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Clinical trial and clinical pharmacology in neonates. Experience of Global Research in Paediatrics (GRIP) group

1st April 2016

I Reunion SERURNEO-SEN Cuidados Intensivos Neonatales

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GRiP

Global Research in Paediatrics

Some considerations to keep in mind

Paediatric drug development is an “infant science”

Regulatory policy must be balanced with science to successfully complete pediatric drug development studies

New tools, as M&S tools, are needed to optimally design complex trials and test assumptions avoiding large clinical trials

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State of the Art clinical trials in paediatrics

- FDA→ of 189 products studies under paediatric exclusivity (1998-2012) 78 did not get the paediatric labelling, i.e. **42% FAILED** [1]
- Main reasons for failure: dosing, differences in disease processes, trial design, placebo response.

How can we improve the success rate of paediatric (or more specifically neonatal) trials?

[1[Wharton GT, Murphy MD, Avant D et al. Impact of Pediatric Exclusivity on Drug Labeling and Demonstrations of Efficacy. *Pediatrics* 2014: **134**:e512–e518.

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Key considerations for neonatal CT

Patients

- Better identify similar populations (gestational age, confounding conditions)
- Identify biomarkers to define subpopulations (diagnostic, prognostic biomarkers)
- Effect of cofounding conditions and analyze the data base on subpopulations

Conditions

- Understanf the pathophysiology of unique conditions
- Need to differenciate from the adult conditions
- Diagnostic test with good sensitivity and specificity

Drug

- Differences in ADME processes and its implication of PK/PD studies
- Formulations

Endpoints

- Better definition of clinically relevant efficacy endpoints and the differences with the adult endpoints
- Safety endpoints
- Innovative study designs: CT simulations, adaptive designs

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM342994.pdf

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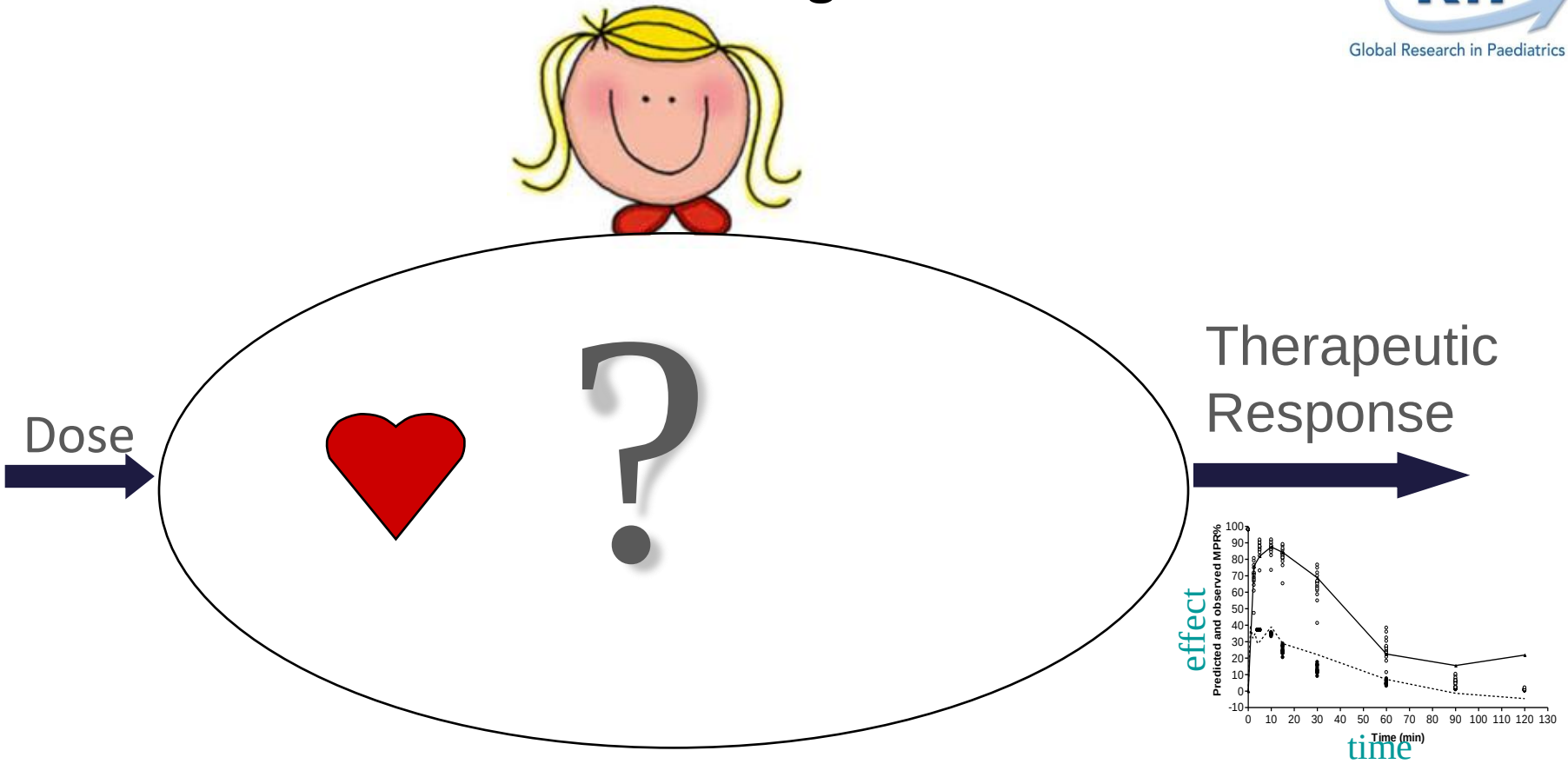
What comes after the Dose given to a creature?



- A lot can be learned or already known about how the drug passes through the body, the Pharmacokinetics
- Pharmacokinetics (PK) and Pharmacodynamics (PD): The drug – organism interaction
- Not much is usually known about the effect of the drug, Pharmacodynamics

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Differences between children and adults can be in PK (ADME) and/or PD

- **A**bsorption processes
  - Maturation of gastric properties (4-fold pH decrease from neonate to adult); efflux pumps; permeability (= Bioavailability)
- **D**istribution processes
  - Water/total volume ratios; Plasma protein binding; BBB more permeable in newborn
- **M**etabolism processes
  - Maturation of Hepatic and extra hepatic enzymes, flows
- **E**limination processes
  - 10-fold increase in GFR from birth to adult; Active processes

- **P**harmaco**D**ynamics
  - Changes in receptor expression; effect site access; pathway maturation

Conclusion = Toxicity risks due to PK/PD!

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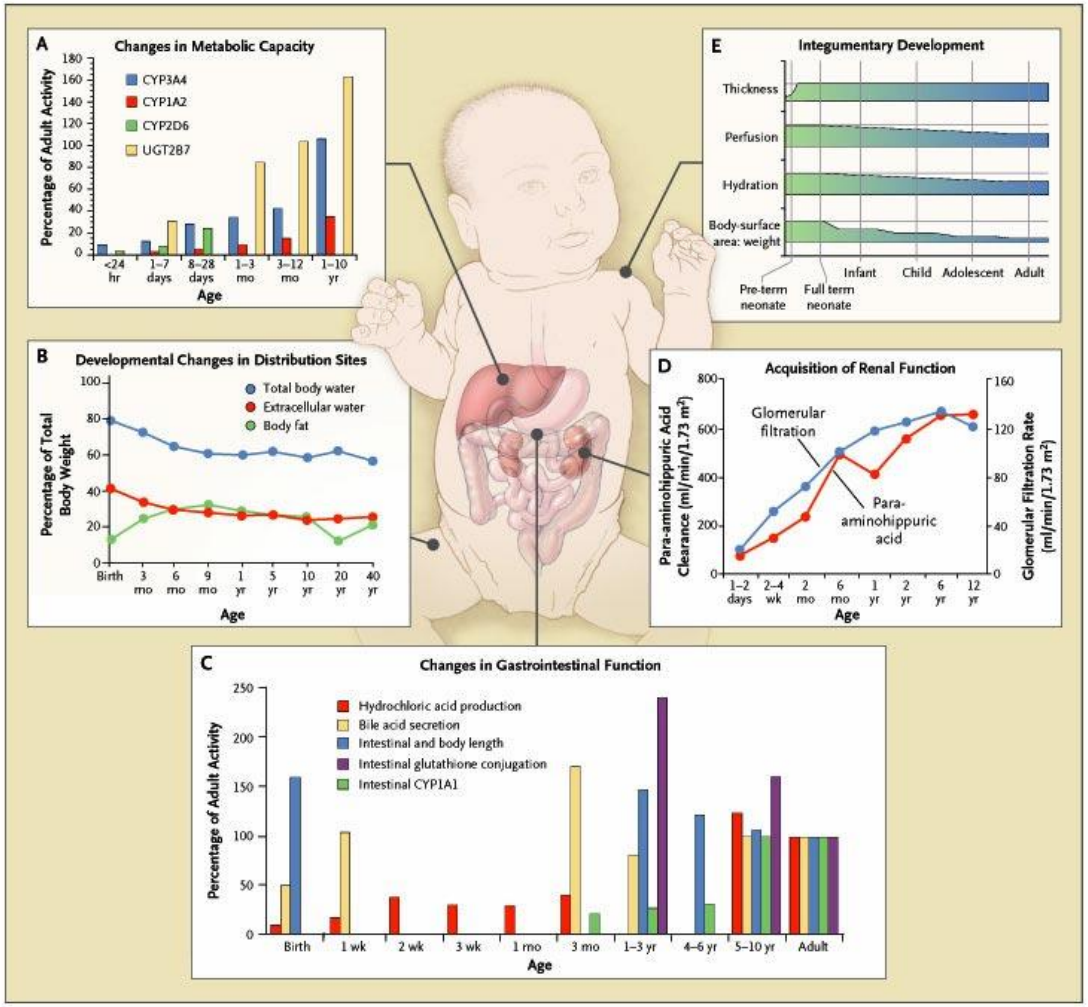
Including the influence of ontogeny in the PK processes



Developmental changes which occur during growth and may influence the disposition of drugs in the body (Kearns et al., 2003)**.**

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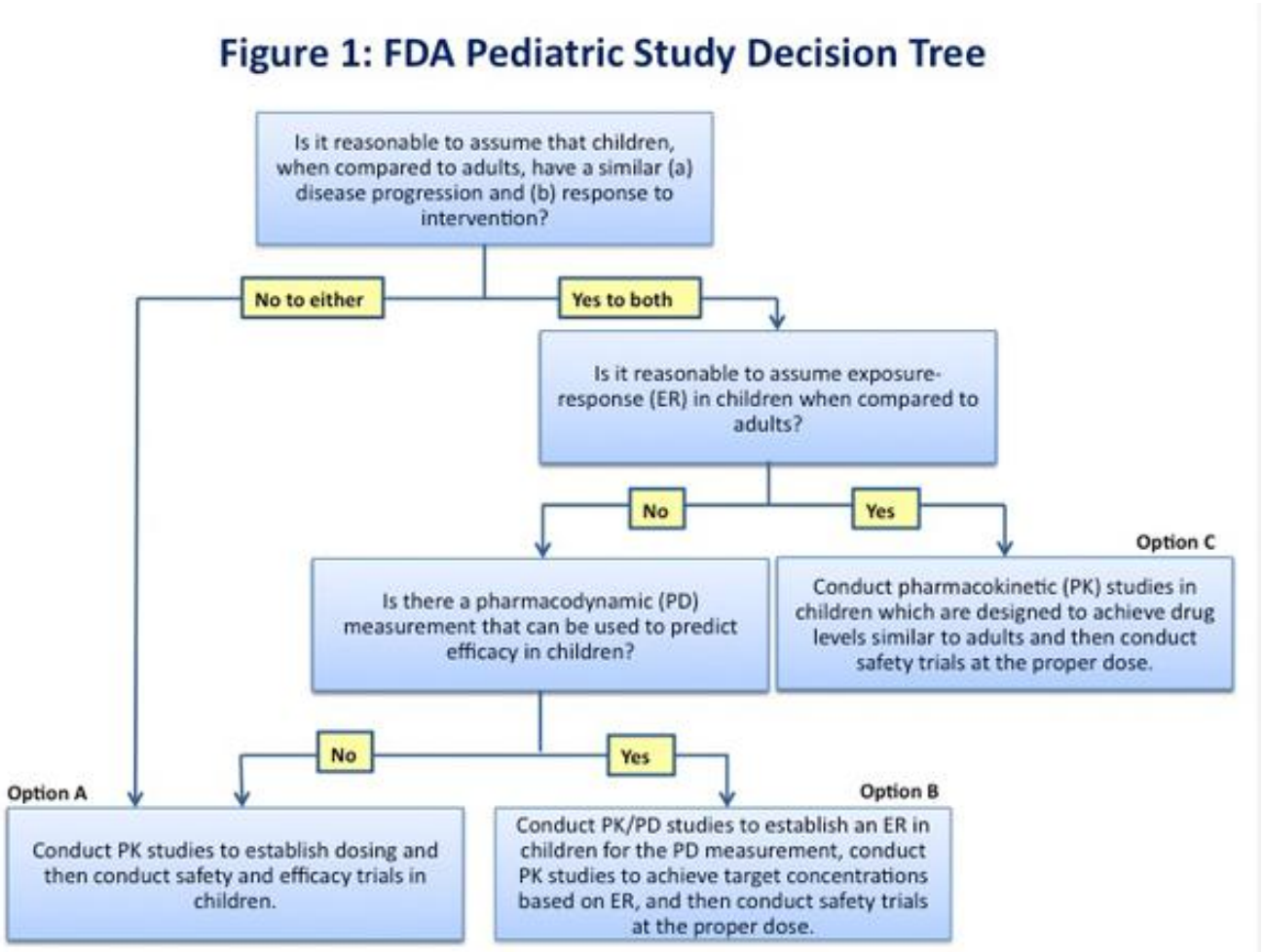
FDA assumptions-based framework



Starting point to determine the pediatric studies (excluding oncology studies) necessary for labeling based on the ability to extrapolate efficacy from adult or other data

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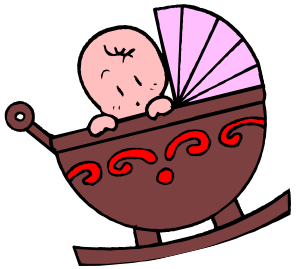
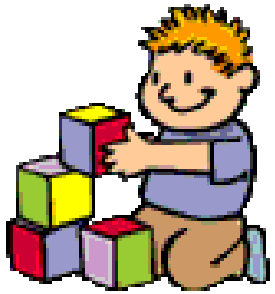
Age range definitions



Premature newborn < 37 weeks

Full term newborn ≥ 37 weeks

Term newborn infants
(0 - 27 days)



Infants and toddlers
(2 to 23 months)

Children
(2 - 11 years)

Adolescents
(12 to 16-18 years*)
*US 16 years/ EU 18 years

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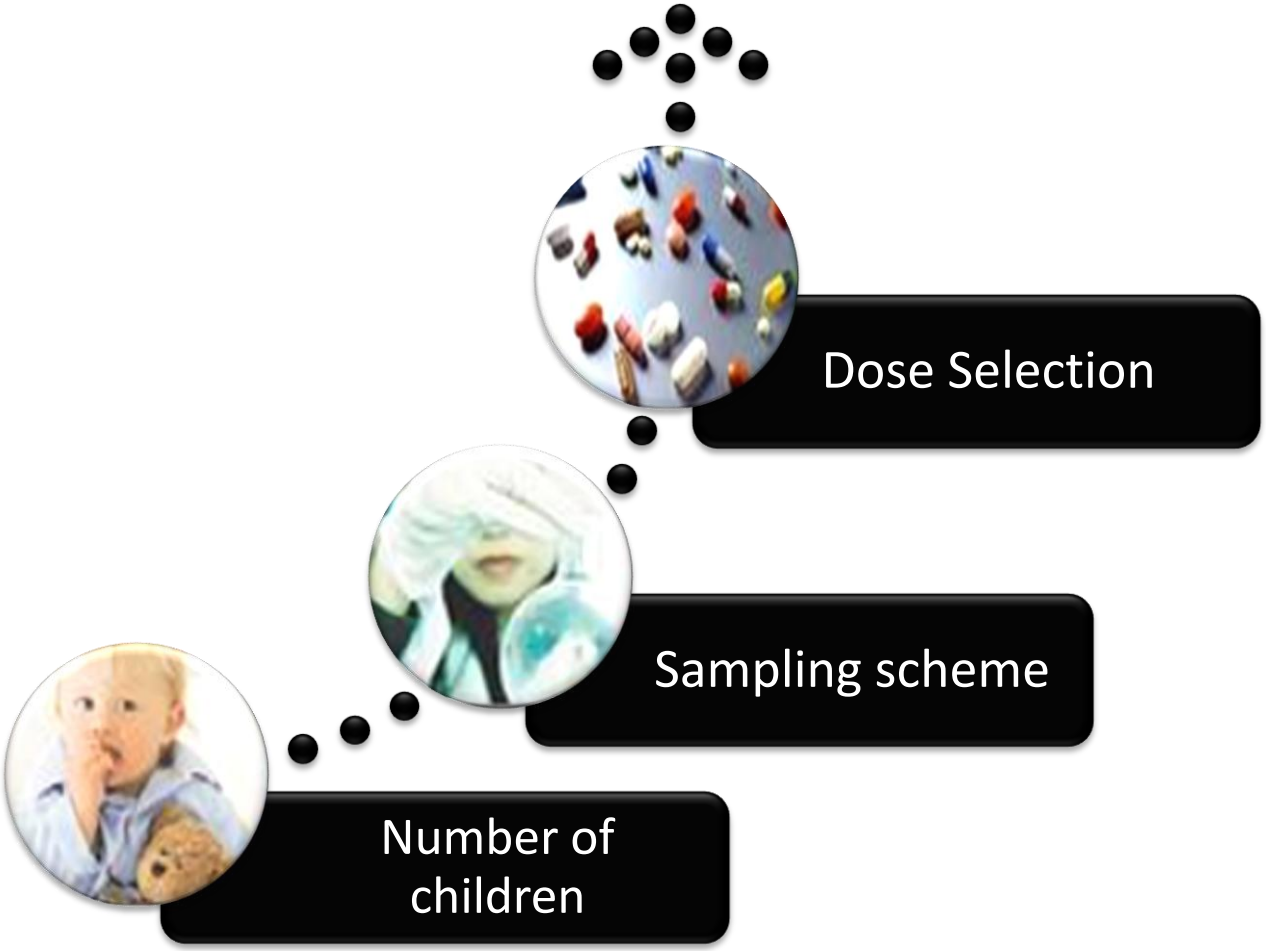
Clinical trial design in the pediatric population: key factors



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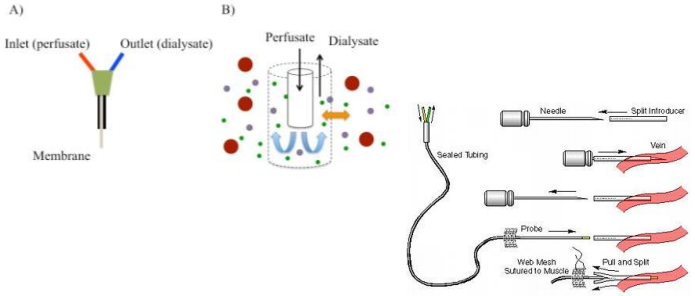
Strategies to optimize pediatric PK CT

Optimal laboratory bioanalytical techniques

Optimal pharmacostatistical methodologies

96 wells plate, SLE-LC-MS/MS, DBS, microdyalisis



- Design improvement: less blood, less sampling, less children
- Less ethical concerns: less blood, less sampling, less children
- Better acceptance from the point of view of parents

Mixed effect modeling strategies, MBDD

When and how? …
Case by case basis

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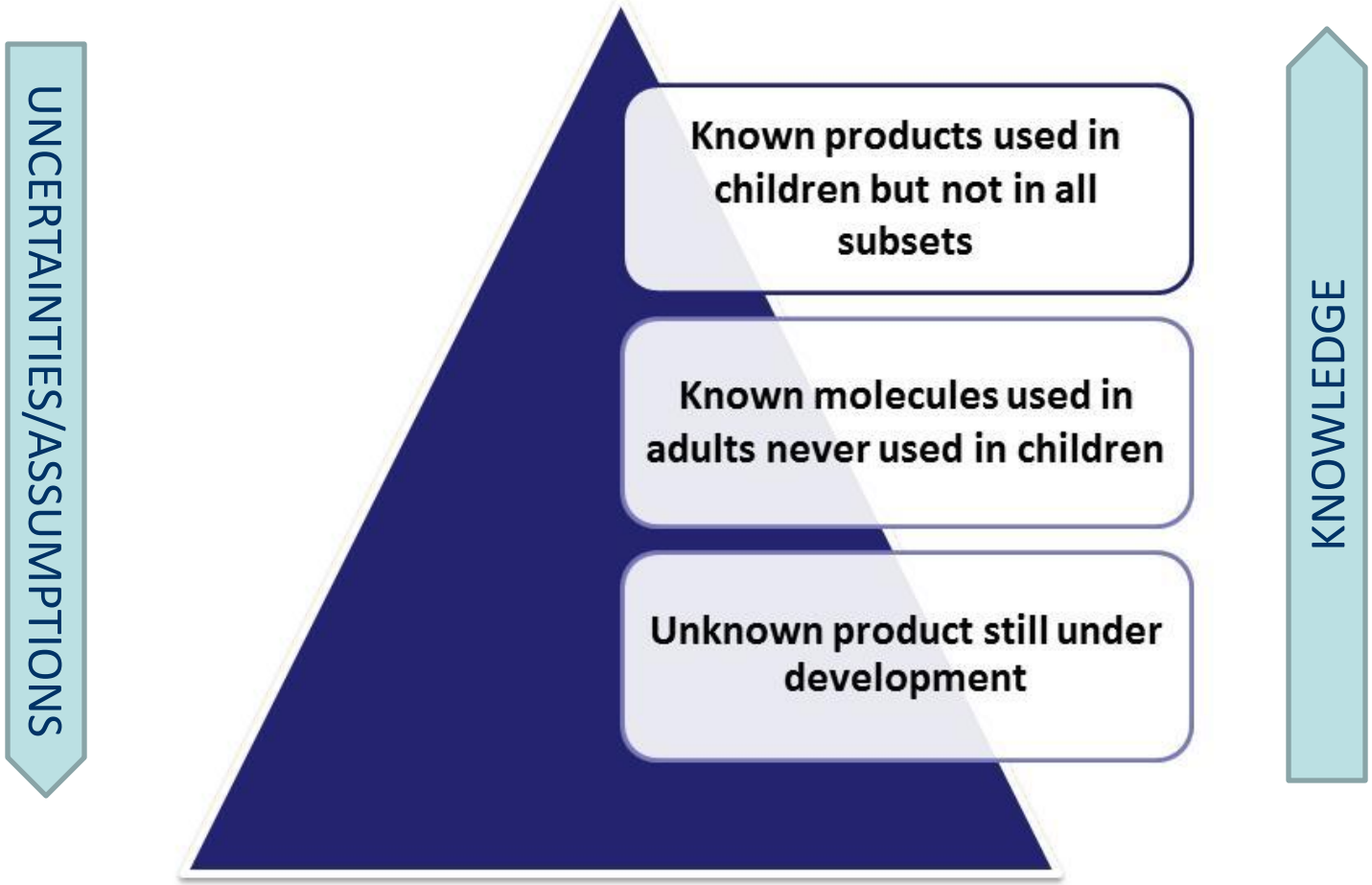
Application of different methods: *Case by Case basis*



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Quantitative extrapolation: What do we know?

Developmental changes

Clinical pharmacology of drug in adults:

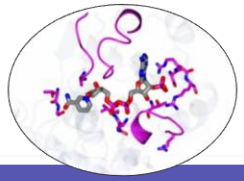
ADME

PD Properties

Safety and Tolerability

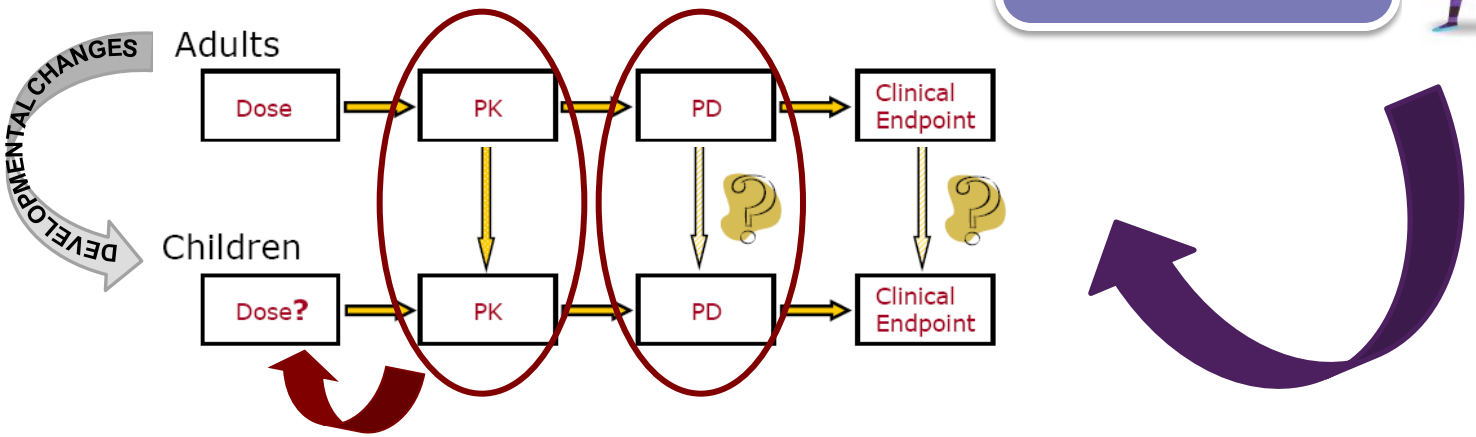
Knowledge integrated into

Predictive PK/PD Model



Physicochemical characteristics + ***in vitro*** data

Knowledge on the physiological systems involved



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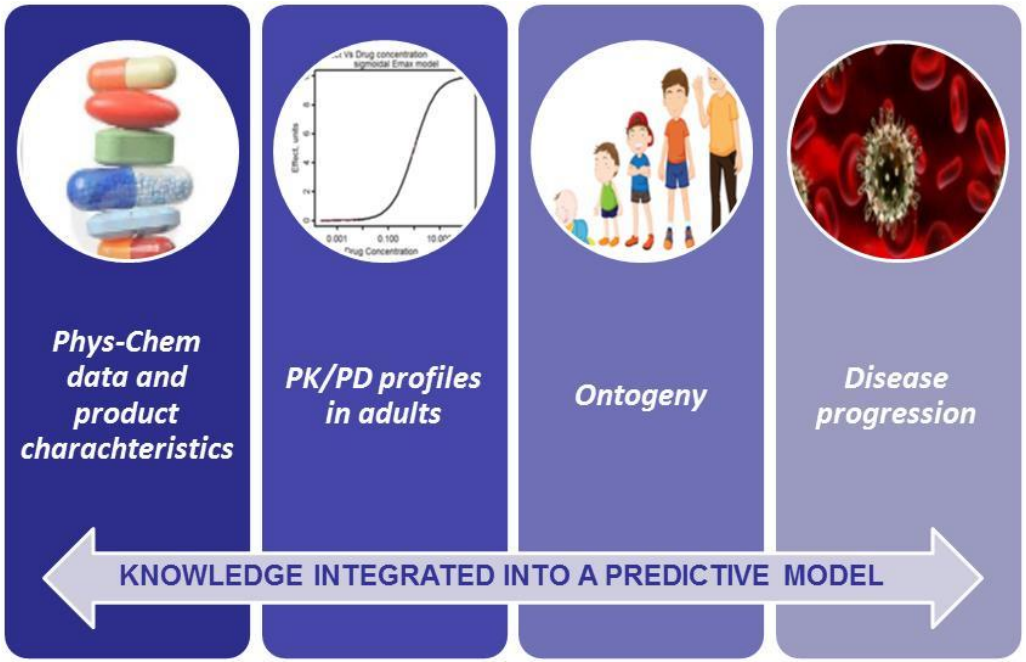

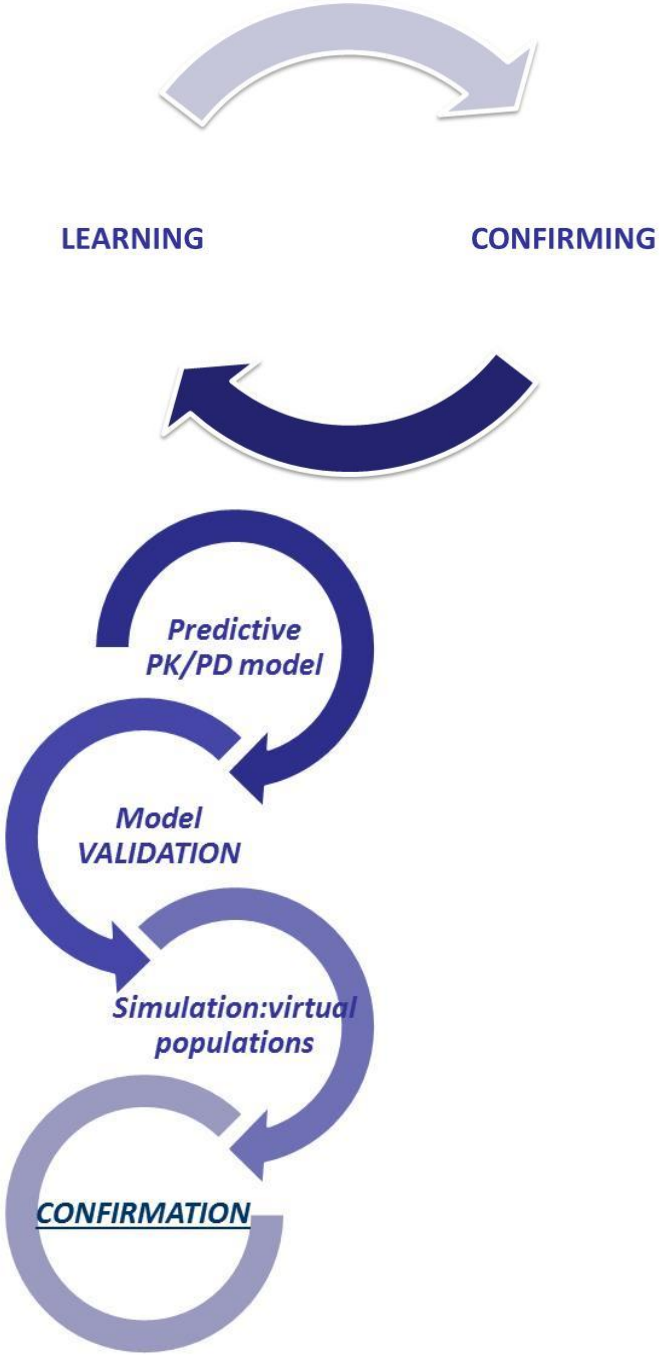

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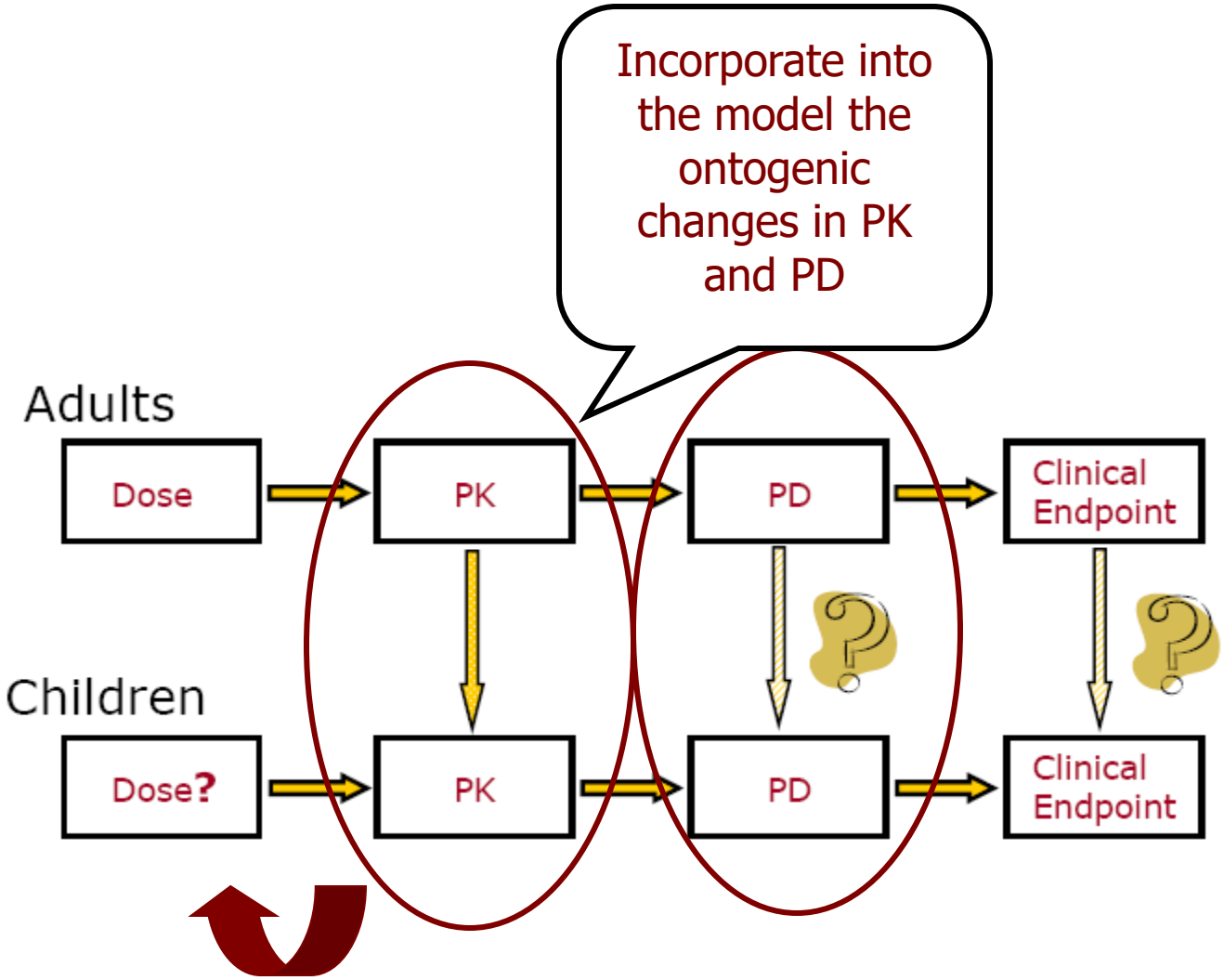
1st Step: development of a predictive model in pediatrics



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Prediction of elimination process

$CL_S = CL_H + CL_R$

CL_H_adult = 94 % ⇒ 0.583 L/min

CL_R_adult = 6 % ⇒ 0.037 L/min

$$CL_{H\_adult} = \frac{Q_H \times fu \times CL_{int}}{Q_H + fu \times CL_{int}}$$

1.72 L/min

0.160

Hayton

$$CL_{R\_neonate} = \frac{GFR_{neonate}}{GFR_{adult}} x \frac{fu_{neonate}}{fu_{adult}} \times CL_{R\_adult}$$

$$CL_{int\_neonate} = GLW \times F_{CYP} \times CL_{int\_adult}$$

130/1800 = 0.072

20 %

0.22 L/min

$$CL_{H\_neonate} = \frac{Q_H \times fu \times CL_{int}}{Q_H + fu \times CL_{int}}$$

$$fu_{neonate} = \frac{1}{1 + \frac{(1 - fu_{adult}) \times [P]_{neonate})}{[P]_{adult} \times fu_{adult}}}$$

AGA_{adult}=0.77g/L

0.160

$$AGA(g/L) = \frac{0.887 \times edad^{0.38}}{0.89^{0.38} + edad^{0.38}}$$

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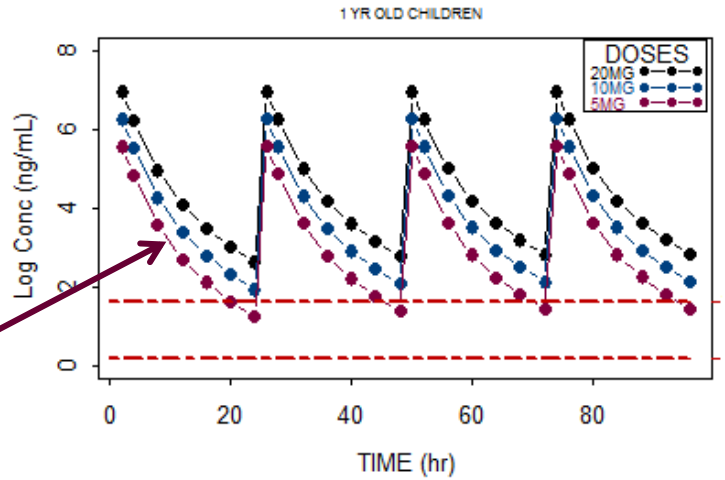
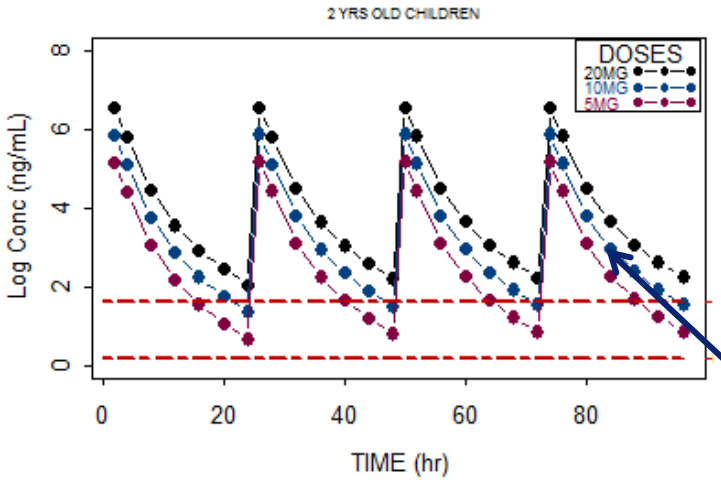
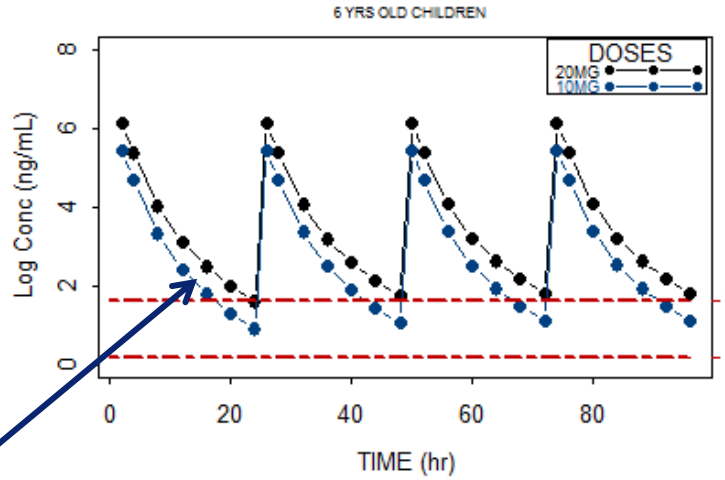
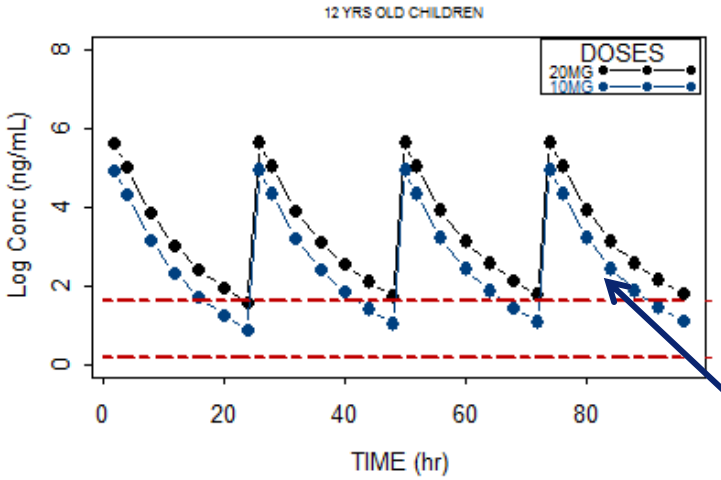
2nd step: dose selection in children using M&S techniques









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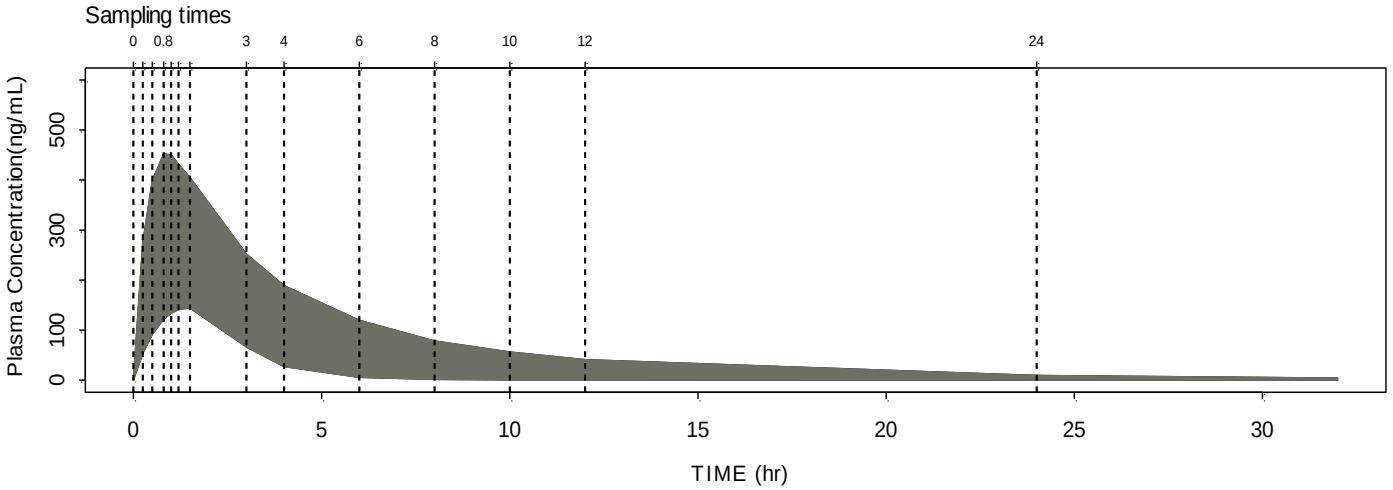
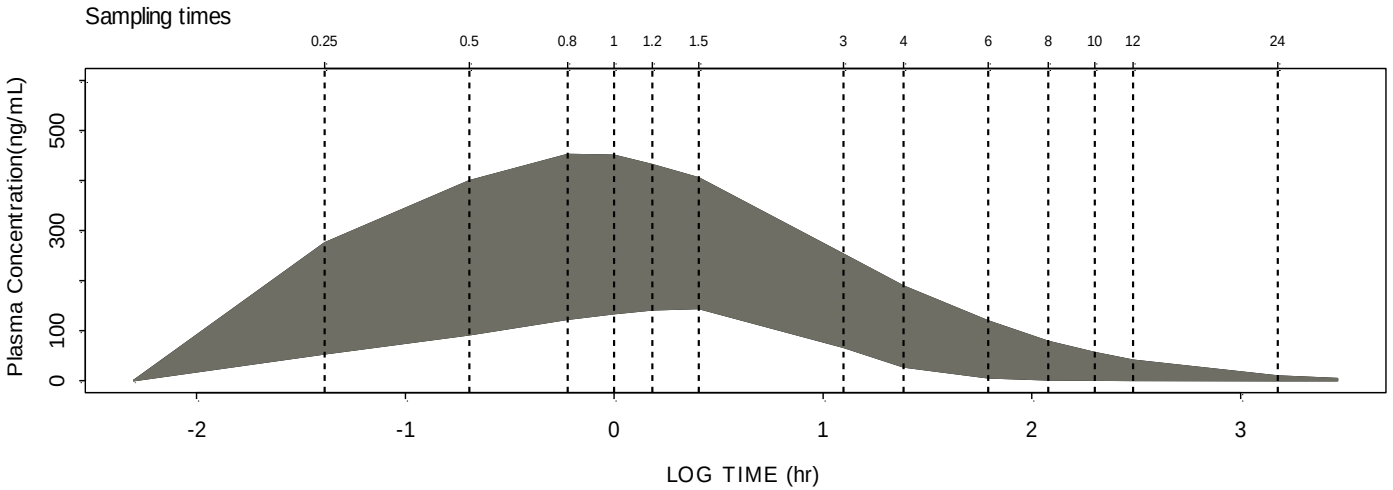
3rd step is selection of samples to adequately describe the PK or PK/PD profile in each age subset





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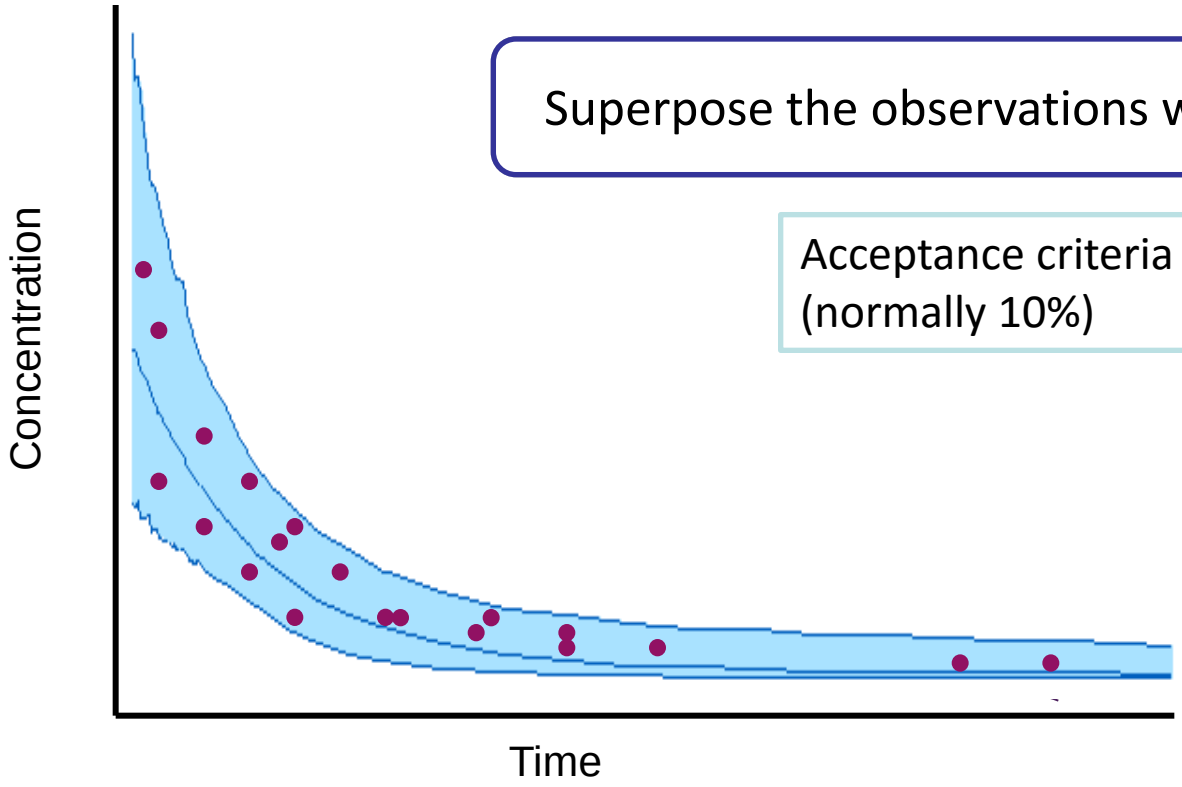
Validation of predictive capacity of the model with few children for older ages

37 OBS., 7 CHILDREN (10 mg/day)

Predictive check (VPC, PC-VPC, PPC)



Superpose the observations within the simulation

Acceptance criteria 30%
(normally 10%)

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Learn & Confirm: Adaptive designs

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Innovative M&S tools

- Strengths
  - Use limited PK data to optimize doses to be tested
  - Better understanding of the mechanisms of disease to predict efficacy, safety and off-target effects
  - More precise understanding of neonatal drug ADME/PD processes
- Challenges
  - Need more basic science information for neonatal specific disease models
  - Need more information on the ontogeny of enzyme systems to improve

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Q&A

Thank you for your attention!!

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