

Preclinical studies for paediatric programmes

**4th Annual SwedenBIO Clinical Trials Day
Uppsala, Sweden
8 November 2006**

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Summary of presentation

- Introduction
- Regulatory guidance
- Species Differences in Development
- Considerations and Conclusions

Non-clinical studies during drug development

Clinical trials /marketing authorisation in **ANY** human

- Extensive non-clinical testing - described in a number of guidelines

Why **ADDITIONAL** data for young populations?

- Additional/other risks due to 'immature' / growing organism ?
- Children may be included earlier in drug development, before more extensive adult data available

Potential key organs /systems

- Central nervous system
- Immune system
- Pulmonary system
- Reproductive system
- Skeletal system
- Renal function

Current Regulatory Situation

- ICH M3 mentions non-clinical studies in relation to paediatric patients in clinical trials
- Detailed guidelines on juvenile toxicity testing
 - **European Union**
 - Concept paper (2001)
 - Draft Guideline - Consultation period ended April 06
 - **FDA**
 - **Guidance for Industry:** Non-clinical Safety Evaluation of Pediatric Drug Products (Feb 2006)

ICH Guideline M3 - Non-clinical studies for conduct of human clinical trials*

Paediatric patients in clinical trials

- Most relevant safety data usually from adult human exposure, should generally be available

In addition

- Repeated dose toxicity studies
- Genotoxicity testing
- Complete reproductive/developmental toxicity package (includ. peri-postnatal studies)
- Juvenile animal toxicity studies - case-by-case basis

* CPMP/ICH/286/95

Guideline On Need for Preclinical Testing of Human Pharmaceuticals in Juvenile Animals*

- Guidance on need for, role and timing of juvenile animal studies; for product being developed for paediatric use
 - If safety concerns not adequately assessed in adults, standard non-clinical studies, or in clinical trials.
 - Dependent on e.g. therapeutic indication; critical periods in **developmental** processes
 - Study design / testing strategies

Juvenile toxicity studies may be justified when...

- Potential effects on growth/development cannot be studied in standard non-clinical and/or clinical studies
- Available data indicate toxicity in developing systems
- Effects on growth/development in intended age group?!
- Pharmacology affects developing organ(s).
- Address already known concerns further e.g. reversibility or aggravation; establish safety factors

Key elements for Need for Juvenile Studies

- **Age dependent development of major organs**
- **Clinical aspects**
 - Disease predominantly/exclusively in paediatrics
 - Serious or life-threatening disease
 - Duration of paediatric treatment
 - Age of paediatric population
 - Paediatric data with product of similar chemical structure and/or pharmacological class
 - Primary pharmacodynamic effects in target organs/tissues
 - Adult data
 - Adverse reactions
 - Pharmacokinetic data

Key elements for the Need for Juvenile studies

Non-clinical Aspects

- Data from existing studies
- Adverse; irreversible reactions, target organs/tissues
- Mechanism of action
- Exposure of organs with significant postnatal development
- Pre-postnatal studies
 - with sufficient exposure of pre-weaning animals
 - severe reactions in offspring
- Exposure margins vs. human adult - low or high?
- Juvenile animal data from product of similar chemical structure and/or same pharmacological class

Guidance on study conduct

Consider

- Intended/ likely use children
- Timing of dosing in relation to growth/development in children and juvenile animals
- Potential differences in pharmacology and/or toxicity profiles between mature and immature systems.

Guidance on study conduct

- **Duration** – systems with long developmental periods
→ 13 weeks in rats; 9 months in dogs.
- **Route of administration**
- **Species** – one generally sufficient
- **Pharmacokinetics/Toxicokinetics**
- **Dose selection**
- **Endpoints**

Additional points

- Could modified pre-postnatal study address (some) developmental toxicity issues?
 - milk excretion and pup exposure?
 - exposure of developing organs pre-weaning; physical development, histopath investigation?
- Neurotoxicity, Immunotoxicity or Nephrotoxicity studies only required if chemical/pharmacological class of compound or previous studies give cause for concern for the these systems.
- Specific studies designed to address relevant endpoints.

Species Differences in Development

Challenges...

- Important differences in timing of developmental events at birth in experimental animal species and humans that must be recognised in designing studies and interpreting experimental animal data for potential human risk
- Significant gaps remain in the knowledge for the comparative age of major organ development in laboratory animals compared with human

ILSI/HESI* project started in 1999/2001

- Public, non-profit scientific foundation, with participation from government, academia and industry.
- International forum for understanding & application of scientific issues related to human health, toxicology, risk assessment, and the environment.
- **Project on Role of Juvenile Animal Studies in Assessment of Paediatric Safety**

* International Life Sciences Institute / Health and Environmental Sciences Institute

ILSI/HESI project

Reviews published in 2003

- Species comparison of postnatal **bone** growth and development*
- Species comparison of anatomical and functional **renal** development*
- Species comparison of **lung** development*
- Development and maturation of the **male reproductive** system*
- Landmarks in the development of the **female reproductive** system*
- Species comparison of anatomical and functional **immune** system development**
- Postnatal anatomical and functional development of the **heart**: A species comparison**
- Species comparison of postnatal **CNS development**: functional measures***

* Birth Defects Research (Part B), Vol. 68: no 2; ** Birth Defects Research (Part B), Vol. 68: no 4; *** Birth Defects Research (Part B), Vol. 68: no 5

Example

Species comparison

Equivalent Ages

Species	Neonate	Infant	Child	Adolescent
Rat (week)	0-1	1-3	3-10	10+
Dog (month)	0-0.5	0.5-2	2-10	10+
Primate (year)	0-0.1	0.1-1	1-5	5+
Human (year)	0-0.1	0.1-2	2-12	12+

Weaning

Example

Species Comparison

Renal system - anatomical development

Species	Time of Nephrogenesis Completion
Human	Before birth (gestation week 35)
Sheep	Before birth
Guinea Pig	Before birth
Mouse	Before birth
Dog	After birth (week 2)
Pig	After birth (week 3)
Rat	After birth (week 4 – 6)

(from Zoetis in Birth Defects Research 2003 (Part B), Vol. 68: 111-120 Birth Fouser & Avner. 1993. American Journal of Kidney Disease 21(1):64-70; Gomez and Norwood. 1999. Current Opinion in Pediatrics 11:135-40 Kleinman 1982. Physiologist 25(2)104-10.)

Example

Species Comparison

Renal system: Conclusion

‘Design and interpretation of studies in prenatal and juvenile animals regarding renal development should include careful consideration of maturation of both anatomical and functional developmental mile stones between species’ *

(* Zoetis in Birth Defects Research 2003 (Part B), Vol. 68: 111-120)

Example

Species Comparison

Alveolar Development

<u>Species</u>	<u>Onset</u>	<u>At Birth</u>	<u>Critical Period</u>	<u>Completion</u>
Human	GWK36	Beginning	Birth - 2 years	6 - 8 years
Dog	?	Beginning	0-16 weeks	16 weeks
Monkey	?	Completed	<i>in utero</i>	Birth
Rat	PND4	Not Started	4 - 14 days	3 weeks
Mouse	PND4	Not Started	3 - 14 days	3 weeks

Modified from Zoetis, 1999 & Zoetis Birth Defects
Research 2003 (part B), Vol. 68:121-124

Example

Species Comparison

Lung development: Conclusion

- Main lung development considered complete at 2 years of age in humans
- Potential for local toxicity most critical in children <2 years of age
- Rat and dog acceptable models for testing safety of inhaled drugs for paediatric population
- The primate not suitable model for postnatal lung development

Considerations and Conclusions

Considerations for juvenile toxicity studies

- Is there an appropriate comparative species?
- What systems are undergoing maturation and when, in animal models in relation to humans ?
- What effect(s) does the compound have on postnatal growth and development?

Considerations for juvenile toxicity studies

- The selection of toxicological end points to be monitored in a juvenile animal study is critical
- Not considered feasible with standard study design that will address all potential issues. Instead, studies be designed to determine drug effects on specific organ systems that develop post-natally.
- Certain practical limitations to consider e.g. feasibility to obtain adequate samples for analysis, particularly in the case of rodents

Conclusions

Need of study considered on case-by-case basis

- Indication, patient population
- Pharmacology, class effects
- Available safety data (clinical/non-clinical) e.g. known target organ toxicity
- Suspected effects on growth and/or development
- Particular concern for long term exposure in relation to human developmental stages

Endpoints and duration of study based on individual case

Studies should include **TK/PK assessment**

Discuss with regulators !