

WORKSHOP

PAEDIATRIC INVESTIGATION PLAN



**New paediatric indication for a marketed drug:
Preclinical extrapolation vs bridging**

Klaus Olejniczak
**Federal Institute for Drugs and
Medical Devices (BfArM), Germany**



K. OLEJNICZAK



Seht, ihr lieben Kinder, seht,
Wie's dem Philipp weiter geht!
Oben steht es auf dem Bild.
Seht! Er schaukelt gar zu wild,
Bis der Stuhl nach hinten fällt;
Da ist nichts mehr, was ihn hält.
Nach dem Tischtuch greift er, schreit.
Doch was hilft's? Zu gleicher Zeit
Fallen Teller, Flasch und Brot.
Vater ist in großer Not,
Und die Mutter blicket stumm
Auf dem ganzen Tisch herum.

**Wird mit AD(H)S
eine Krankheit
konstruiert?**

**Methylphenidate
Verbrauch**

1993: 34 Kg

2001: 639 Kg

DIE WELT, 18. Dezember 2008

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New Toxicological Data?

El-Zein, R.A. et. al. **Cytogenetic effects in children treated with methylphenidate.** Cancer Letters xx, 1-8. (2005)

WITT, KRISTINE L.et.al. **Methylphenidate and Amphetamine Do Not Induce Cytogenetic Damage in Lymphocytes of Children With ADHD.** Journal of the American Academy of Child & Adolescent Psychiatry. 47(12):1375-1383, December 2008.

General Consideration

The following studies should be available prior to the commencement of trials in a paediatric population:

Repeat dose toxicity studies

Standard battery of genotoxicity

Reproductive toxicity studies

Carcinogenicity studies should be completed prior to long term exposure in children

General Consideration

For marketed drugs: The full non-clinical testing program are available

Additional studies may be needed

Change of the population (children)?

Change of the treatment duration?

Change of the route of administration?

General Consideration

The conduct of studies in juvenile animals should be considered when human safety data and previous animal studies are considered insufficient for a safety evaluation in the intended paediatric age group

General Consideration

Even if adverse effects on developing organ(s) can be predicted from adult human or animal data, studies in juvenile animals might be warranted in order to address a specific concern or to study reversibility or possible aggravation of the expected findings, as well as to establish safety factors.

General Consideration

The predictability for the paediatric population, based on clinical and non-clinical study results in adults, will be the key issue for the decision on whether studies in juvenile animals are needed prior to the inclusion of paediatric participants onto clinical trials. This predictability could be high, *e.g.* in children 2 to 11 years, or low, *e.g.* in preterm newborn infants and children up to 2 years old.

Key Elements for the Need for Juvenile Animal Studies

Major functional differences exist between human neonates/infants and adults. The development of the major systems is age dependent, *e.g.*:

- ❖ Nervous system: Development up to adulthood**
- ❖ Reproductive system: Development up to adulthood**
- ❖ Pulmonary system: Development up to two years old**
- ❖ Immune system: Development up to 12 years old**
- ❖ Renal system: Development up to one year of age**

Clinical Aspects

- ❖ **Drug for diseases predominantly or exclusively affecting paediatric patients**
- ❖ **Drug intended to treat serious or life-threatening diseases**
- ❖ **Duration of paediatric treatment**
- ❖ **Age of paediatric population**
- ❖ **Results from paediatric treatment with a similar drug (chemical/ pharmacological class)**
- ❖ **Primary pharmacodynamic target organs/tissues**
- ❖ **Adult human data**
- ❖ **Adverse effects data**
- ❖ **Relevant pharmacokinetic (ADME) data**

Nonclinical Aspects

- ❖ **Relevant data from existing animal studies**
- ❖ **Adverse and/or irreversible effects observed**
- ❖ **Target organs/tissues identified**
- ❖ **Mechanism of action**
- ❖ **Pharmacokinetic data show exposure of organs with significant postnatal development**
- ❖ **Pre- and postnatal toxicity studies show sufficient exposure of the pre-weaning animals**
- ❖ **Pre- and postnatal toxicity studies show severe effects in offspring**
- ❖ **Safety margins of nonclinical effect in relation to human adult exposure, low or high**
- ❖ **Juvenile animal data from a similar drug (chemical/pharmacological class)**

Duration

When adverse effects are expected on systems with a long development period, *e.g.* brain development, bone growth, immune function *etc.*, animals should be investigated up to reaching adulthood (approximately up to 13 weeks in rats and 9 months in Beagle dogs).

Route of administration

Ideally, the intended clinical route of administration should be used, unless non-clinical studies in adult animals have indicated that an alternative route is more relevant to human use

Selection of species

The juvenile animal species should be appropriate for evaluating toxicity in endpoints relevant for the intended paediatric population. With respect to repeat dose toxicity studies, rats and dogs are traditionally the species of first choice.

Pharmacokinetics

It is recognised that the collection of blood samples to obtain a full kinetic profile of a test compound under study in juvenile animals might sometimes be impractical. However, sampling at a few time points, using pooled samples if necessary, should be performed to obtain an estimate of basic kinetic characteristics, *e.g.* C_{max} and AUC.

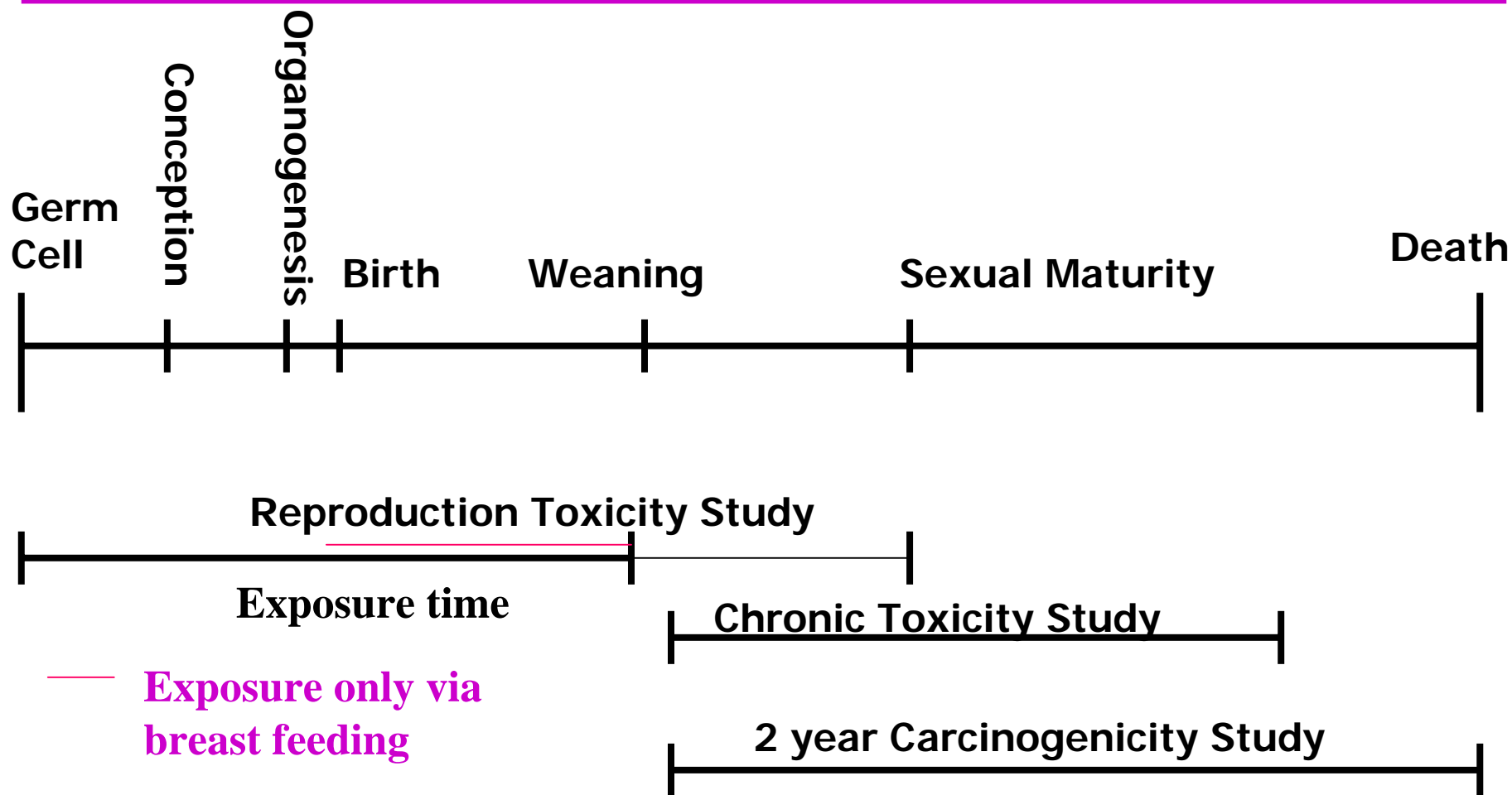
Dose selection

The primary purpose of juvenile animal studies is to assess whether young animals are more sensitive to an effect of a medicinal product than adult animals, and to identify effects on developing organs. Therefore, the high dose should be selected such that **frank toxicity does not occur** and it is recommended that doses in the lower part of the dose response curve established in adult animals are selected.

Pre- and Postnatal Reproduction Studies

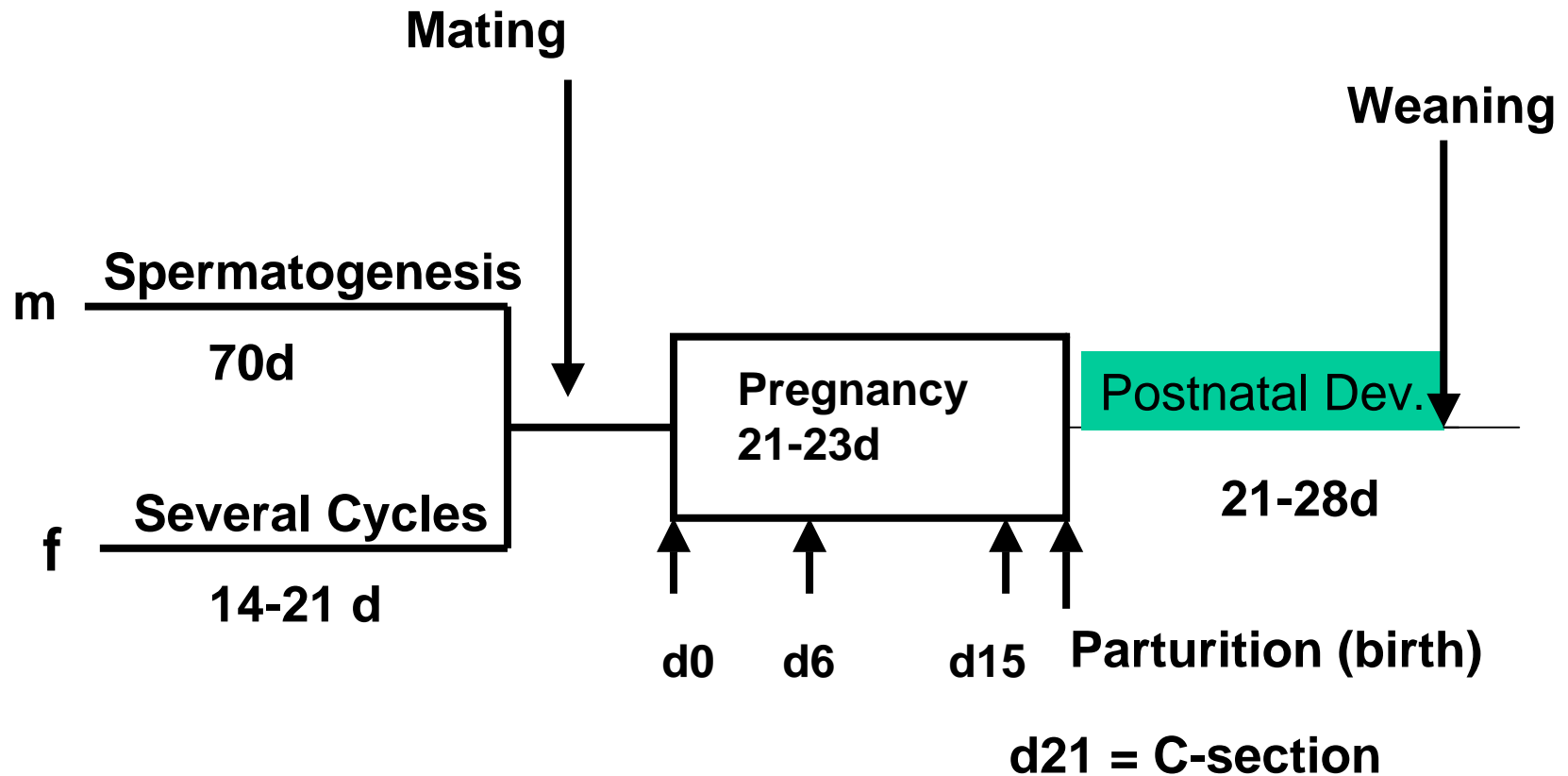
Before performing a juvenile animal toxicity study, it should be considered whether a developmental toxicity issue could be addressed in a modified pre- and postnatal development study in rats. Key factors that need to be examined include, but are not restricted to, the amount of the active substance and/or relevant metabolites excreted via the milk and resulting plasma exposure of the pups

Lifespan in relationship to the timeline of existing toxicity tests



Reproduction Toxicology

Model Diagram (Rat)



Timing of Toxicological Studies in Relation to Clinical Development(1)

Safety data from previous adult human exposure would usually represent the most relevant information and should generally be available before paediatric clinical trials. However, on a case by case basis, the extent of adult human data to support paediatric indications may be less extensive.

Timing of Toxicological Studies in Relation to Clinical Development(2)

Studies in juvenile animal, if considered necessary, should be available before the initiation of trials in paediatric populations. Pharmacokinetic data should also be evaluated before the proposed paediatric clinical trial(s). Drugs under development for specific paediatric indications or in life-threatening or serious diseases without current effective therapies warrant a case-by-case approach. In some cases, some studies may then be adapted, deferred or omitted.

New paediatric indication for a marketed drug: Preclinical extrapolation vs bridging

Need for a new formulation?

Need for other excipients?

New Vitamine E preparation E-Ferol

Intravenous application in low-birth-weight infants

>20U/kg/day a-tocopherol acetate

9% polysorbate 80

1% polysorbate 20

water

**Results: 38 deaths and 43 cases of severe symptoms
thrombocytopenia, renal dysfunction, cholestasis,
hepatomegaly and ascites**

NO PREMARKETING TESTING WAS REQUIRED

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Parenteral Formulation with Benzyl alcohol

- **Children < 3 years**
metabolic pathway of benzyl alcohol
not fully established → accumulation
- **Results:**
encephalopathy, Gaspung-Syndrom
(breathing cramps, death)

Excipients: Pediatric Contraindication

- **AGENERASE[®] (amprenavir) oral solution is contraindicated in children below the age of 4 years**

WHY?

- **Agenerase[®] containing 15 mg/ml amprenavir and 550 mg/ml propylene glycol**
- **Maximum dose for children: 2400 mg/day and propylene glycol 88 g/day**

Drug Delivery: Fibrosing colonopathy (1)

- **In 1993 cases of colonic fibrosis were identified in children with cystic fibrosis.**
- **A review of the cases showed that all of the patients had transferred to formulations of high-strength pancreatin 12-15 months before diagnosis.**
- **Pancreatin is an enzyme mixture, which supplements the defective pancreatic secretion.**
- **The products are formulated with polymethacrylate (Eudragit L30D-55)**

C.J. Powell, Lancet 1999; 353: 911-15

Drug Delivery: Fibrosing colonopathy (2)

Hypotheses

- **pH of the small intestine in cystic fibrosis is abnormal low, the dissolution (which occurs only > pH 5,5) would be delayed until the enzymes reached the distal small intestine or the colon.**
- **High local concentration of pancreatic enzymes would be delivered to an anatomical site not normally exposed to pancreatic secretion.**

C.J. Powell, Lancet 1999; 353: 911-15

Conclusion

Marketed drugs

Additional non-clinical studies (juvenile animal study) may be needed if

- **Clinical data are insufficient**
- **Change of the treatment duration**
- **Change of the route of administration**
- **Concern from the pharmacological / chemical class**

