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ILSI Health and Environmental Sciences Institute

H E S I

**WORKSHOP ON THE VALUE OF JUVENILE ANIMAL STUDIES WASHINGTON DC 5/6 MAY 2010**

# **A Pediatric Clinical Perspective**

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# Adam & Eva

- A&E talk here would be: off-label drug use in children, history, etc: Boring & repetitive
- Two personal encounters with preclinical tox & safety: In 1991, liver tumors in rats almost stopped development of pantoprazole; quinolone cartilage damage in young dogs quoted in 2005 as successful contribution of preclinical tox & safety to drug safety
- PPIs: 2 y carc studies used too high doses; general warnings against quinolone use in children are perpetuated but not true in a generalized way
- Two issues: general role of preclinical tox & safety AND its specific role in children



\* Lucas Cranach, The Fall of Man

# Some Elements Of A&E May Be Helpful (1)

- Naïve definition of preclinical tox & safety: trying to prevent harm to patients by matching animal organs / ADME / behaviour with man
- Drug development has traditionally focused on adult development ; now suddenly we have to think of children very early
- Terms such as preclinical toxicology, preclinical development, animal testing etc. assume – without saying so – that we look into another species to prevent harm in our own species
- Differentiation of humans into age groups with mandatory requirements for children is new in history - we are just beginning
- We know already much about correspondence man & animal per organ, age & species – “technical knowledge“
- Technical knowledge tends to develop new sub-specialties, with new regulations and dedicated specialists

## Some Elements Of A&E Are Always Helpful (2)

- When I studied medicine, I had 2 courses on pharmacology, 1 on pediatrics, nothing about drug development or clinical trials. Drug development in children did not even exist as an academic topic.
- Much of our academic formation is outdated soon. Adjustment of academic curricula to the world is slow. Medical & other students should know clinical trials, drug development and preclinical testing
- Two groups welcomed me warmly in the 2 global pharmaceutical companies when I built up pediatric groups 2000/2005: technical development (pediatric formulations); and preclinical tox & safety
- Both functions are key in drug development.. Both functions can stop a drug development. Few care as long as boxes are ticked
- Conclusion: both felt disconnected from main-stream dev, welcomed opportunity to show their clinical value [big pharma bias?]

# Some Elements Of A&E Are Always Helpful (3)

- During adult life, we work hard to forget much of the things we learned in school & university.
- Small size of preclinical tox & safety departments has allowed trust between professionals, leading to an inofficial meeting 2009 in Basel
- Juvenile animal studies: I advocate an iterative return to A&E in the sense of asking for the clinical usefulness of animal studies
- This approach should not be limited to juvenile animal studies. Basic questions are by some perceived as stubborn, by others as helpful
- Apart from building new careers in new sub-specialties, we need a better interaction between development / clinical development and the involved sub-specialties

# Suggested Subtitle: A Clinical view on Non-Clinical work

- Usefulness and predictivity of non-clinical findings for pediatric trials
- Examples (toxicities or concerns) when pediatric trials can not be conducted ethically / safely / adequately and thus require data from juvenile toxicity studies before clinical trial initiation
- Influence of non-clinical outcome on recruitment, additional safety parameters, labeling
- Special issues and risks associated with each pediatric age-group
- Risk-benefit analysis (curing a disease vs. taking known or unknown risks for toxicity)

# Scope Of Today's Workshop / Of This Presentation

- To answer the quoted list would require an encyclopedic knowledge of at least pediatric medicine, veterinary medicine, adult & pediatric drug development, and more
- I do not have final answers
- Science & society are teamwork, so here my thoughts

# Usefulness & Predictivity of non-clinical findings for pediatric trials

- Same question as with adult tox: is the young animal more susceptible to the general organ toxicity of the drug?
- What could be the consequence of the finding?
  - Labelling: e.g. not recommended in some age groups
  - Safety: post-marketing surveillance studies
  - False positive vs. false negative findings, e.g. quinolones & cartilage damage in young dogs
  - Species-specific or general finding?
- No potential therapeutic conclusions: study should not have been performed



# Examples when pediatric trials cannot be conducted ethically / safely / adequately and thus require juvenile tox studies before clinical trials

- Q probably regards new compounds in development
- Depends of risk-benefit assessment. E.g. lethal disease, all options exhausted, a new drug is available – would you hesitate for your child or wait for animal data? What if your child might get blind?
- We see now requests for compounds used since ages in adults and children where now preclinical animal data are requested. Value of potential outcomes: doubtful
- It may sound logical, but may not reflect reality. If there is a high medical need, a new drug must be tried in children. If there is sufficient alternative therapy around, the drug should not be tried in children. Then also the animal studies are unnecessary.

# Influence of non-clinical outcome on recruitment, additional safety parameters, labeling

- Safety warnings for specific age groups can make sense.
- Again, is in the framework of risk-benefit assessment. If the potential therapeutic benefit is worth the risk ...
- Recruitment: all parents do risk-benefit-assessment. The more serious a disease, the more parents are prepared to let their child participate in a clinical trial
- Animal data with clear warnings would probably discourage recruitment

# Special issues and risks associated with each pediatric age-group

- The younger children are, the farther they are away from adult ADME
- A large part of the knowledge of today comes from observations over the past decades. E.g. anilin dye in the nappies was absorbed through the skin in babies
- Problem: the younger animals are, the smaller they are. Where will be put the limit of feasibility? Will the additional efforts increase the safety of the later drugs?

# **Risk-benefit analysis (curing a disease vs. taking known or unknown risks for toxicity)**

- This is a clinical question
- Non-clinical toxicology & safety can help in thinking
- Warnings have a tendency to remain on the web even when competent professionals regard them as adequate

# The Multitude Of Challenges In Pediatric Drug Dev

- Ped oncology: Most drugs are highly toxic. They save life, at a cost
  - Use of Botulinum Toxin in children: cerebral palsy
  - Treating allergic rhinitis with natural allergens; ~140 drugs need registration due to new German law → 140 PIPs expected → new standard PIP on EMA website (1<sup>st</sup> on H1N1)
  - CMV (cytomegalovirus) is probably the most frequent cause of infectious congenital malformations → how would you design a PIP in a drug targeting CMV disease?
  - Does pediatric cardiology need contrast ultrasound imaging agents?
- Medicine is complex. Standards are necessary as framework – but should not obstruct meaningful questions at appropriate interfaces.

# EMA PDCO Pre-Clinical Decisions On Allergenes

- House dust mites allergen extract EMEA-000319-PIP01-08-M01 P/252/2009; Stallergenes, France. Three non-clinical studies:
  1. Teratogenicity study in the rat
  2. Teratogenicity study in the rabbit
  3. Juvenile toxicity study
- Aqueous extract of grass pollen; EMEA-000337-PIP01-08, P/147/2009 Allergopharma J. Ganzer KG. No non-clinical studies
- Modified grass pollen extract; EMEA-000284-PIP01-08 P/18/2009 Allergy Therapeutics. One 7 week toxicity study in juvenile rats
- Rather different requirements for naturally occurring allergens

# Conclusions

- As parents, we should always ask the physician / pediatrician if a proposed diagnostic procedure has therapeutic consequences
- If the answer is negative, deny permission
- [The frequency of nonsense requests is directly correlated to the quality of your child's health insurance]
- As scientists caring for children we need to ask for the potential therapeutic consequences of a potential juvenile animal study, e.g.
  - A more precise labelling or a specific warning
  - A potential contribution to prevent harm
  - A potential avoidance of wrong warnings
- If, however, more boxes are to be ticked, we should push back



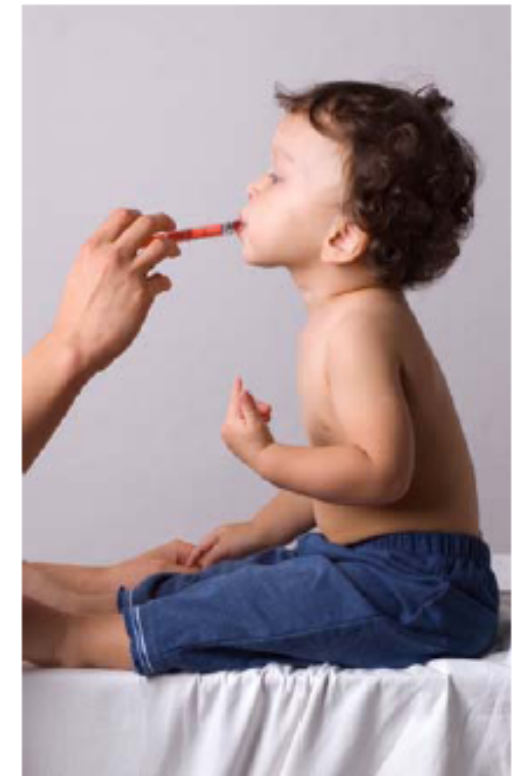
# Joint EFGCP Children's Medicines Working Party 6<sup>th</sup> Annual Conference & DIA 4<sup>th</sup> Paediatric Forum

*Current & Future Perspectives for Paediatric Medicines:  
Vision, Daily Challenges, & Ways Forward*

28 & 29 September 2010, London, United Kingdom

The EFGCP Children's Medicines Working Party and DIA Europe are pleased to announce their second joint paediatric conference. Traditional paediatric meetings of both societies in the past and the joint meeting in 2009 have attracted top level speakers from the European Medicines Agency (EMA), FDA, national authorities, WHO, academia, pharmaceutical industry and parents & patients' organizations. This second joint program will again offer the opportunity for intensive discussion among stakeholders in different topics relevant for pediatric medicines. We will address visions, daily challenges and ways forward in paediatric drug development. On this basis, the conference will also offer excellent networking opportunities for all attendees.

The conference will include three parallel breakout sessions on each day for a lively interactive discussion. Furthermore, it will provide participants with the opportunity of asking questions by e-mail before the conference and during the morning of day 1, which will be in the afternoon addressed by a speaker panel chaired by Paolo Tomasi, European Medicines Agency (EMA).





**Thank You For  
Your Attention!**

# Back-Ups

## Conference objectives

- Update participants how to deal with paediatric regulatory requirements, scientific and operational challenges
- Exchange experiences with regulatory authorities, academia and industry
- Discuss visions, daily challenges and potential ways to move forward and further improve processes for paediatric drug development

## Who should attend?

- Regulatory, clinical and drug development professionals from Health Authorities and Industry
- Pediatricians, Representatives from Academia, Paediatric Societies and Networks
- Employees from Clinical Research Organisations (CROs) involved in paediatric clinical trials
- Any stakeholder interested in the development of better medicines for children

## Session overview

- Political opportunities to optimize clinical trials and ethics approvals in Europe
- Challenges of the EU paediatric regulation as perceived by industry
- Strengths and weaknesses of academic European paediatric research
- Operational challenges for paediatric trials and how to overcome them
- Special challenges in neonatal research
- Common features of rare conditions and the way forward: Pediatric Oncology & Rheumatology
- Logistic and resource requirements for paediatric drug development for paediatric drug development: Venture capital and its role in promoting innovation in paediatric medicine
- EU Small & Medium Enterprises and paediatric research
- Media, parents & clinical research: challenges & opportunities
- Speakers panel discussion: participants addressing/clarifying issues and seeking advice

## Programme Committee

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# Guide to Paediatric Clinical Research

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# Guide to Paediatric Drug Development and Clinical Research

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