The importance of D-E-R characterisation in dose selection, labelling and B/R

- children

EMA EFPIA workshop on the importance of dose finding and dose selection for the successful development, licensing and lifecycle management of medicinal products

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Disclaimer

The opinions expressed during this presentation are those of the speakers, and not necessarily those of the EMA or one of its committees or working parties.

Paediatric developments

Dose selection is instrumental in paediatric developments

Huge diversity in the paediatric population: understanding appropriate scaling methods is crucial

Age range – premature neonates to 17 years

- different needs with regard to formulations
- differences in opportunities for PK/PD sampling
- differences in availability for inclusion in studies
- differences in size
- differences in status of maturation
- differences in relevance of clinical efficacy and safety endpoints

Need for a general strategy

Presently huge variability in strategies taken

A general outline of a strategy would be useful

- to ensure use of all relevant available information
- to ensure use of appropriate methodology
- to compare PK scaling across similar compounds and PD outcomes in similar disease areas

Proposed general strategy for paediatric dose finding and selection

Collect and systemize prior information

- **Collect and systemize drug and system data**
- *In vitro* drug data
- Non clinical drug data
- Adult drug data
- Paediatric drug data
- Adult and paediatric drug data on similar (model) substances, indications etc
- Adult and paediatric system data (such as relevant physiological, pathophysiological and PK and PD ontogeny data)

Define D-E-R in animals, adults, children

- **Define D-E-R and estimate relevant parameters and variability based on available data**
- PK parameters (F/ka, CL and V) and variability
- PD parameters and variability
- Efficacy and safety parameters and variability
- Establish covariate relationships
- Qualify the models for the existing data at the key interim and final stages

Potential methods
- Population PK/PD/response /safety models
- PBPK/PBPD
- system pharmacology models
- Bayesian methods

Predictions for the selected paediatric age subsets

- **Scale available predictions to the relevant paediatric population**
- Address major assumptions and potential impact of violating assumptions
- Uncertainty quantification

such as sensitivity analysis of the important/main parameters (worst/best case scenarios)

- Evaluate if there are assumptions that mandate a conservative approach (titration from lower doses etc) or if there are opportunities for interpolation or partial extrapolation

Potential methods
- Allometric scaling
- Organ function
- Maturation function
- Co-variate structure

Study design optimization

- **Determine type of study(ies) needed**
- separate PK study, separate PK/PD study, microdosing study, confirmation of PK/PD within a E&S study in an adaptive manner etc
- Determine the need for several doses in order to further inform on the D-E-R relationship also in paediatric patients
- Optimization of number of patients and sampling scheme for the PK and PD parameters

Potential methods
- Clinical trial simulations etc.

Learn & confirm paradigm - updating and refining the models with new information

Scaling of D-E to children

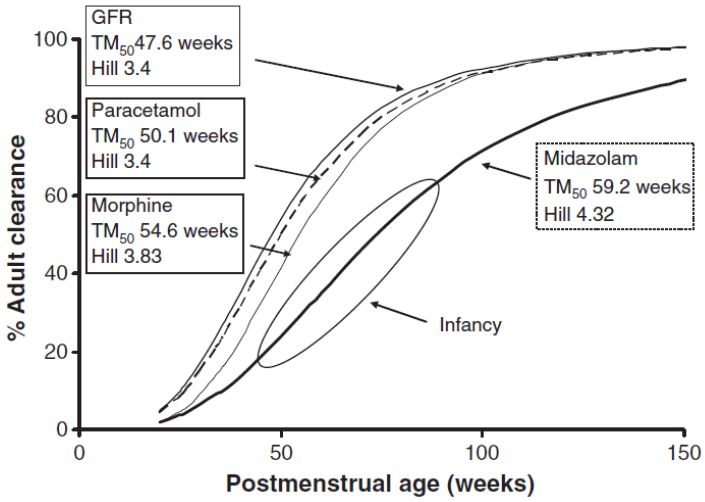
The standard methods to account for developmental changes in PK

- **Size**
  - Weight
  - Allometric scaling
- **Maturation**
  - Organ function
  - Maturation functions
- **Co-variates**
  - Disease
  - Co-medication (DDIs)
  - Nutrition
  - Formulation
  - Pharmacogenetics
  - Ethnicity
  - …

All available information should be taken into consideration in an explicit manner.

Scaling of D-E to children

The standard methods to account for developmental changes in PK



Standardised parameterisation ?

Size
- Weight
- Allometric scaling

Maturation
- Organ function
- Maturation functions

Co-variates
- Disease
- Co-medication (DDIs)
- Nutrition
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- Pharmacogenetics
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- …

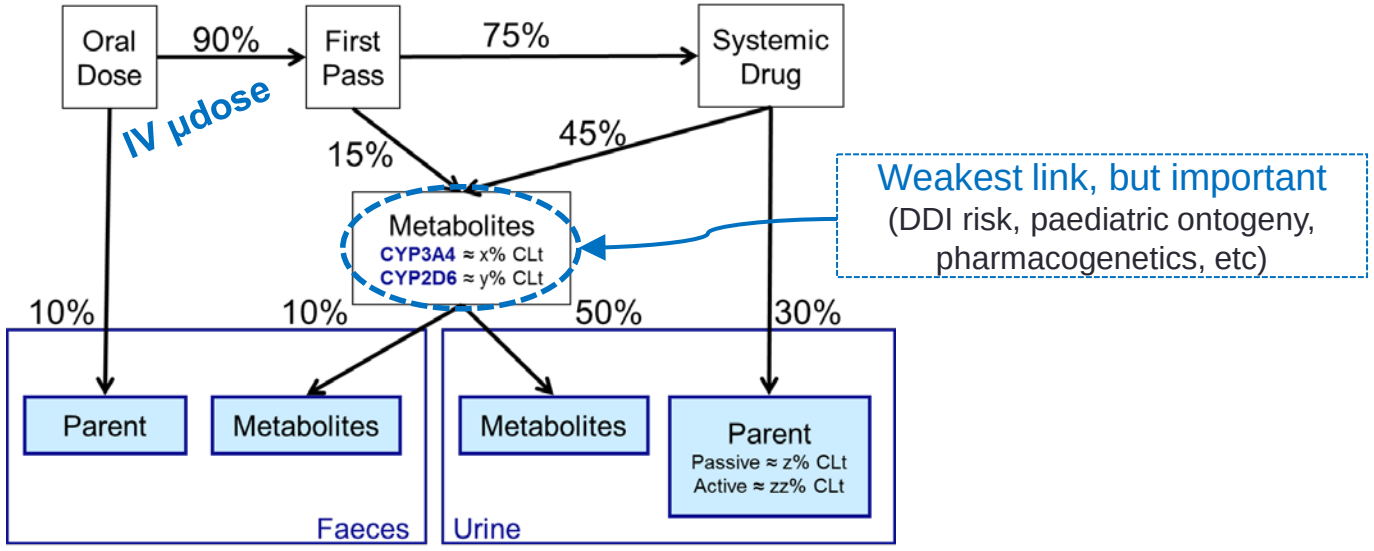
All available information should be taken into consideration in an explicit manner.

Anderson and Larsson, Paediatr Anaesth. 2011 Mar;21(3):302-8

Prerequisite for extrapolation of PK from adults to children

Integrated, quantitative understanding of contribution of pathways to drug ADME

Quantitative Mass Balance Diagram



MISG New Technologies Forum on Physiologically-based Pharmacokinetic (PBPK) Modelling and Simulation, June 2013
http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con457615.pdf

Scaling of R to children

- Often dose selection based only on D-E relationship
  - goal is similar drug exposure across the whole paediatric population
  - can lead to failure of clinical paediatric trials if the assumption of no maturation or population effect on the PD of the drug is not valid - in all or in specific paediatric subpopulations.
- PD modelling often neglected: little knowledge at present

System data

- Knowledge of developmental pharmacology is indispensable to justify the selection of first dose in children.

- knowledge of the D-E-R in adults
- linked with an early stage plan for the paediatric development

  ⇨ would make it possible to describe/collect required system data to support assumptions prior to initiating the paediatric development

- in the long run such an approach would influence and potentially decrease the burden of studies required for the paediatric developments…

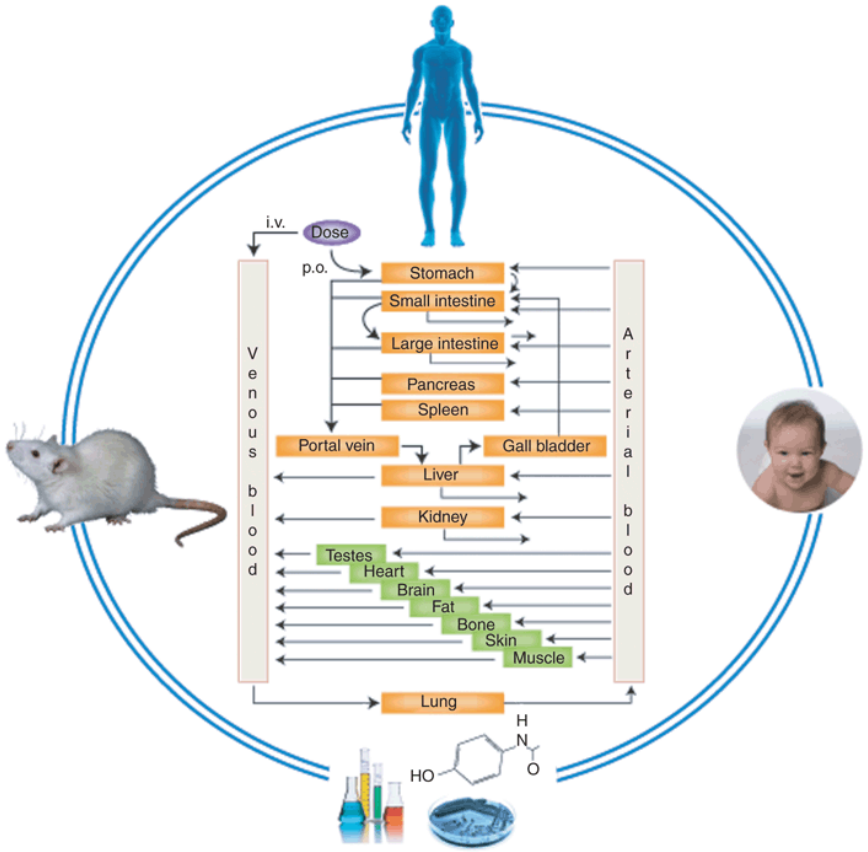


Figure from Barret et al, 2012 Clinical Pharmacology & Therapeutics **92**, 40-49

System data

- Knowledge of developmental pharmacology is indispensable to justify the selection of first dose in children.

System data are needed to characterize the effects of growth and maturation, such as

- ontogeny
- physiology
- pathophysiology

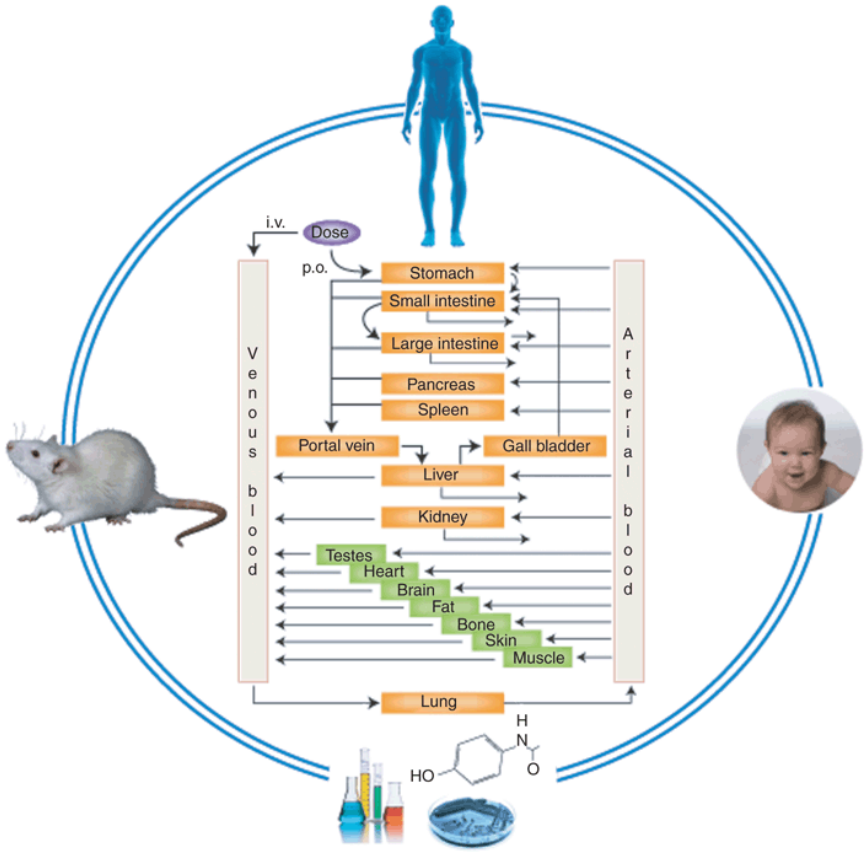


Figure from Barret et al, 2012 Clinical Pharmacology & Therapeutics **92**, 40-49

Learn from experience

How to ensure this?

- learn and confirm; always updating models
- share models and outcomes
  - publish methods, system data and outcome of M&S approaches
  - qualification procedures for relevant methodologies
- potential for regulatory databases on system data and outcome of different strategies
  - to evaluate how well the predictions turn out in order to learn for next experiments across companies and therapeutic areas
- harmonisation
  - methodology
  - regulatory requirements

Questions ?

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