Pharmacotherapy in children – small populations of human subjects who are not just small adults

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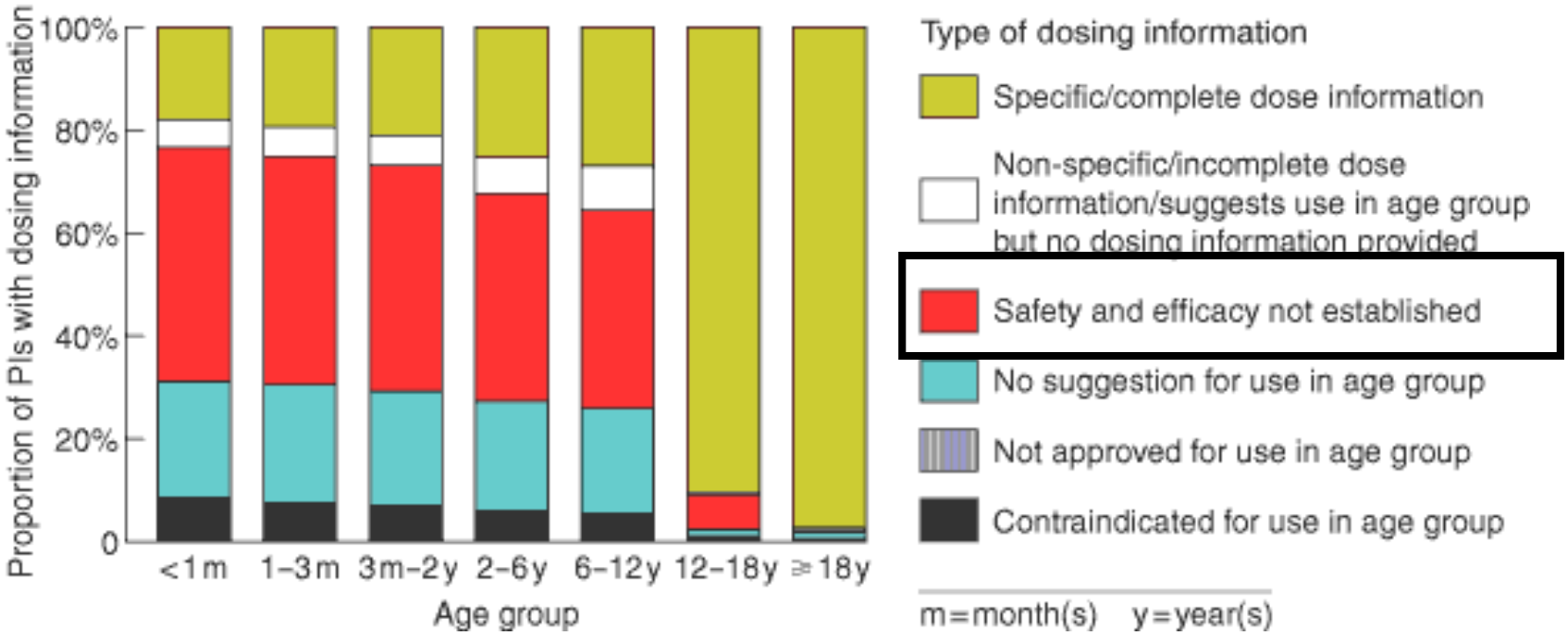
Children?


Proof of Age Card
ONEID4U
Name
Paula Jenkins
DoB
16 July 1999
PASS
4563 2445 9843 2303
16/17

'…no *adequate scientific basis* info for 80% of prescription medicines.'



Tan et al. MJA 2003

Brief history of drugs in children

- Disasters:
  - 1937 Sulphanylamide
  - 1956 Sulphisoxazole
  - 1959 Chloramphenicol
  - 1982 Benzyl alcohol
- Legislation to stimulate drug research in children
  - 1997 FDA Modernization Act
  - 2002 Best Pharmaceuticals for Children Act
  - 2007 European Paediatric Regulation

Drug and human body (1)

- ‘drug’: active ingredient + excipient
- Route of administration:
  - Oral: capsule, tablet, fluid, …
    - sublingual
  - Intravenous
  - Rectal
  - Intramuscular
  - …..

Drug and human body (2)

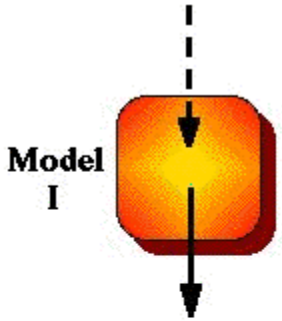
- Absorption
- Distribution
- Metabolism
- Excretion

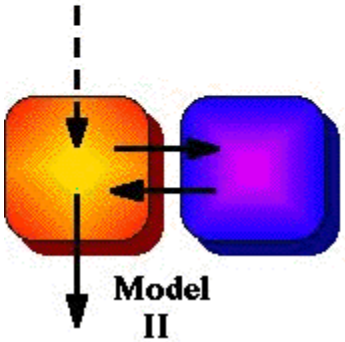
} Pharmacokinetics, PK

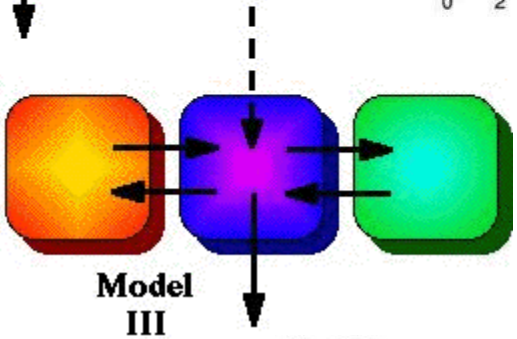
- Relation between concentration and effect:

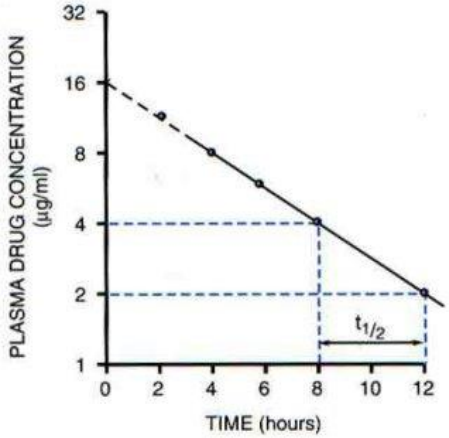
Pharmacodynamics, PD

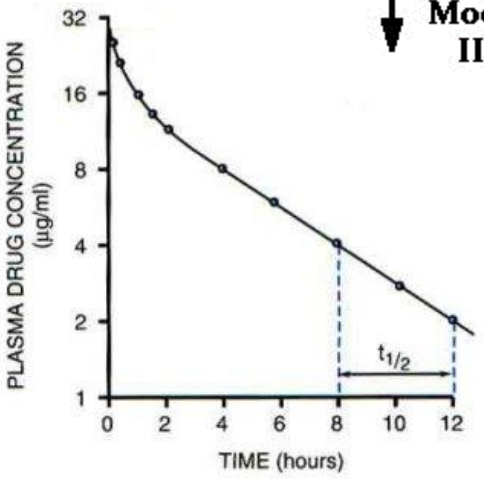
PK models


Model
I


Model
II


Model
III


PLASMA DRUG CONCENTRATION
(µg/ml)
32
16
8
4
2
1
0
2
4
6
8
10
12
$t_{1/2}$
TIME (hours)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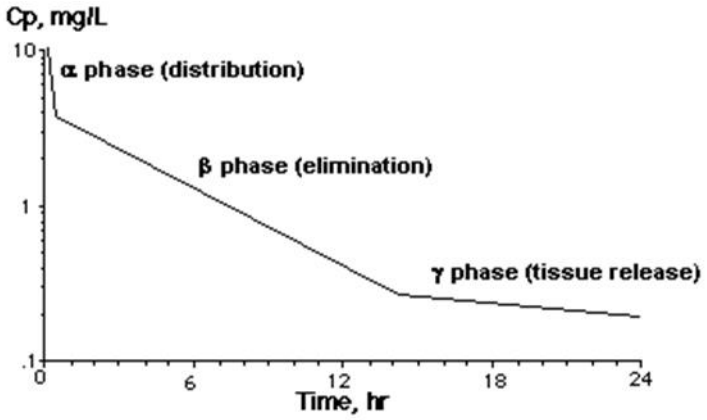
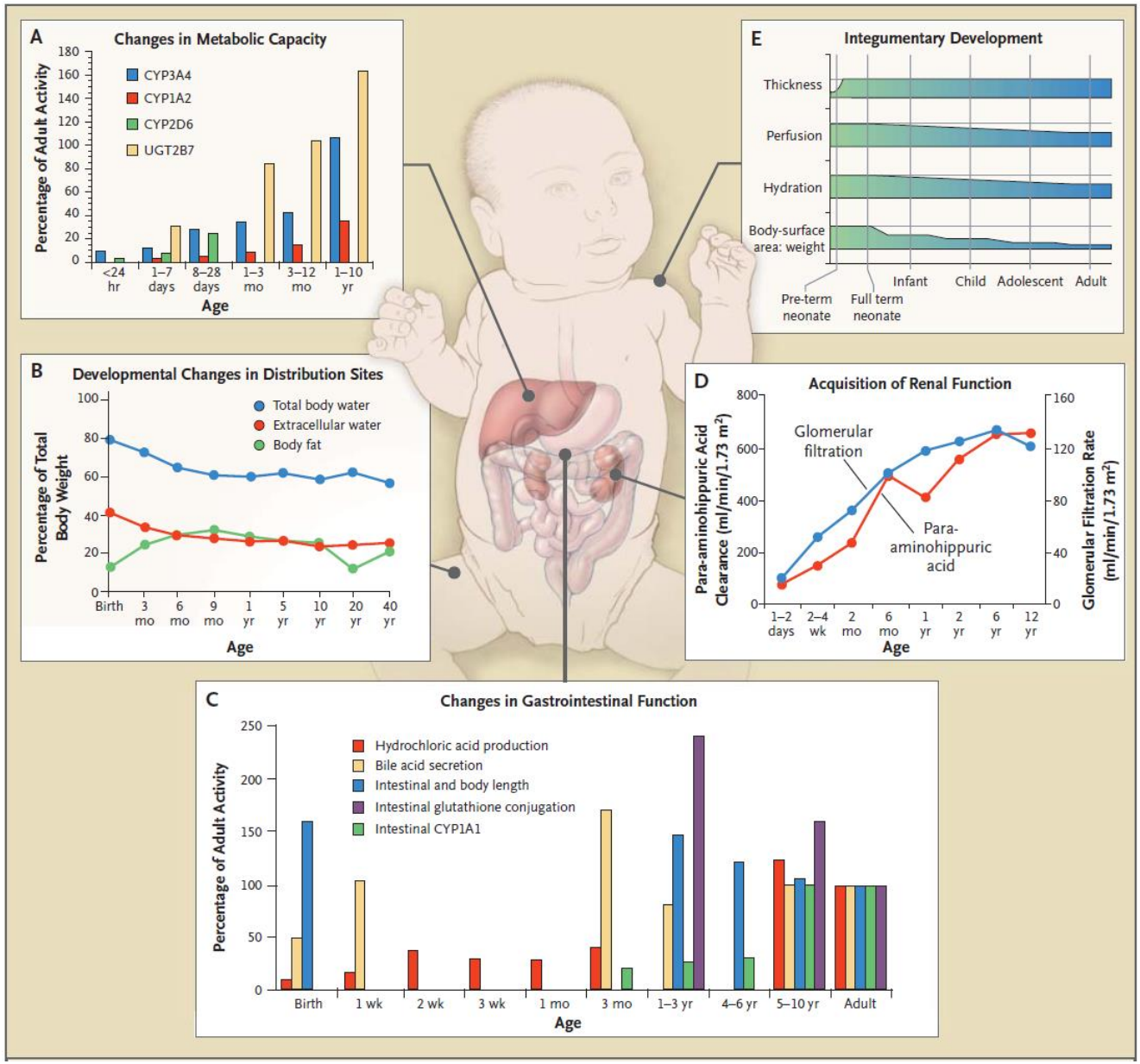

Cp, mg/L
10
1
.1
α phase (distribution)
β phase (elimination)
γ phase (tissue release)
0
6
12
18
24
Time, hr

Changes during development

• Absorption	• Gastric pH, intestinal function
• Distribution	• Body composition, availability of binding proteins, permeability of membranes
• Metabolism	• Expression of enzymes in the liver
• Excretion	• Renal function
• PD	• Availability of receptors, drug-receptor interaction

Kearns et al. NEJM 2003



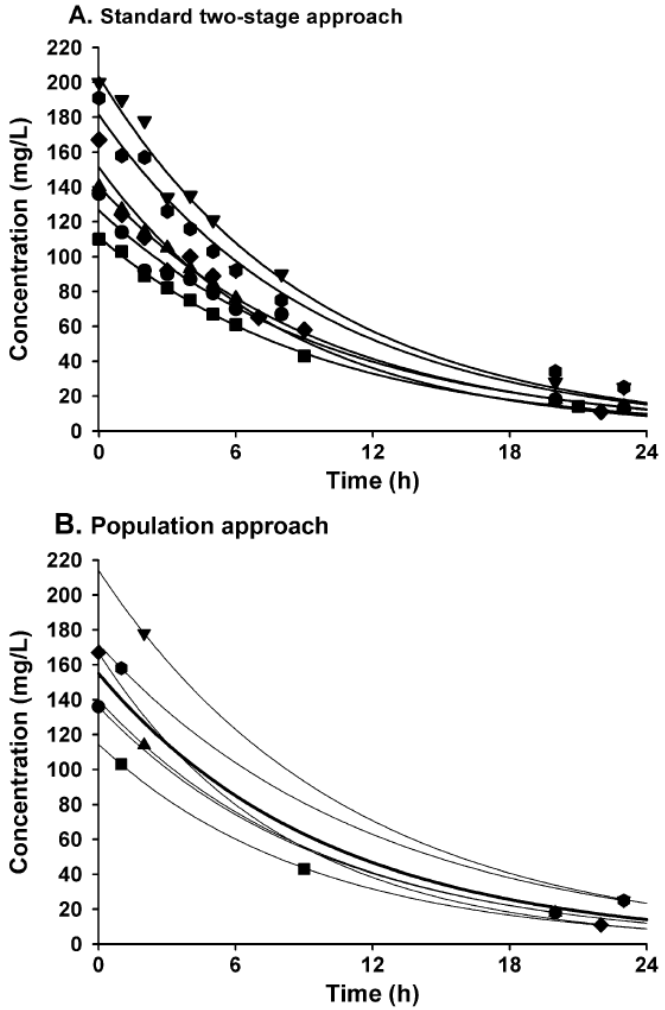
Kearns et al. NEJM 2003

PK/PD studies

- Adults:
- 12 blood samples taken in 24 hours

  (Data-rich approach)

- Children:
- Population approach



De Cock et al. Eur J Clin Pharmacol 2011

What is the right dose?

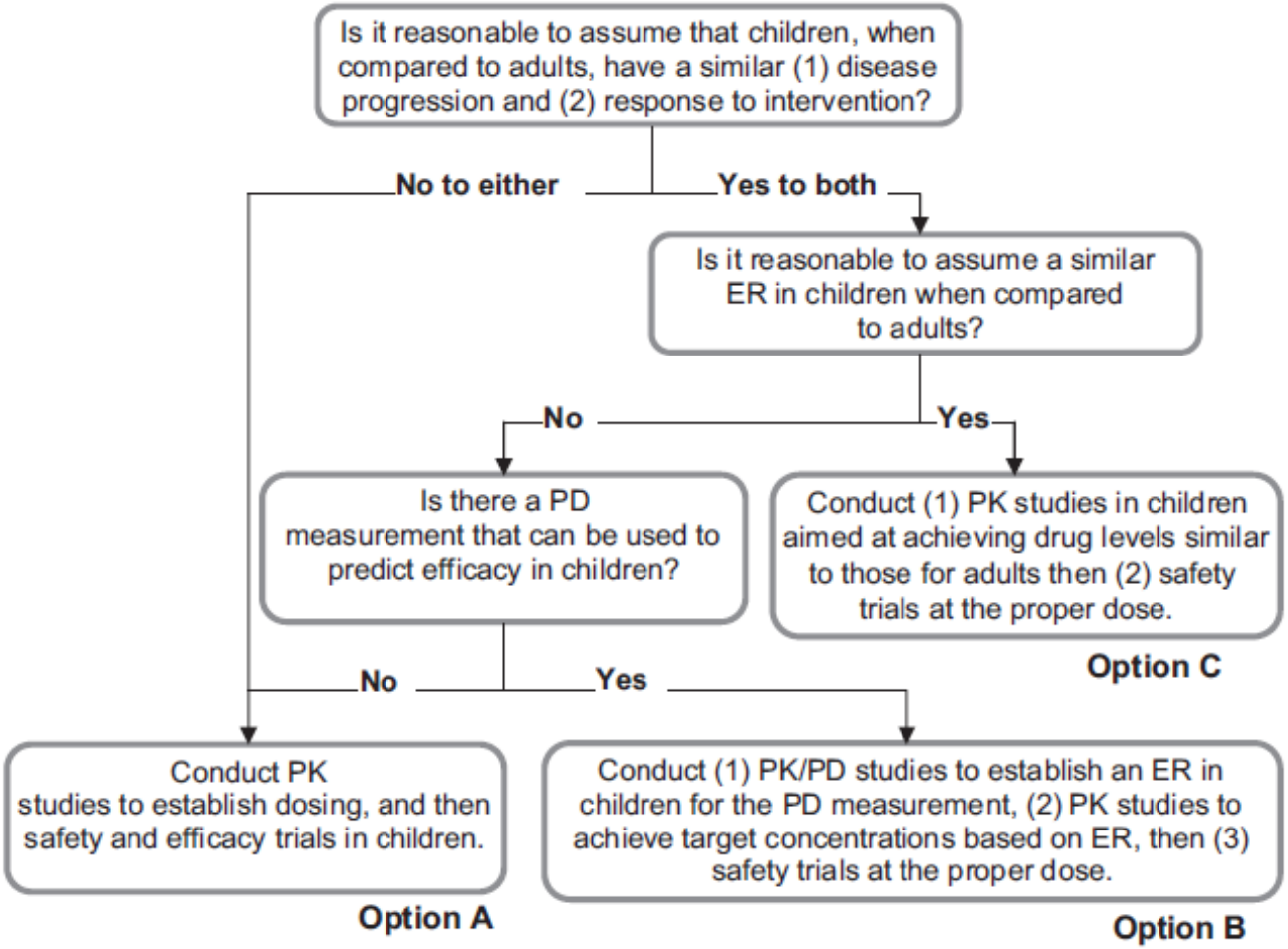
- Not useful:
  - Calculate based on weight or BSA
  - 80% of the adult dose
- Recent developments:
  - Extrapolation
  - Modelling and simulation

Extrapolation …

‘use of data (in vitro, in silico, PK, PD, safety, efficacy) acquired in one population and/or experimental setting to make inference about another population of interest.’

- Dose
- Efficacy
- Safety
- Assumptions for sample size calculations

FDA decision tree



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 April 2016
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Reflection paper on extrapolation of efficacy and safety in paediatric medicine development

Draft

Draft agreed by Biostatistics Working Party	March 2016
Draft agreed by Modelling and simulation group	March 2016
Draft agreed by PKWP	March 2016
Draft agreed by Scientific Advice Working Party	March 2016
Draft Adopted by PRAC	17th March 2016
Draft Adopted by PDCO	31st March 2016
Draft Adopted by CHMP	31st March 2016

Keywords	Paediatrics, extrapolation, medicine development, biostatistics, modelling and simulation

Table 1: Extrapolation framework table

			Pharmacology Drug disposition & effect	Disease manifestation & progression	Clinical response to treatment Efficacy & safety
SOURCE POULATION Adults	Extrapolation concept	Mechanisms	Age-related differences in - ADME - mode of action - PD effects (E-R) - toxicity	Age-related differences in - aetiology - pathophysiology - manifestation - progression - indicators	Age-related - differences, - applicability, - validation of efficacy & safety endpoints
		Quantitative evidence	PB-PK/PD models Pop-PK/PD models Covariates: - age, maturation, etc - disease, comorbidity,	Quantitative synthesis of natural disease data Disease progression models Covariates: - age - disease types, severity - comorbidity	Quantitative synthesis or meta-analysis of treatment data Disease response models Covariates: - age - disease types, severity - comorbidity
			➢ existing data ➢ progressive input of emerging data		
		Prediction	Predict doses to achieve - similar exposure, or - similar PD effect, and - acceptable safety per age group	Describe/predict differences in natural course of disease progression by age group	Given similar drug exposure or PD response, predict degree of differences in - efficacy - safety - benefit-risk balance by age group
			➢ refine predictions using emerging data		
TARGET POPULATION Children, different paediatric age groups	Extrapolation plan		PK studies or PK/PD studies needed for confirmation of doses in target population	Epidemiological data - natural disease course - SOC treatment in target population	- Design of clinical studies - Sample size(s) required in target population to conclude on benefit-risk balance
	Validation & Extrapolation		Validate - modelling approaches - modelling assumptions - confirm predicted differences in PK and PD Establish appropriate doses in the target population	Confirm predicted differences in disease progression Conclude on disease progression in target population	Confirm predicted differences in clinical response Conclude on positive benefit-risk in target population
			➢ alternatively, adapt extrapolation concept and plan		
	Further validation		PK/PD data from - phase III trials - post MA studies	Epidemiological data Other drug developments	Post MA studies Prospective meta-analyses Pharmacoepidemiological data Other drug developments

EMA review

Pediatric Anesthesia

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REVIEW ARTICLE

Role of modeling and simulation in pediatric investigation plans

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European Medicines Agency, Canary Wharf, London, UK

Summary

Ethical and practical constraints encourage the optimal use of resources in pediatric drug development. Modeling and simulation has emerged as a promising methodology acknowledged by industry, academia, and regulators. We previously proposed a paradigm in pediatric drug development, whereby modeling and simulation is used as a decision tool, for study optimization and/or as a data analysis tool. Three and a half years since the Paediatric Regulation came into force in 2007, the European Medicines Agency has gained substantial experience in the use of modeling and simulation in pediatric drug development. In this review, we present examples on

Way forward

- Empirical data are always needed
- Make use of available data
- Stimulate paediatricians to improve the quality of their (clinical) data
- Don’t just do ‘what we always do’, but develop new methods

Thank you!