Juvenile toxicity studies with biopharmaceuticals : considerations and current practices

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Presentation Overview

1. Considerations impacting the need and design of juvenile animal toxicity studies
2. Juvenile Toxicity Testing of Biologics
   Biopharmaceuticals are different: Impact on approach to evaluation of biopharmaceuticals in juvenile animals
3. NHP : Enhanced PPND Study Design Study
   NHP : Juvenile Toxicology Studies

Considerations……

Some key questions to address when designing juvenile animal studies

- The relevance of the animal model
- The sensitivity of the animal model (to the drug, drug class or a particular toxicity)
- The ability of animal model to produce reliable and reproducible results
- Overall feasibility of using the animal model in a nonclinical safety evaluation study
- Understanding of developmental stages of the target organ(s) in the animal model as it relates to the paediatric population
  - Ensure a comparison can be made with relevant paediatric age groups

Key considerations impacting the need and design of juvenile animal toxicity studies

- Age of population in clinical paediatric program
- Duration of treatment (Acute vs Chronic)
- Pharmacology (mode of action)
- Class history of effects on developing systems
- Known adult target organs in adult clinical program
- Known adult targets organs in adult toxicity assessments
- Identified reproductive / developmental toxicity
- Pharmacokinetic and metabolism data in adult animals and human
- Route of administration
- Unique formulation requirements / novel excipients

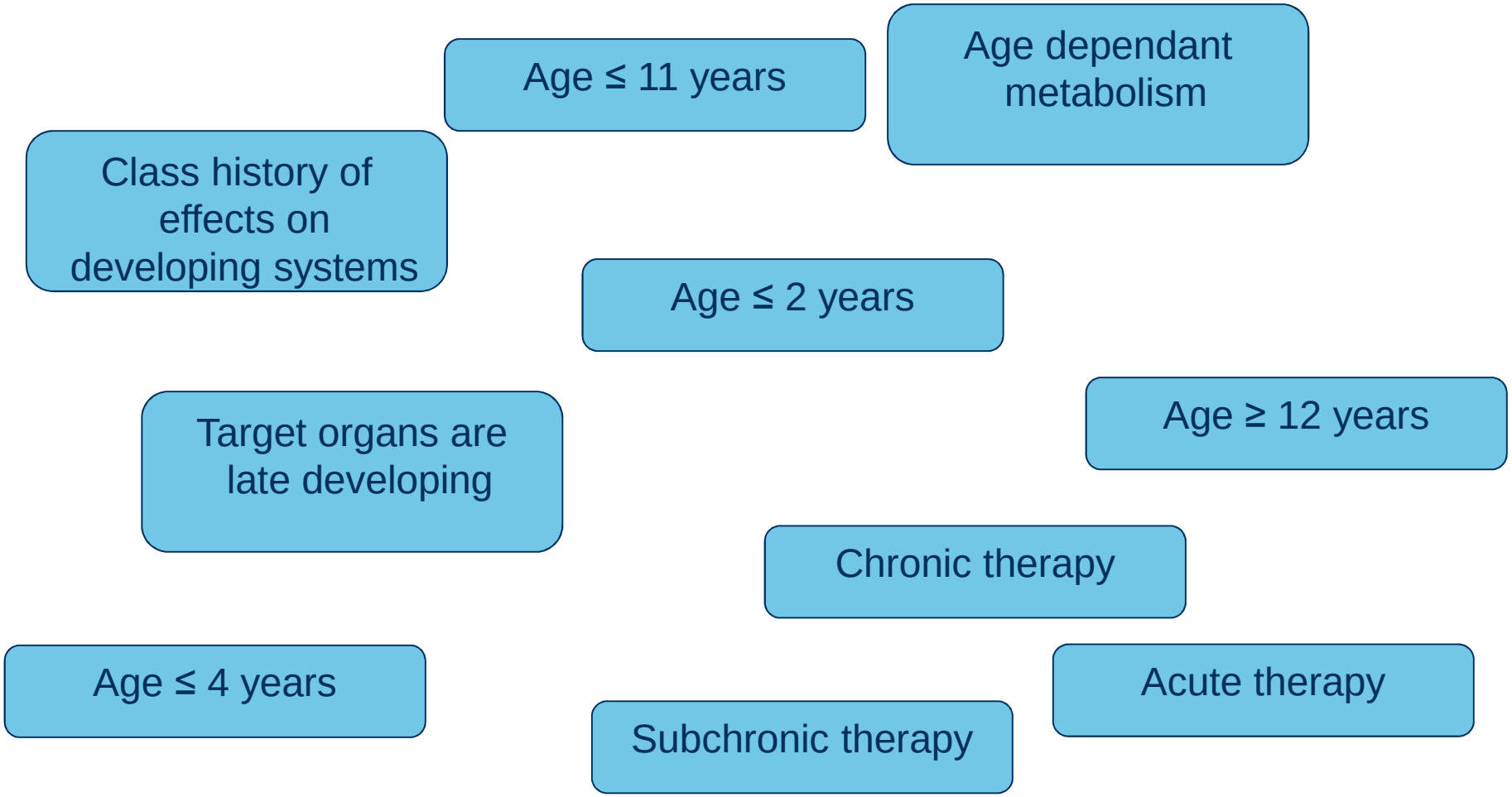
→ Develop rationale regarding the need for a study

Do we need to do a Juvenile Study to support the clinical plan??

Justify need for a non clinical study!

Prepare rationale for regulatory interactions

What is the likelihood of conducting a nonclinical Juvenile toxicity study?



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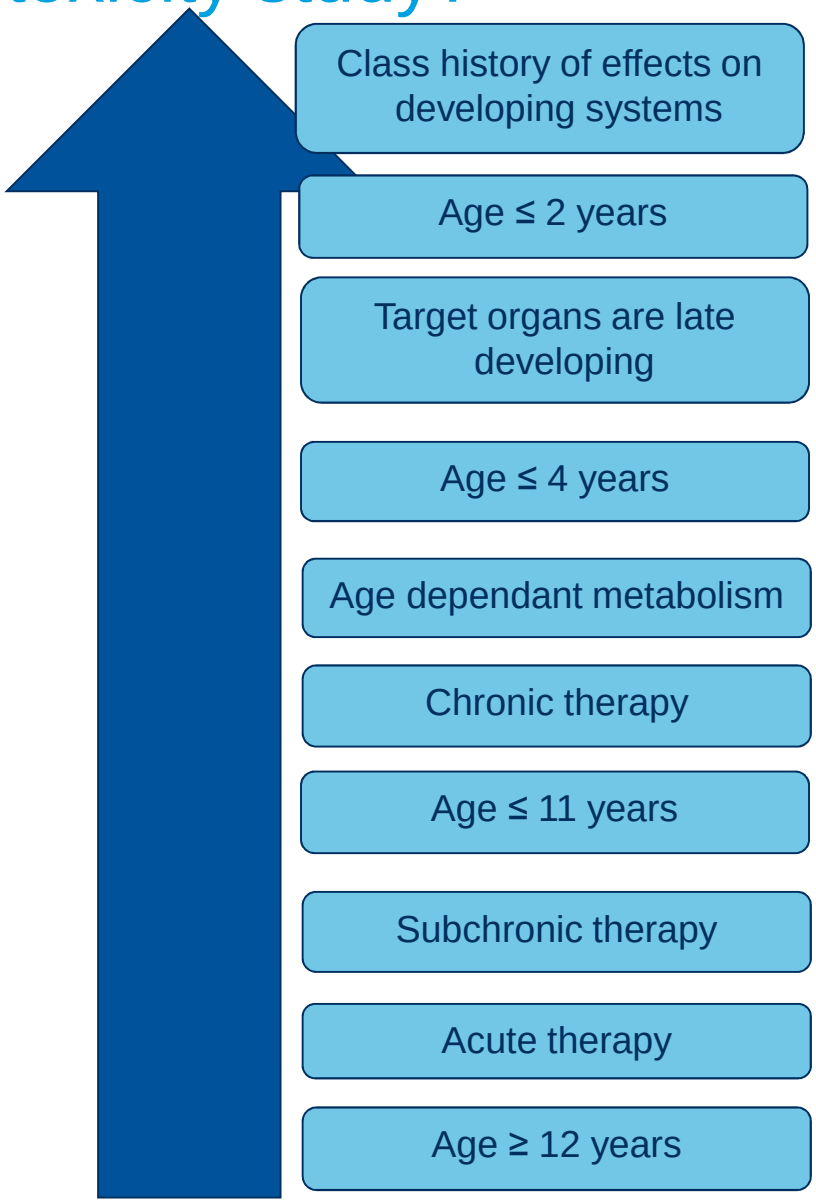

Juvenile Toxicity Testing of Biologics

Biologics

Box 1 | **Range of biotech-product classes**

Hormones
Growth hormone, insulin (analogues) and erythropoietin

Blood products
Albumin, thrombolytics, fibrinolytics and clotting factors

Cytokines and growth factors
Interferons, interleukins and colony-stimulating factors

Antagonists/inhibitors
Soluble receptors

Monoclonal antibodies and related products
Mouse, chimeric or humanized; whole molecule or fragment; single chain or bispecific; and naked or conjugated

Modified human proteins
Fusion (IgFc), polyethyleneglycol (PEG)ylation, liposome encapsulation and drug–toxin conjugate

Vaccines
Recombinant proteins or peptides, DNA plasmid and anti-idiotype

Gene-transfer products
Viral and non-viral vector-delivery systems and DNA–RNA chimaeras

Cell-based therapies
Autologous, allogeneic and xenogeneic

Tissue-engineered products
Cells, tissues, naturally occurring/synthetic biomaterials, extracorporeal and long-term implants

Cavagnaro, 2002

- Wide range of different molecular entities

Some General Differences Between Small Molecule Drugs and Biologics

Small molecule drugs	Biologics
Species 'independent'	Species specific
Non-immunogenic	Immunogenic
Metabolised	Degraded/catabolised
Short acting	Long acting
Chronic daily dosing	Intermittent dosing
Toxicity	Exaggerated pharmacology
Linear dose response	Linear/bell-shaped dose response
Direct effects	Complex temporal effects
Complex formulations	Simple formulations
Typically oral route	Parenteral routes

Biologics toxicity usually understood: exaggerated pharmacology, not off-target effects

Adapted from Cavagnaro, 2002

Biopharmaceuticals are different: Impact on approach to evaluation of biopharmaceuticals in juvenile animals

- Species Selection Cross-Reactivity
- Dosage Selection
- Immunogenicity
- PK/TK Distribution and Elimination
- Pharmacodynamics

ICH S6(R1): Guiding Principles for Species Selection for Nonclinical Safety Studies with Biologics

- 2 species toxicology is required - 1 rodent + 1 non-rodent
  - Only pharmacologically relevant species should be used
- Pharmacological relevance based on:
  - Target sequence homology/identity, expression of receptor or epitope
  - *In vitro* binding affinity, receptor occupancy, on/off rate vs human
  - *In vitro* potency/bioactivity vs human
  - Pharmacological or pharmacodynamic activity *in vivo*
- Single species toxicology program is acceptable if only 1 relevant species can be identified

⇒ **Key principle is that species relevance or irrelevance needs to be formally demonstrated**

Species Selection / Cross-reactivity

- Need to demonstrate pharmacologic relevance
  - Small molecules key concern is ADME
  - Even in the absence of pharmacologic activity a selected species could provide an assessment of toxicity (off target).
- Owing to high target specificity (esp mAbs) often restricted in their pharmacologic activity
- Lack of concern for off target activity driven acceptability of single species – if pharmacologically active across multiple species then testing required in two species (rodent/non-rodent)

- **For Juvenile studies** same rationale

Dose Selection

- Dose selection differ from biopharmaceutical vs small molecule
  - Small molecules : MTD or 2g/kg
- Owing to high target specificity, toxicity is a function of exaggerated Pharmacology and is often limited
- High dose usually selected to achieve multiple of the highest projected clinical dose or max feasible dose
- Allows assessment of exaggerated pharmacology without confounding nonspecific tox due to high amounts of protein/antibody

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- **Juvenile animal** dose selection can be an issue for small molecules (differing regulatory expectations)
- For biopharmaceuticals a similar philosophy as adult chronic tox assessment should be used

Immunogenicity

- Anti Drug Antibody (ADA) can impact assessment of toxicity
- Number factors influence ability to elicit ADA
  - Route / dose levels and interval
- ADA response can result in decreased exposure through enhanced clearance via ADA-complex or diminished pharmacologic effect (neuralising ADA)
- ADA response may limit the value of assessments conducted
- Other toxicity-related issues with ADA
  - Hypersensitivity reactions, nephrotoxicity

- **For Juvenile studies** as adult toxicity studies, an ADA response may impact interpretation.
- For studies in very young animals mature pattern of immune response may not exist

PK/TK Distribution and Elimination

- For small molecules ontogeny of metabolising and transport systems (eg p450) key role in understanding toxicity and efficacy
- Age affects expression and function of these systems which can lead to alterations in PK and elimination
- For mAbs number of factors can influence PK including :
  - antigen properties (soluble vs membrane bound)
  - mAb format and protein engineering.
  - ADA can also affect kinetics
- IgG homeostatsis neonatal FcRn

Pharmacodynamics

- Need to establish species relevance including a pharmacodynamic response

- An added consideration in testing of biophamaceuticals in Juvenile animals is age
  - *At what age in development is this a pharmacologically relevant species*?
  - *How does this compare to Human?*
    Would assume the clinical plan designed around the appropriate age group

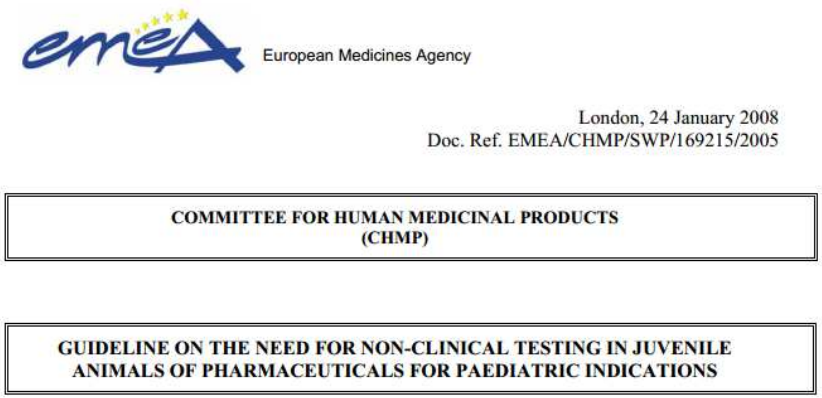
  - ??Testing of a biopharmaceutical in juvenile animal where the target is only expressed in older animals may be irrelevant?

Strategy for assessing the preclinical safety of biopharmaceuticals in juvenile animals

Strategy for assessing the preclinical safety of juvenile animals

- Goal of the strategy is to design a preclinical development plan that adequately addresses safety concerns for the intended paediatric population

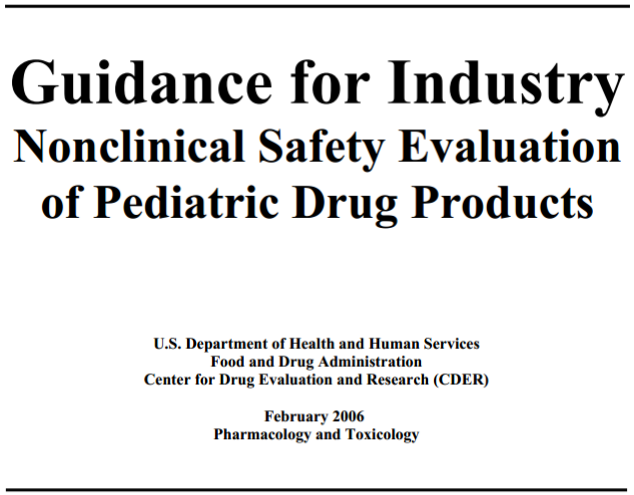
- Guidelines (EU/US/Japan) for Juvenile testing


European Medicines Agency

London, 24 January 2008
Doc. Ref. EMEA/CHMP/SWP/169215/2005

COMMITTEE FOR HUMAN MEDICINAL PRODUCTS
(CHMP)

GUIDELINE ON THE NEED FOR NON-CLINICAL TESTING IN JUVENILE ANIMALS OF PHARMACEUTICALS FOR PAEDIATRIC INDICATIONS


Guidance for Industry

Nonclinical Safety Evaluation of Pediatric Drug Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

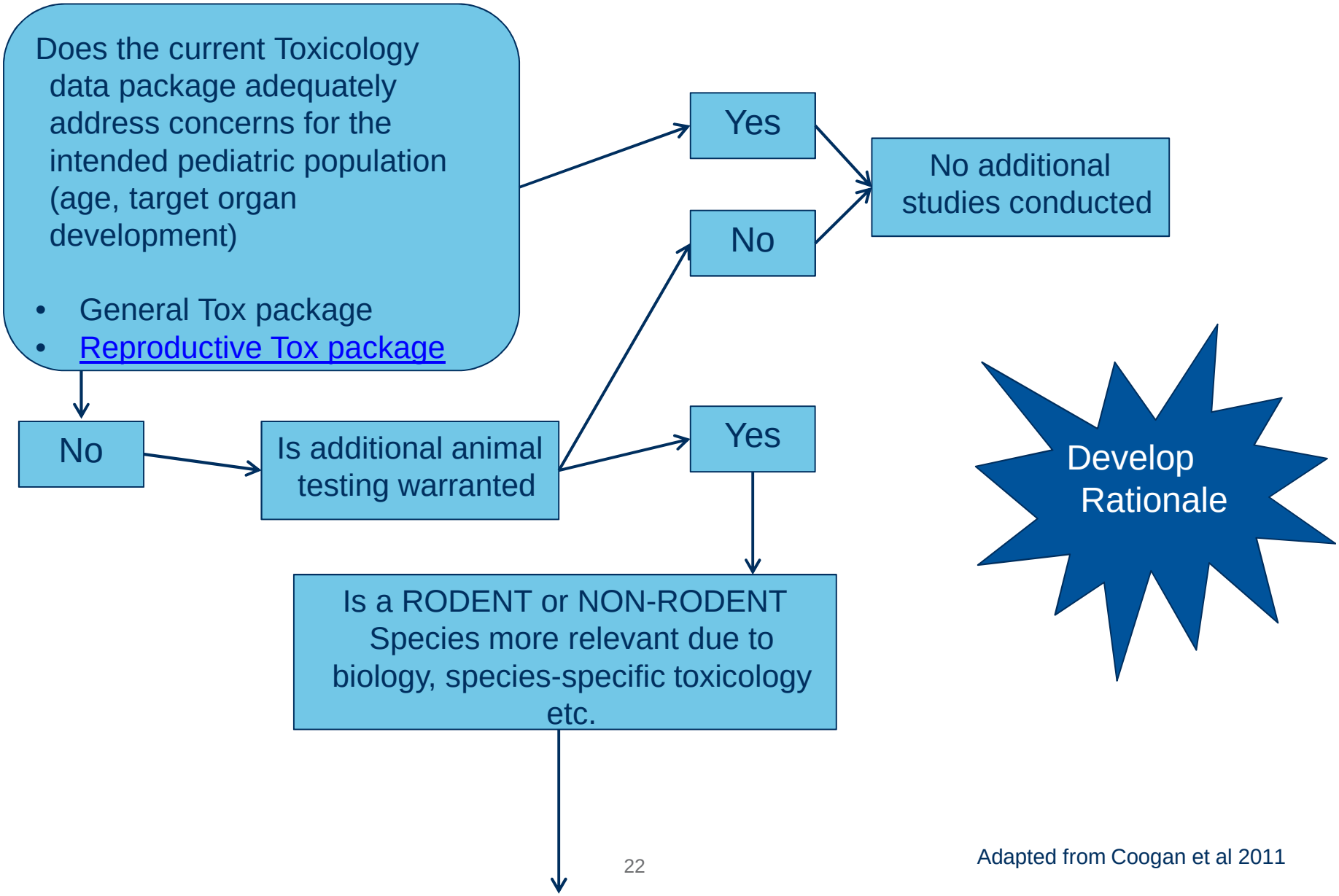
February 2006
Pharmacology and Toxicology

ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals

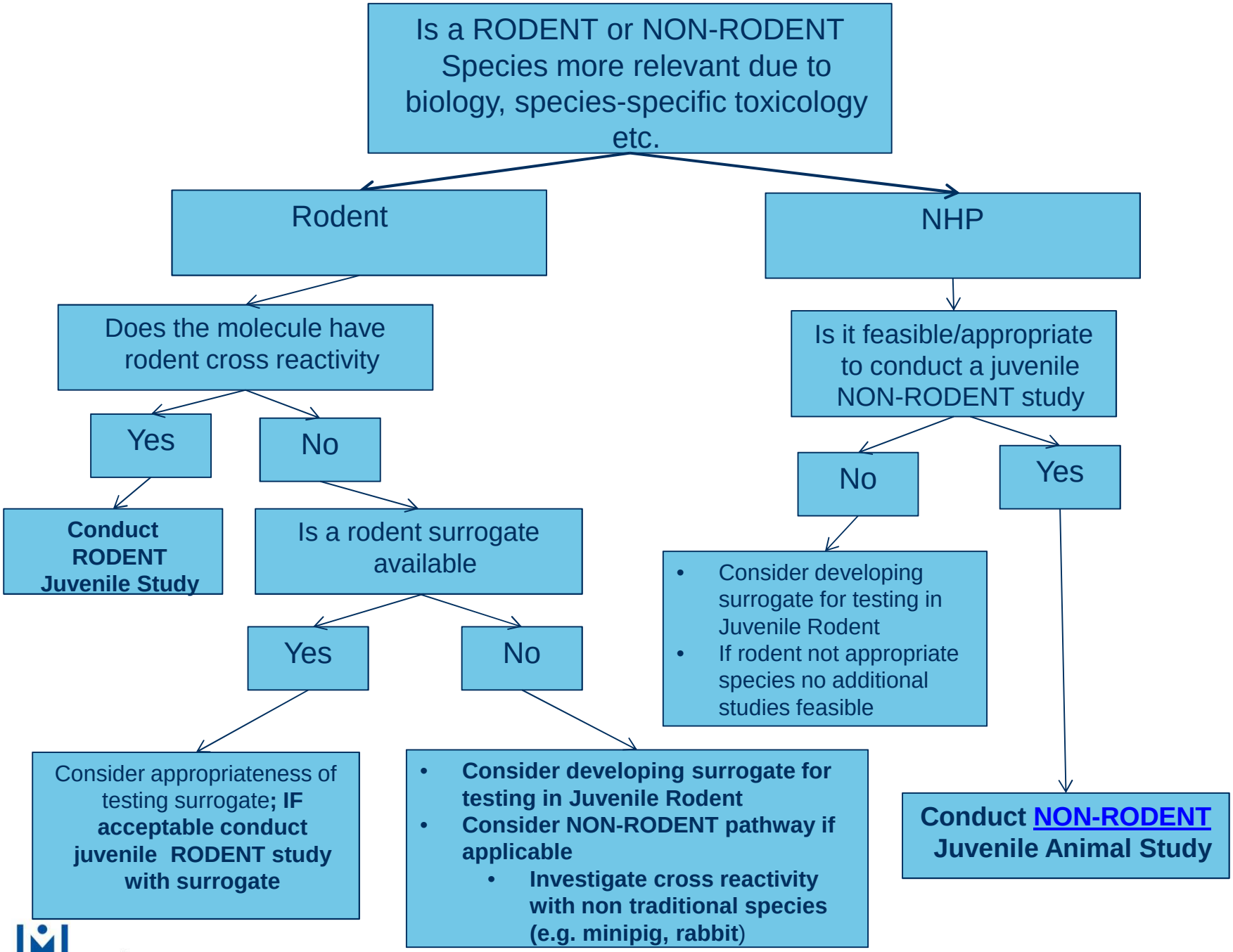
The appropriateness of juvenile animal toxicity studies should be considered only when previous animal data and human safety data are judged to be insufficient to support pediatric studies. One rodent species is generally considered adequate, although studies in non-rodent species can be appropriate when justified. If a juvenile animal study is considered important for conduct of a specific trial, it should be available prior to initiation of that pediatric clinical trial.

PRECLINICAL SAFETY EVALUATION OF BIOTECHNOLOGY-DERIVED PHARMACEUTICALS
S6(R1)

Strategy for assessing the preclinical safety of biopharmaceuticals in juvenile animals



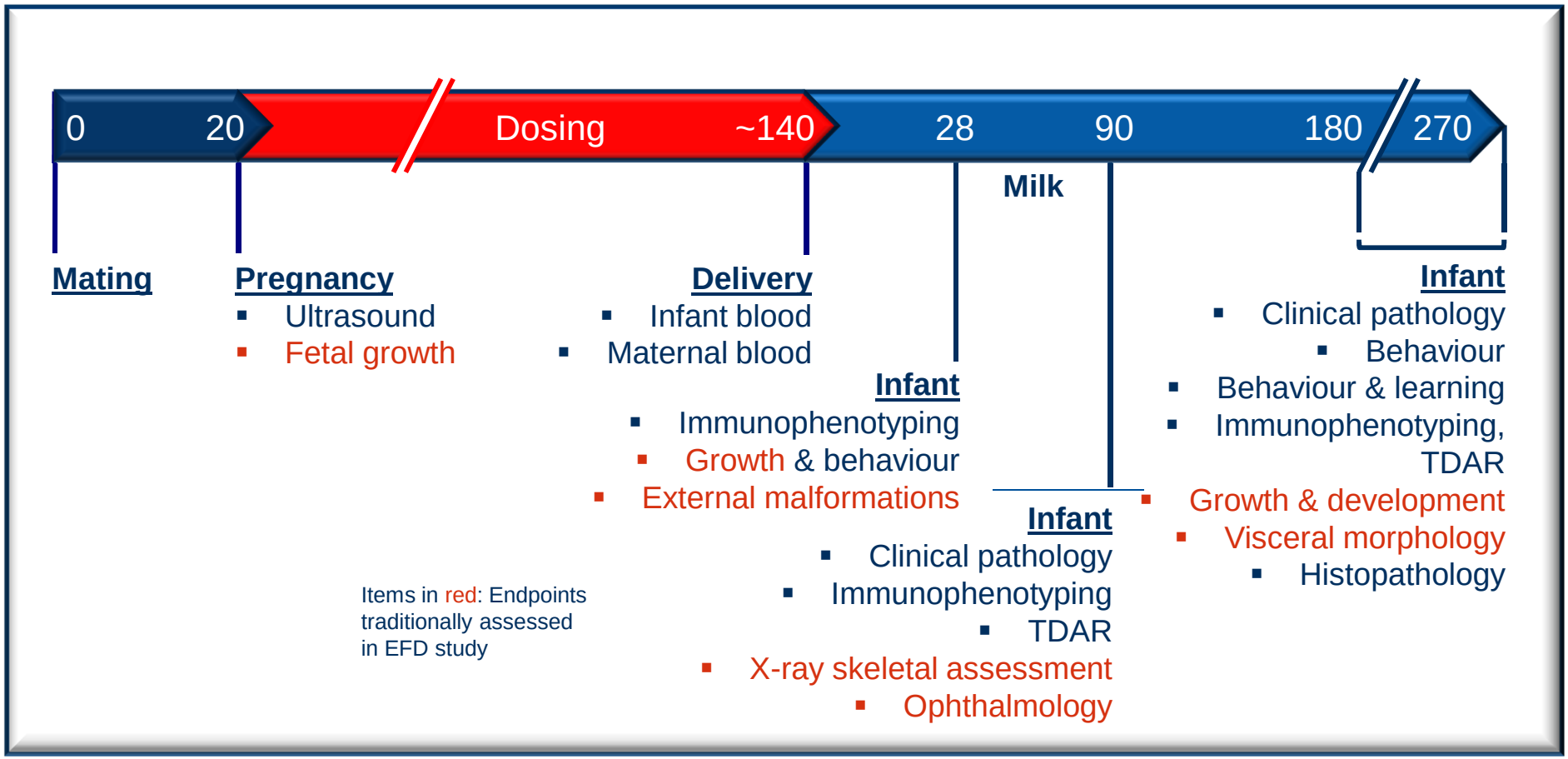
Adapted from Coogan et al 2011


Is a RODENT or NON-RODENT Species more relevant due to biology, species-specific toxicology etc.
Rodent
NHP
Does the molecule have rodent cross reactivity
Yes
No
Conduct RODENT Juvenile Study
Is a rodent surrogate available
Yes
No
Consider appropriateness of testing surrogate; IF acceptable conduct juvenile RODENT study with surrogate
• Consider developing surrogate for testing in Juvenile Rodent
• Consider NON-RODENT pathway if applicable
• Investigate cross reactivity with non traditional species (e.g. minipig, rabbit)
Is it feasible/appropriate to conduct a juvenile NON-RODENT study
No
Yes
• Consider developing surrogate for testing in Juvenile Rodent
• If rodent not appropriate species no additional studies feasible
Conduct NON-RODENT Juvenile Animal Study

MedImmune

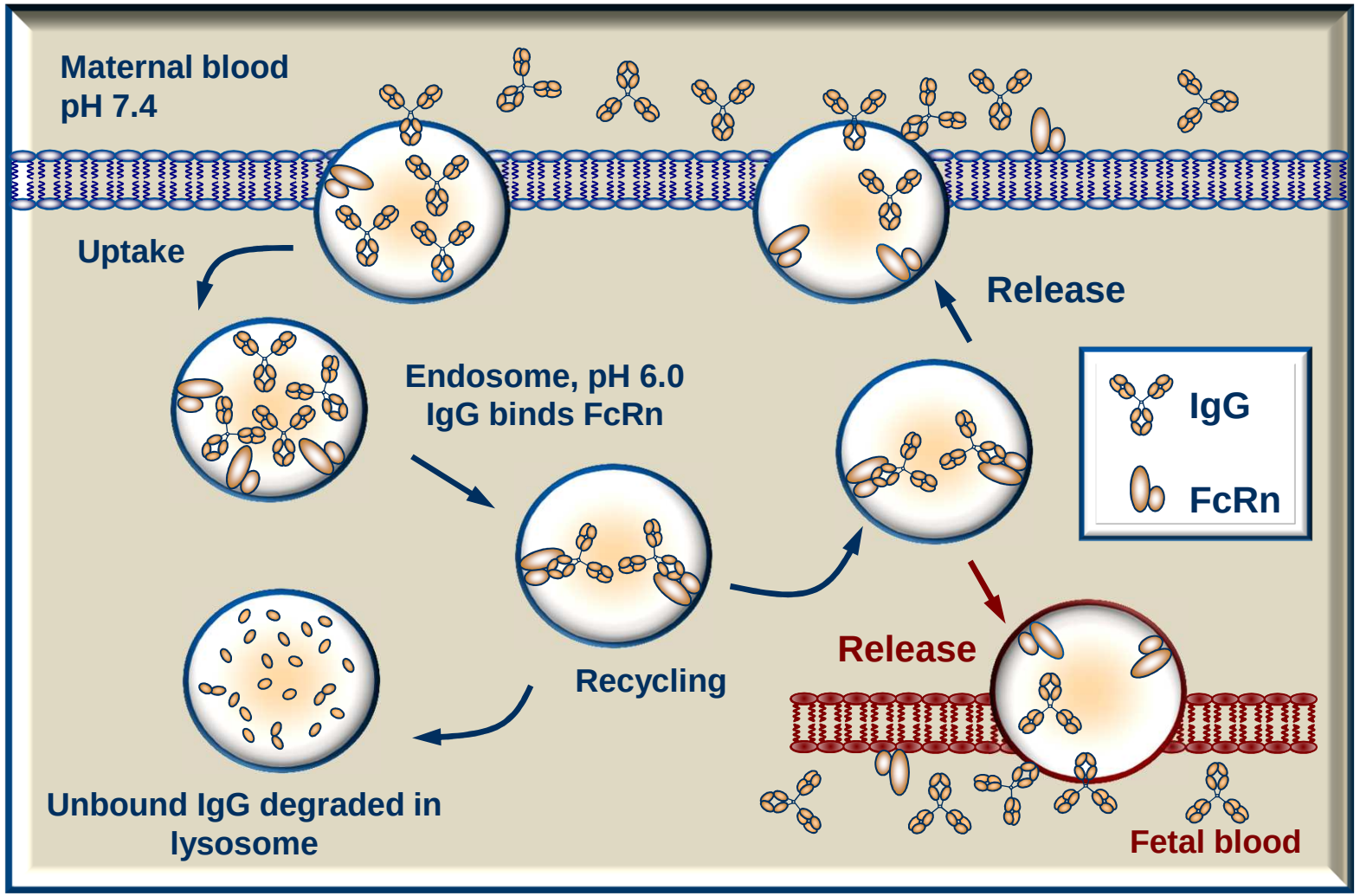
Enhanced PPND Study Design

Adapted from slides by Gerhard Weinbauer & Jane Stewart



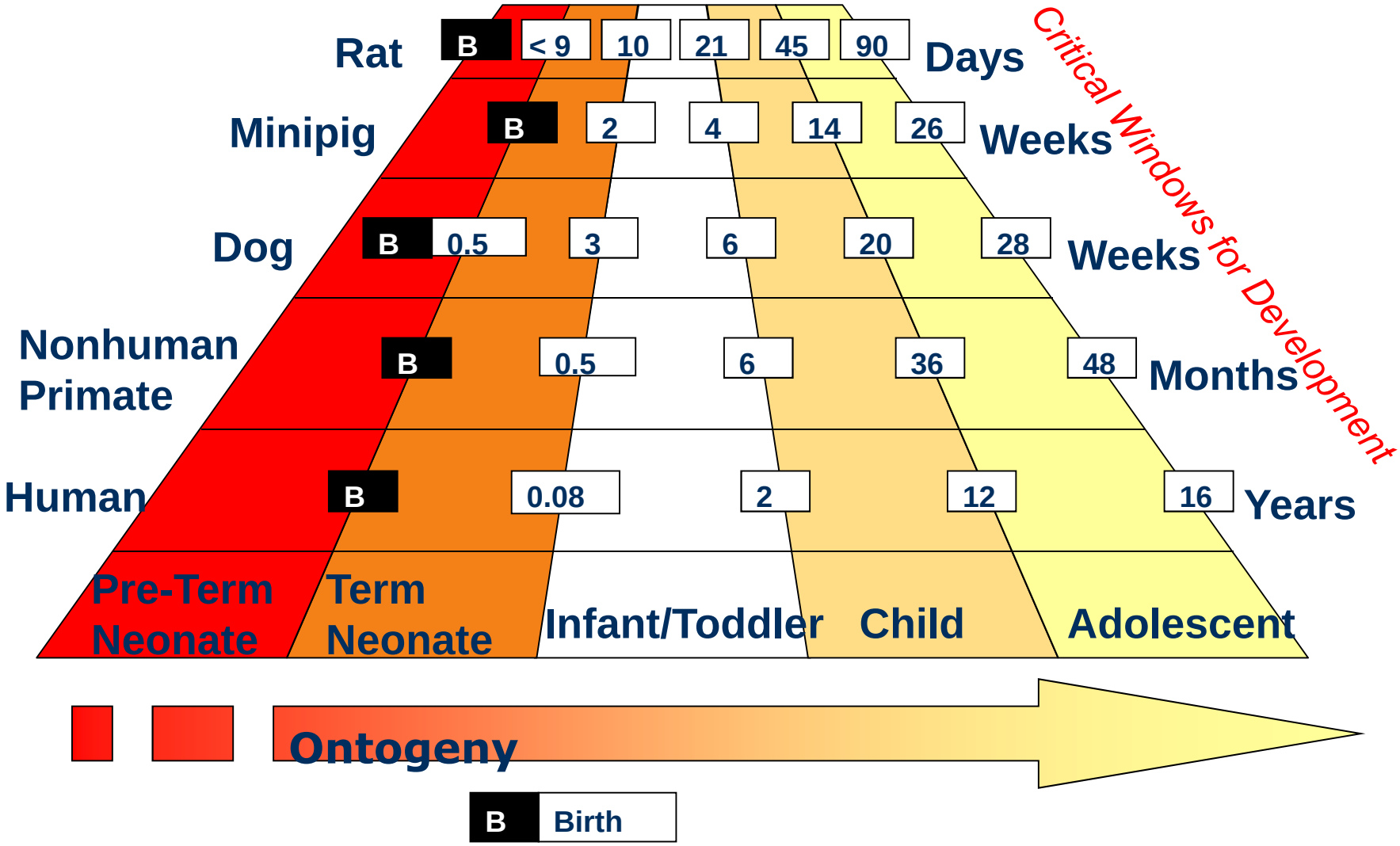
Postnatal duration & endpoints designed to address specific mAb concerns,
e.g. ontogeny of immune system, target organ histopath, duration of PD effect etc

Transport of Antibodies During Gestation: Role of the Neonatal Fc Receptor (FcRn)



Non Rodent Juvenile Toxicology Studies
Non Human Primate (NHP)

NHP : Comparative ages



Macaque/Human Age Equivalent

	Cynomolgus	Rhesus	Human
Newborn	24-hr postnatal	24-hr postnatal	At term
Neonate	0-4 months	0-1 months	0-1 months
Infant	Up to 8 months	1-12 months	1-24 months
Juvenile	Up to 36 months	12-24 months	*Not defined*
Adolescent	3-5 years	2-4 years	12-16/18 years
Adult/ Young Adult	>5 years	>4 years	>16/18-20 years

(Morford et al, 2011, Birth Defect Research Part-B 92:359)

NHP : Juvenile Toxicity Testing

- Study design developed case by case based on consideration of the properties of the test article and clinical plan
- **Practical** and **ethical** challenges exist
  - Animal Numbers : challenge to have number of relevant age (breeding on site)
  - CRO capabilities
- Lead times
- Cost

Blood Volumes : Everyone wants blood…..PK, PD, ADA, clinical pathology, TDAR……..

Blood collection volume and frequency

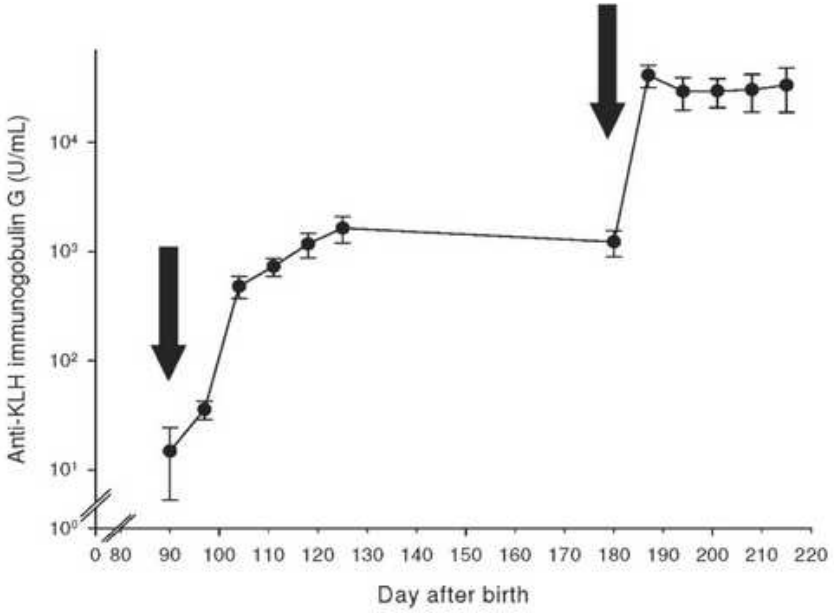
- Maximum blood collection volume usually within 1% of body weight in two weeks.

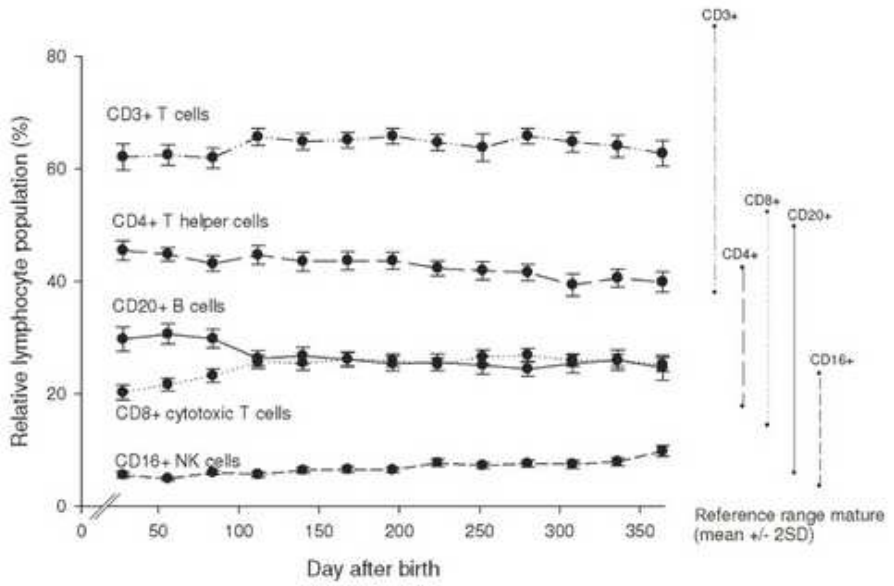
Age (Months)	Average Body Weight (g)	Maximum Blood Collection Volume in 2 Weeks (mL)
0 (one week)	350	~3
1	420	~4
3	700	~7
6	1100	~11
9	1400	~14
12	1650	~16

NHP : Juvenile Toxicity Testing : Model

- NHP can provide an effective model for Juvenile toxicity testing
- Similarities in late developing organ systems
  - Immune System, bone, nervous system

Source: Modified from Weinbauer et al.





Example Design for a 13 Week Toxicity Study in Juvenile Cynomologus Monkeys with Recovery

Animal Age	12–18 mo (most common)			
Dosing regimen	Daily, weekly, or as appropriate			
Routes of administration:	All standard routes possible (PO, IV, SC)			
Test system		Dose level	Number of animals in main study (recovery)	
	Group	(mg/kg)	Male	Female
	1	Control	3 (2)	3 (2)
	2	Low	3 (2)	3 (2)
	3	Mid	3 (2)	3 (2)
	4	High	3 (2)	3 (2)
Total population	$n = 40$ (24 main study and 16 recovery)			
Duration of pretreatment/dosing/recovery periods	1–4 wk/13 wk/4–13 wk			
Clinical signs	1–2 × daily, including 1 wk prestudy			
Body weight	Prestudy, weekly thereafter			
Food consumption	Daily, including 1 wk prestudy			
Clinical pathology parameters	Hematology, serum chemistry, coagulation, and/or urinalysis: prestudy and at end of dosing and recovery periods			
Special assessments (as applicable)	Toxicokinetics: after first and last dose and/or recovery (biologics) Ophthalmology: slit lamp biomicroscopy and indirect ophthalmoscopy Cardiovascular: heart rate, blood pressure, and/or ECGs. Immunology: flow cytometry, immunoglobulins, TDAR (e.g., KLH) assay, NK cell assay, cytokines, lymphocyte proliferation Skeletal growth evaluation: radiographic evaluation of long bone prestudy and at end of dosing and recovery periods. Can also conduct quantitative measures of bone density (DXA, pQCT) Neurobehavioral testing: if applicable (based on test article pharmacology)			
Terminal procedures	Complete necropsy of all animals, including gross pathology and organ weights Full tissue collection and histopathologic evaluation Immunohistochemistry possible			

Abbreviations: TDAR, T-cell-dependent antibody response; NK, natural killer cell; KLH, keyhole limpet hemocyanin; DXA, dual-energy X-ray absorptiometry; pQCT, peripheral quantitative computed tomography, PO = oral, IV = intravenous, SC = subcutaneous, ECG = electrocardiogram.

Regulatory Interactions : expect the unexpected *be prepared* for all outcomes/requests

- Feedback from a submission to PDCO
- Completed tox program including a NHP chronic study and a ePPND study with follow-up in offspring until ~6 months of age so that functional immune assessments could be performed (no adverse effects noted).
- In the Day 30/60 comments, PDCO had asked for the NCWG to comment - PDCO raised a concern to NCWG about the potential need for juvenile studies with this molecule especially to be done with focus on the immature immune system.
- The NCWG said the strategy was fine and no juvenile studies need be conducted (rationale in PIP why we considered a stand alone Juvenile study is not needed – waiver <5yr)
- PDCO disagreed with the NCWG opinion and have asked us to perform juvenile NHP study. The concern was they felt we did not have adequate exposure for the duration of the 6 month follow-up on infants in the PPND study. We've drafted our justification on why our position still remains against performing juvenile NHP studies for this molecule, but have not yet submitted to PDCO for comment/review (were a number of key clinical comments from PDCO to address as well).
- No US request for Juvenile Study

Conclusions
Juvenile toxicity studies with biopharmaceuticals : considerations and current practices

- Biopharmaceutical drug development differs from small molecule drug development with regard to specific challenges related to the type of molecule and how we approach preclinical safety assessment
- Study design case by case
- Regulatory interaction and agreement important

- With the increased interest in developing biopharmaceuticals for paediatric use comes the challenge of designing an appropriate strategy to asses the preclinical safety of biopharmaceuticals in juvenile animals – thus supporting safe testing in paediatric clinical trials