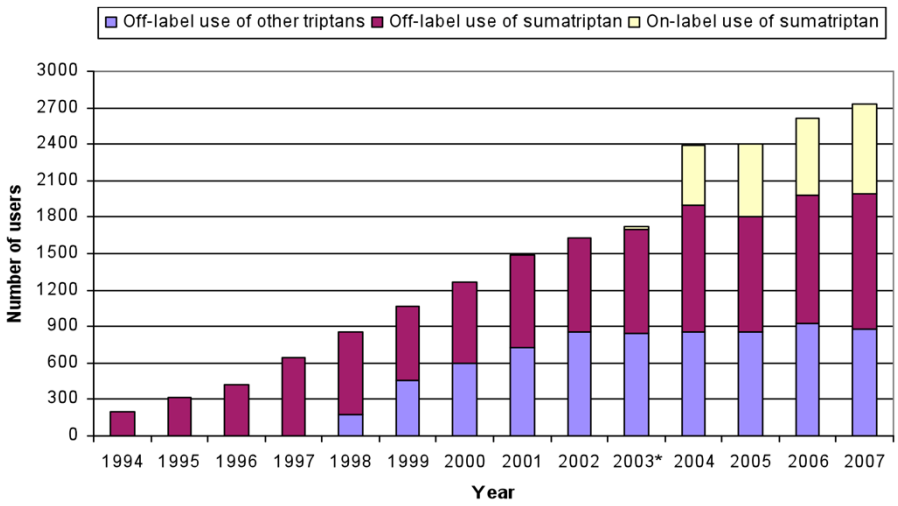
Triptan use in children aged 0-17 years in 1994-2007 in Finland (off-label use of sumatriptan and other triptans** and on-label use of sumatriptan) in 2003-2007



*Approval of nasal sumatriptan to adolescents 12-17 years old in August 2003.
**zolmitriptan, rizatriptan, naratriptan, almotriptan, eletriptan and frovatriptan

When specific data in the paediatric population is not available?

- *Risk for adverse effects*
  - Unknown adverse effects
  - Use of (older) drugs with data available, but more adverse effects
- *Risk for suboptimal efficacy*
  - Use of (older) drugs with data available, but lesser effect
  - Underdosing, if data for correct dosing n.a.

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Major developments in the field of Better Medicines for Children

- Important **regional** developments
  - US Paediatric legislations 1998 -
  - EU paediatric legislation 2007 –
- Important **global** development
  - Resolution WHA60.20 "Better medicines for children" adopted May 2007

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Medicines for children

Objectives of the proposal

- To improve the health of the children of Europe, by:
  - increasing high quality research into medicines for them
  - promoting the development and authorisation of such medicines
  - improving the information on medicines designed for children
- While avoiding unnecessary studies in children and not delaying the authorisation of medicines for adults

Effects of paediatric initiatives in the developed world on children elsewhere

- In the worst case the current initiatives could increase exploitation of the children of the developing countries
- In the best possible case the initiatives could be of enormous benefit also for the children of the developing world
  - Development of a formulation suitable even for newborns and not requiring cold-chain transport and storage

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SIXTIETH WORLD HEALTH ASSEMBLY WHA60.20

Agenda item 12.18 23 May 2007

Better medicines for children

The Sixtieth World Health Assembly,

Having considered the report on better medicines for children;

Recalling resolutions WHA39.27, WHA41.16 and WHA47.13 on the rational use of drugs, WHA41.17 on ethical criteria for medicinal drug promotion, WHA43.20 and WHA45.27 on the WHO Action Programme on Essential Drugs, WHA47.12 on the role of the pharmacist in support of the WHO revised drug strategy, WHA49.14 and WHA52.19 on the revised drug strategy, WHA54.11 on the WHO medicines strategy, and WHA58.27 on improving the containment of antimicrobial resistance;

Recognizing the efforts of WHO in collaboration with governments, other organizations in the United Nations system, universities, the private sector, nongovernmental organizations and funding agencies in areas related to improving access to better medicines for children;

Aware of the core components of WHO's global framework for expanding access to essential medicines;

Wishing to promote evidence-based selection and use of medicines for children by health providers and carers;

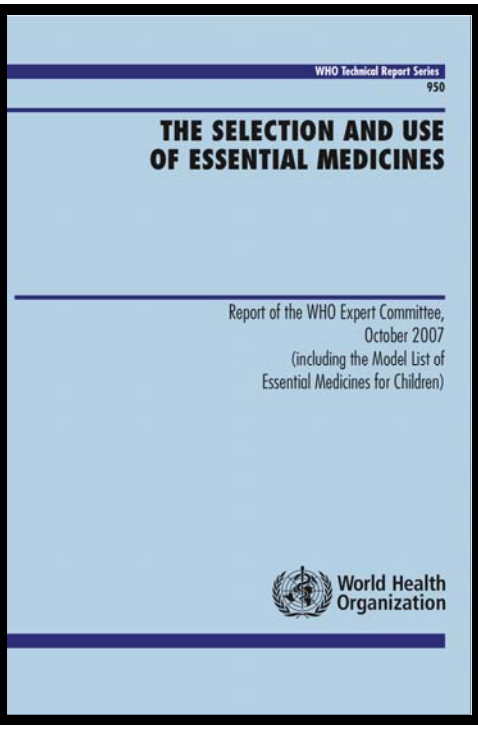
Aware that there are regional initiatives to address inadequate access to essential medicines for children;

Wishing to ensure better access to essential medicines for children as a prerequisite for achieving health outcomes as set out in the internationally agreed health-related development goals, including those contained in the Millennium Declaration;

Aware that the lack of access to essential medicines of assured quality continues to pose significant risks of high morbidity and mortality in children, especially those under five years of age;

Recognizing the ongoing work of the Intergovernmental Working Group on Public Health, Innovation and Intellectual Property and the need to ensure harmonization of WHO's work on access to essential medicines;

Concerned that children can be further disadvantaged by lack of physical and economic access to essential medicines, especially in vulnerable communities;



Suggested causes for lack of paediatric medicines

- Lack of interest by the pharmaceutical industry due to small market size (insufficient return of investment)
- Challenges of paediatric clinical studies
  - Ethical problems
  - Problems in recruiting patients
  - Methodological problems
  - However, the most important problem may be lack of expertise and experience in planning and performing paediatric clinical trials leading to failure of the protocols.

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Ethics of paediatric clinical studies

The 1st question by uninitiated persons:

"Is it ethical to do clinical trials in children?"

My question to them:

Is it ethical to leave children without treatment or treat them without appropriate knowledge of the dose, safety or efficacy of the medicine?

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Ethical prerequisites for research

- Scientifically valid design
- Acceptable benefit:risk ratio
- IRB/Ethics committee approval
- Informed consent

Scientifically valid design

- Valid aim of the study/question
  - Unnecessary duplication of studies?
- Design able to answer the question
- Power to be able to answer the question
- Assessment of effects with methods validated for the age group

Acceptable benefit:risk ratio

- Benefit › risk
- In paediatric trials acceptable risk is not enough
  - Benefit required
  - Direct benefit – Indirect benefit (?)
  - "Benefit" cannot be incentives or financial inducements
- In addition: Minimal harm

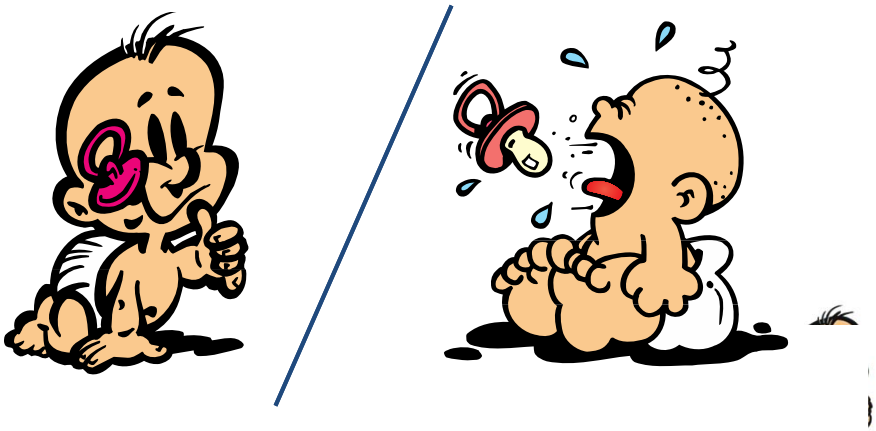
Problems of informed consent

- From:
  - One parent
  - Both parents
  - The whole family
  - The adolescent her-/himself only?
  - Legal guardian

The opinion of the minor

- Consent
  - 18-20 yr. legally of age
  - 12-15 yr. Considered capable of making independent decisions
- Assent of the child (active affirmation)
  - EU: to be determined by IRB/IEC
  - AAP: ≥ 7 yr. (intellectual age)
- Active dissent (?)
  - 5-7 yr.

Interpretation of assent /dissent



Problems in recruiting paediatric patients for CTs

- Children are basically a healthy population
  - Most paediatric diseases in Europe fill prevalence criteria for Orphan Designation in EU
- For common indications – vaccinations for healthy children – large CTs are feasible also in the paediatric population
- Problem areas:
  - False expectations on timelines for recruitment
  - Lack of interest and CT experience among paediatricians and other physicians treating children

Methodological problems of paediatric CTs

- Study design
  - Industry/regulatory interest centred on large CTs
  - Paediatric CTs commonly trials in small populations
    - With exceptions like vaccine trials
- Dose not appropriately determined
- Outcome measures age appropriate and validated?
- Comparator
  - Use of placebo in children
  - Best existing treatment may not have been properly studied

Methodological problems of paediatric CTs..

- Sponsored studies – understanding paediatrics
- Academic trials – understanding CT methodology
- Development and validation of of new innovative methods needed

Building capacity for paediatric CTs

- Networks for paediatric clinical trials
  - National networks
  - Speciality networks
  - Age-specific networks
  - Enpr-EMA*
- Training of paediatric experts and investigators
  - GRIP**

* European Network of Paediatric Research at the European Medicines Agency
** Global Research in Paediatrics

European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA)

- **Enpr-EMA** is a network of research networks, investigators and centres with recognised expertise in performing clinical studies in children
- **Enpr-EMA** aims to foster **high-quality ethical research** on quality, safety and efficacy of medicines to be used in children. It does this through networking and stakeholder collaboration with members from within and outside the European Union (EU)
- **Enpr-EMA** does not perform clinical trials or fund studies or research or decide on areas for paediatric research, as this is the responsibility of Member States, the European Commission or each individual network

Networks fulfilling all minimum criteria (n=18)

ECFS-CTN (European Cystic Fibrosis Society - Clinical Trials Network)
EUNETHYDIS (European Network for Hyperkinetic Disorders)
EPOC (European Paediatric Oncology off-patent medicines Consortium)
FINPEDMED (Finnish Investigators Network for Pediatric Medicines)
GNN (German Neonatal Network)
ITCC (Innovative Therapies for Children with Cancer)
I-BFM-SG (International BFM Study Group)
FIMP-MCRN (Italian Paediatric Federation- Medicines for Children Research Network)
MCRN (Medicines for Children Research Network – The Netherlands)
MICYRN (Mother Infant Child Youth Research Network, **Canada**)
NIHR-MCRN (National Institute for Health Research - Medicines for Children Research Network – UK)
Newcastle-CCLG (Newcastle Children's Cancer and Leukaemia Pharmacology Studies Group
PENTA (Paediatric European Network for the Treatment of AIDS)
PRINTO (Pediatric Rheumatology International Trials Organisation)
Scotmcn (Scottish Medicines for Children Network)
UKPVG (United Kingdom Paediatric Vaccines Group)
EBMT (European Group for Blood and Marrow Transplantation)
CICPed (Paediatric Network of Clinical Investigation Centres, France)

FP7 Cooperation Work Programme: Health-2010

4.2. RESPONDING TO EU POLICY NEEDS

HEALTH.2010.4.2-2: International paediatric initiative. FP7-HEALTH-2010-single- stage.
The initiative is expected to bring together European and US stakeholders, as well as other third countries as appropriate, which are involved in the joint development and testing of medicines for children. It should demonstrate a rationally structured joint programme of activities aimed at integrating research efforts in different multidisciplinary fields (trial methodology, ethics, pharmaco-epidemiology, new formulations and drug safety). The overall objective is to enhance the availability of medicines for children in Europe and in the USA. An expected deliverable will be the successful development of a joint paediatric clinical pharmacology training programme. Others include jointly executed EU/US paediatric medicine research activities in support of the joint programme of activities, mutually agreeable standards for clinical trials, quality assurance, development of integrated tools (e.g. databases) for pharmaco-epidemiological studies etc. Areas of clinical interest should include, but not exclusively, new formulations, the needs of neonates, paediatric gastroenterology, cardiology, neonatology, neuropsychiatric, infectious and rare paediatric diseases. A concrete dissemination plan should be included. The initiative should also establish a joint structure to enhance and consolidate durable integration, with the possibility of adding new groups via competitive Calls for Proposals as necessary. Active participation of SMEs could lead to an increased impact of the research proposed and this will be considered in the evaluation of the proposal. **Note:** Limits on the EC financial contribution apply. These are implemented strictly as formal eligibility criteria. You must refer to the call fiche for details of these limits. **Funding scheme:** Network of Excellence
EC contribution per project: max. EUR 12 000 000
Only up to one proposal can be selected.
Expected impact: To integrate European research programmes in paediatrics. To foster a closer interaction with those in the USA and third countries in order to accelerate the accessibility to new medicines for children. A wide range of stakeholders, including especially patient organisations, should be represented.

No	Name of GRIP Partner	Short name	Country	Lead Scientist
1	Azienda Ospedaliera Di Padova	AOPD	Italy	Carlo Giaquinto
2	US Department of Health and Human Services	NICHD-NIH	United States	Steven Hirschfeld
3	European Medicines Agency	EMA	United Kingdom	Agnes Saint Raymond
4	Erasmus Universitair Medisch Centrum Rotterdam	EMC	Netherlands	Miriam Sturkenboom
5	The University of Liverpool	ULIV-MCRN	United Kingdom	Mark Turner
6	Ospedale Pediatrico Bambino Gesu	OPBG	Italy	Paolo Rossi
7	Institut National de la Sante et de la Recherche Medicale	INSERM	France	Evelyne Jacqz-Aigrain
8	National Center for Child Health and Development	NCCHD	Japan	Hidefumi Nakamura
9	St George's Hospital Medical School	SGUL	United Kingdom	Mike Sharland
10	Consorzio Per Valutazioni Biologiche E Farmacologiche	CVBF-TEDDY	Italy	Ceci Adriana
11	Universiteit Leiden	UL	Netherlands	Oscar Della Pasqua
12	Academisch Medisch Centrum bij de Universiteit van Amsterdam	AMC	Netherlands	Martin Offringa
13	Fundacion Vasca De Innovacion E Investigacion Sanitarias	BIOEF	Spain	Adolf Valls-i-Soler
14	Instytut Pomnik Centrum Zdrowia Dziecka	PCZD	Poland	Marek Migdal
16	World Health Organization.	WHO	Switzerland	Sue Hill
17	The School of Pharmacy, University of London	SoP	United Kingdom	Ian Wong
18	Helsingin ja Uudenmaan Sairaanhoitopiirin Kuntayhtymä	HUS	Finland	Kalle Hoppu
19	Brighton Collaboration Foundation	BF	Switzerland	Jan Bonhoeffer
20	Fondazione Penta-for the Treatment and Care of Children with Hiv-Onlus	PENTA	Italy	Jean Pierre Aboulker
21	Vereniging Samenwerkende Ouder- En Patientenorganisaties	VSOP	Netherlands	C Oosterwijk
22	The Hospital for Sick Children	SICKKIDS	Canada	Shinya Ito

GRIP Work Packages

- WP1: Joint paediatric clinical pharmacology international training program
- WP2: Integrated infrastructure for paediatric epidemiological and post-marketing drug studies
- WP3: Research tools to facilitate interoperability in paediatric research
- WP4: New methods for clinical studies in paediatrics
- WP5: Paediatric formulations
- WP6: Drug development in neonates
- WP7: Dissemination and networking
- WP8: Scientific Coordination
- WP9: Project Management

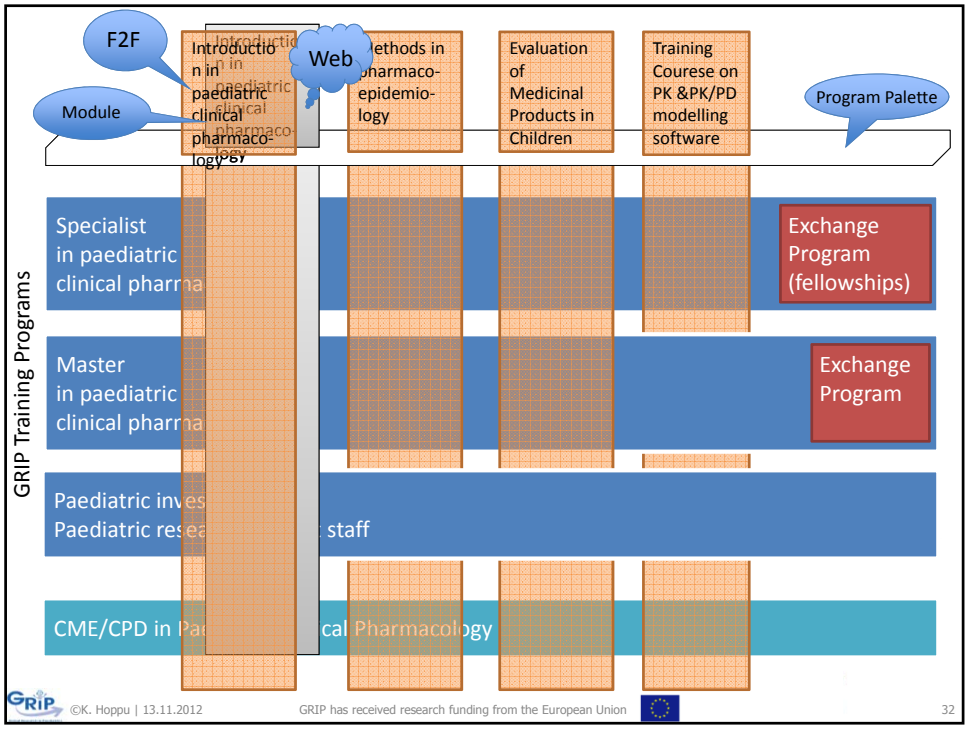
WP1 – Specific objectives (examples)

To establish training programs including:

- Comprehensive fellowship training program leading to certification in paediatric clinical pharmacology
- Masters programme (MSc) in paediatric clinical pharmacology
- Training course for paediatric clinical investigators
- Training course for paediatric clinical trial staff

WP1 – Specific objectives… (examples)

- To set up GRIP Virtual Learning Environment (VLE) – a web-based platform for distance-learning



Conclusions

- Paediatric medicines development and research have had low priority resulting in problems of quantity and quality of paediatric clinical studies
- The paediatric initiatives (US, EU) have increased demand for research of paediatric medicines and provide public and private funding for the studies, capacity building and development of methods
- The most important problem may be lack of expertise and experience in planning and performing paediatric clinical studies

Conclusions: Change is already happening…

- All new medicines becoming available for adults in EU and USA will be studied in all relevant paediatric age-groups, unless the medicine is unsafe or of no therapeutic interest for children
- If found effective and safe in children the medicines will be available in an age appropriate formulation
- In less developed countries children's access to medicines is starting to improve