# Regulatory Considerations on Bridging Approaches for Alternative Dose Schedules or Formulations

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# Disclaimer

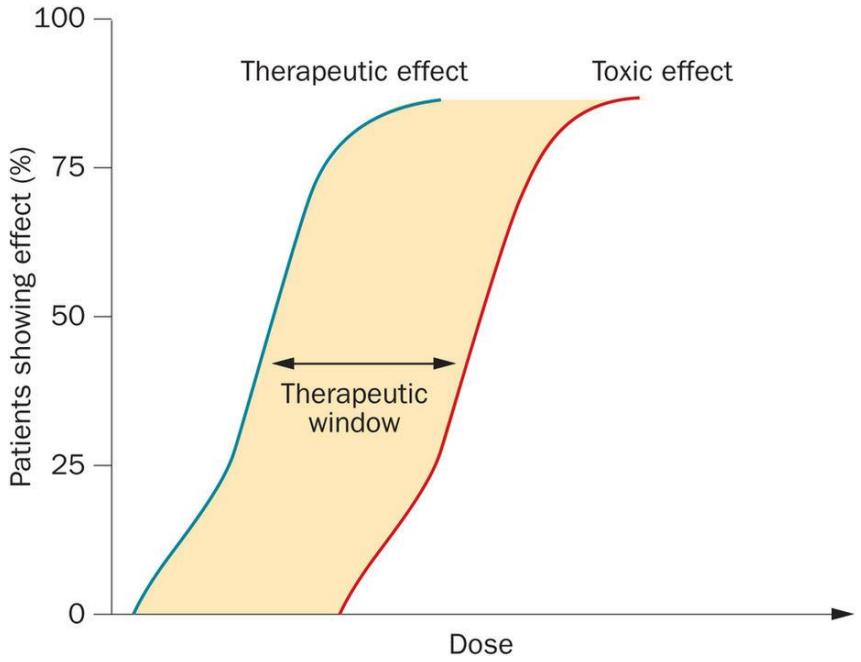
- The views expressed in this presentation are those of the speaker and not necessarily those of the MHRA.

# What Regulatory Pharmacokineticists do?

- Focus on assessment of the clinical pharmacology package of new drug applications and variations
  - Understand dosing in different populations
    - Risks of over- and under-exposure
    - Clinical relevance- Potential impact on efficacy and safety

# Determining the optimal dose

- “What is most helpful in choosing the starting dose of a drug is knowing the shape and position of the population patient (group) average dose-response curve for both desirable (therapeutic) and undesirable (toxic) effects.”




Adapted from Mathijssen, R. H. J. et al. (2014) Determining the optimal dose in the development of anticancer agents
Nat. Rev. Clin. Oncol. doi:10.1038/nclinonc.2014.40

# Challenge in assessing Marketing Authorisation Application

10 % of Major objections (MOs) on centrally approved products (NAS) raised during their evaluation (2010 - August 2014) were related to dose and schedule.

Examples:

1. Unexplored impact of (non)-fasted state and ethnicity on dosing
2. Inconsistency of extrapolation from PK dose finding evidence to final recommended dose
3. Unacceptable high Adverse Drug Reaction (ADR) rates linked to proposed dose
4. Discordance between non-clinical dose-range curve and dose-response relationships
5. Insufficiently justified extrapolation of dose-response curves for dose selection
6. Inexplicable in vitro potency assay relationship with clinical dose selection
7. Not established or justified dosing regimen / recommendations (missing evidence)

**Source: EMA Dose finding workshop Dec 2014**

# Continuous Challenge after Marketing Authorisation

10% (13 out of 135) of centrally approved medicinal products (NAS) had their dose and schedule SmPC (label) section amended during the covered marketing phase:

1. 7/13 products experienced dose changes
2. 4x experienced dose changes in special populations (renal- and hepatic impaired),
3. 3x experienced dose changes due to drug drug interactions (DDI),
4. 2x dose/schedule changes for patients' convenience and compliance,
5. 4x amended label due to safety signals
6. All- dose- and schedule label amendments during marketing phase

**Source: EMA Dose finding workshop Dec 2014**

We can do better

# Consequences?

- Significant delays in the approval of new drugs.
- Added cost of running new clinical studies

## Example

- Cabazitaxel 20 mg/m$^2$ was selected for further development. The clinical trial design allowed for intra-patient escalation up to 25 mg/m$^2$ (MTD = 30 mg/m$^2$).
- Due to uncertainties regarding the dose rationale, EMA asked for the applicant to run a phase 3 study with the primary aim to demonstrate non-inferiority in OS  of cabazitaxel 20 mg/m$^2$ (Arm A) versus cabazitaxel 25 mg/m$^2$ (Arm B)

**Source: Cabazitaxel EPAR public assessment report**

# Other situations which required alternative doses/formulations

- Patient convenience motivated schedule label changes.
- Alternative formulation suitable for pediatric population.
- Dosage regimen using different infusion volumes and schedule to maximize efficacy and minimize toxicity.

# EMA Agencies' position-pharmacometrics

- "Agencies should also be open to the use of various statistical and pharmacometric techniques such as population methods, modeling, and pharmacokinetic-pharmacodynamic approaches."

**Source: EMA Dose–Exposure-Response relationship, Regulatory perspective, 2011**

# Regulatory view?

- ‘therapeutic efficacy’ and ‘benefit-risk’
  - If ‘benefit-risk’ is positive we will (must) license it regardless of dose
- ‘dose-selection is the sponsor’s risk’

# Regulatory view?

- ‘therapeutic efficacy’ and ‘benefit-risk’
  - If ‘benefit-risk’ is positive we will (must) license it regardless of dose (however PK and PK/PD is assessed based on dosing)
- ~~‘dose-selection is the sponsor’s risk’~~ *
- choosing dose on weak foundations is risk for development
- regulators **are** interested in “various statistical and pharmacometric techniques”

* **Practical Considerations for Adaptive Trail Design and Implementation,** edited by Weili He, José Pinheiro, Olga M. Kuznetsova, 2014

# Suggested tools to support dose selection

- Modelling and Simulation during development (both pre- and post marketing authorisation):
  - Population PK models
  - Physiologically-based pharmacokinetic (PBPK) models
  - Dose-Exposure-Response modelling (PK/PD)
  - Incorporating important covariates:
    - Pharmacogenomics and drug-drug interactions.

# We provide advice to support alternative dose selection

- EMA CHMP Scientific advice and protocol assistance is designed to facilitate the development and availability of high-quality, effective and acceptably safe medicines, for the benefit of patients.

- MHRA also provide scientific advice at any stage of the initial development of your medicine, before you have submitted your application for a marketing authorisation (MA) (product licence) and during the pre-submission period for a variation to an existing MA.

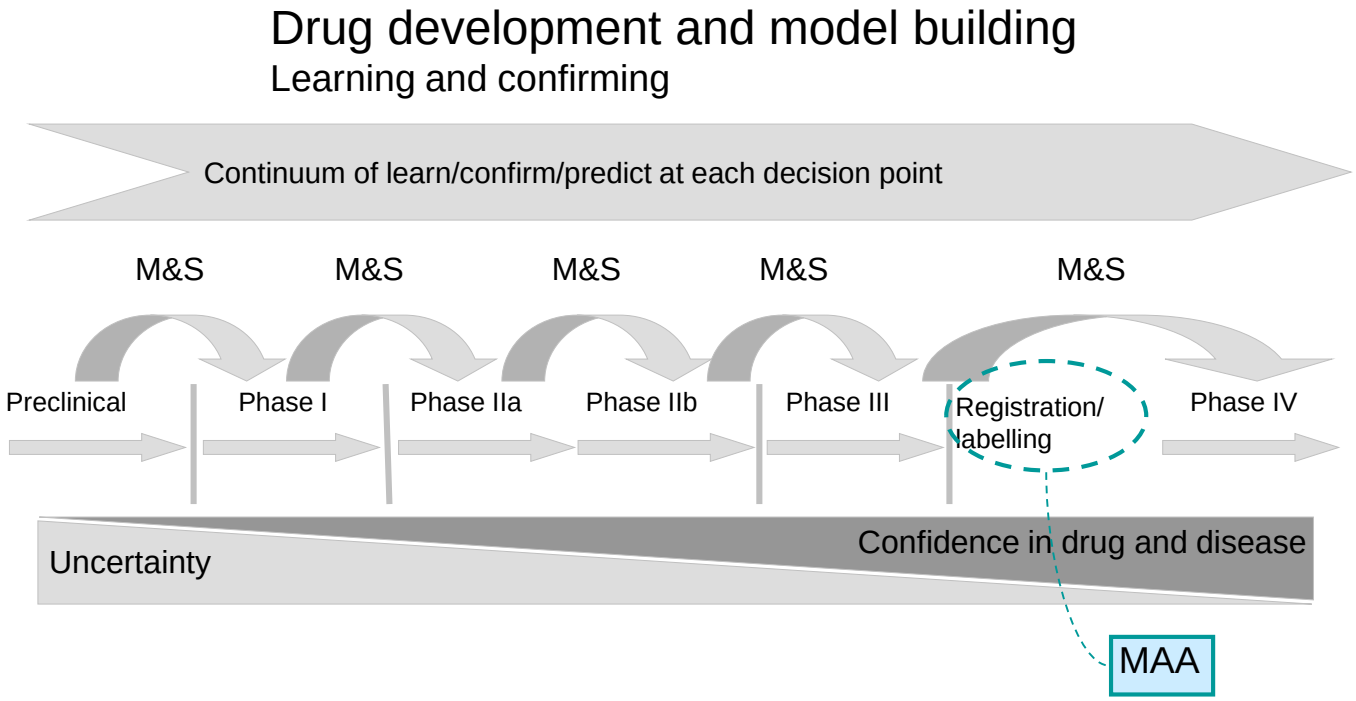
# We also qualify tools

Example

- MCP-mod (Novartis)
- Multiple Comparisons and Modelling
- Approach “qualified” by the EMA
- **Endorsement does not preclude use of other approaches**

# Benefit Risk Decisions

## Uncertainty during drug development




MAA: marketing authorisation application

Adapted from Lalonde RL et al., Model-based drug development. Clin Pharmacol Ther 2007;82:21-32

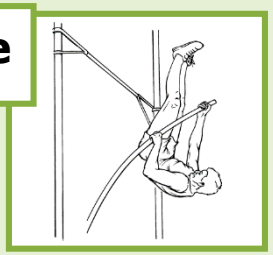
# Framework for M&S in Regulatory Review

## According to impact on regulatory decision

EXAMPLES

## High impact

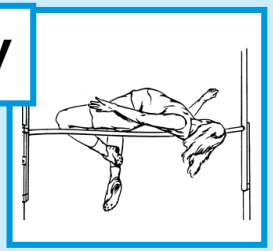
**Replace**



- Extrapolation of efficacy and safety from limited data (e.g. term and preterm neonates, paediatrics, small populations)
- Model-based inference of efficacy/safety in lieu of pivotal clinical data

## Medium impact

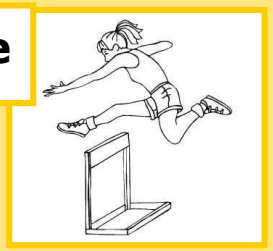
**Justify**



- Identify safe and efficacious exposure range (exposure-response in target population)
- Justify not doing a study (e.g. drug-drug interaction based on PBPK)

## Low impact

**Describe**

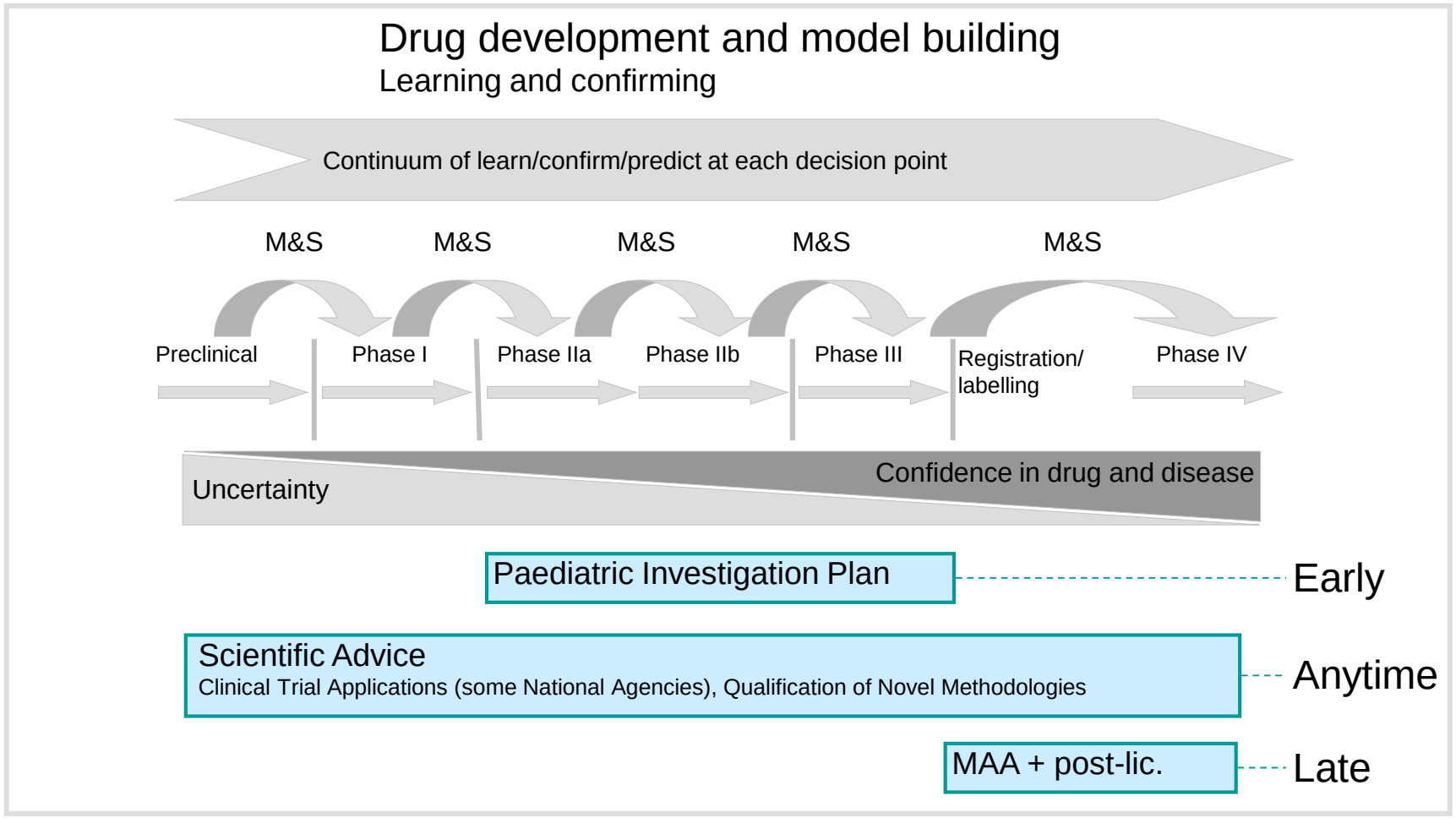


- Internal decision making (hypothesis generation, learning)
- Verify conclusions drawn from preclinical observations and PK data in healthy volunteers

Impact on regulatory decision

# Present Regulatory Status of M&S Review:

## When are regulatory decisions based on M&S made?

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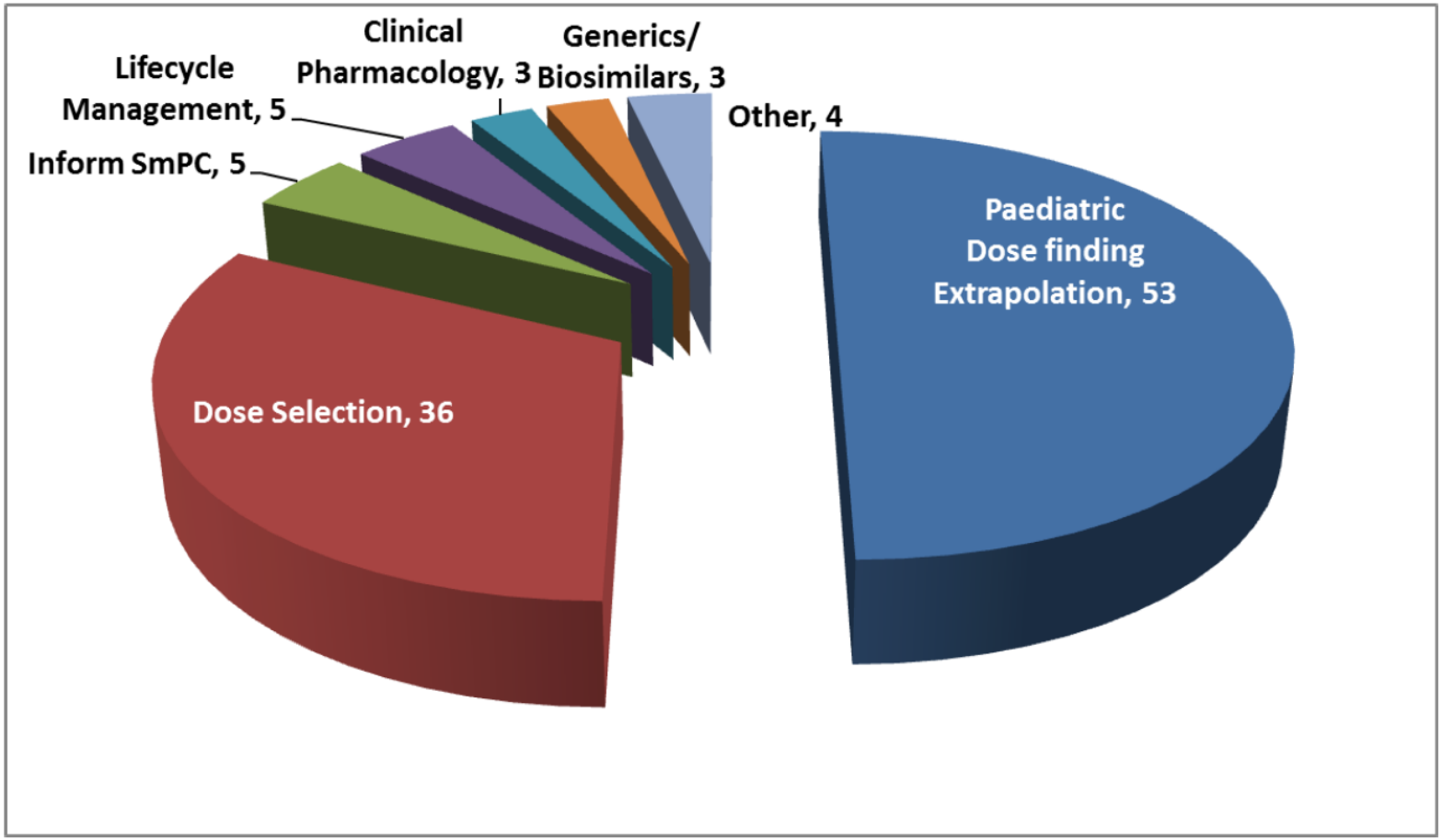
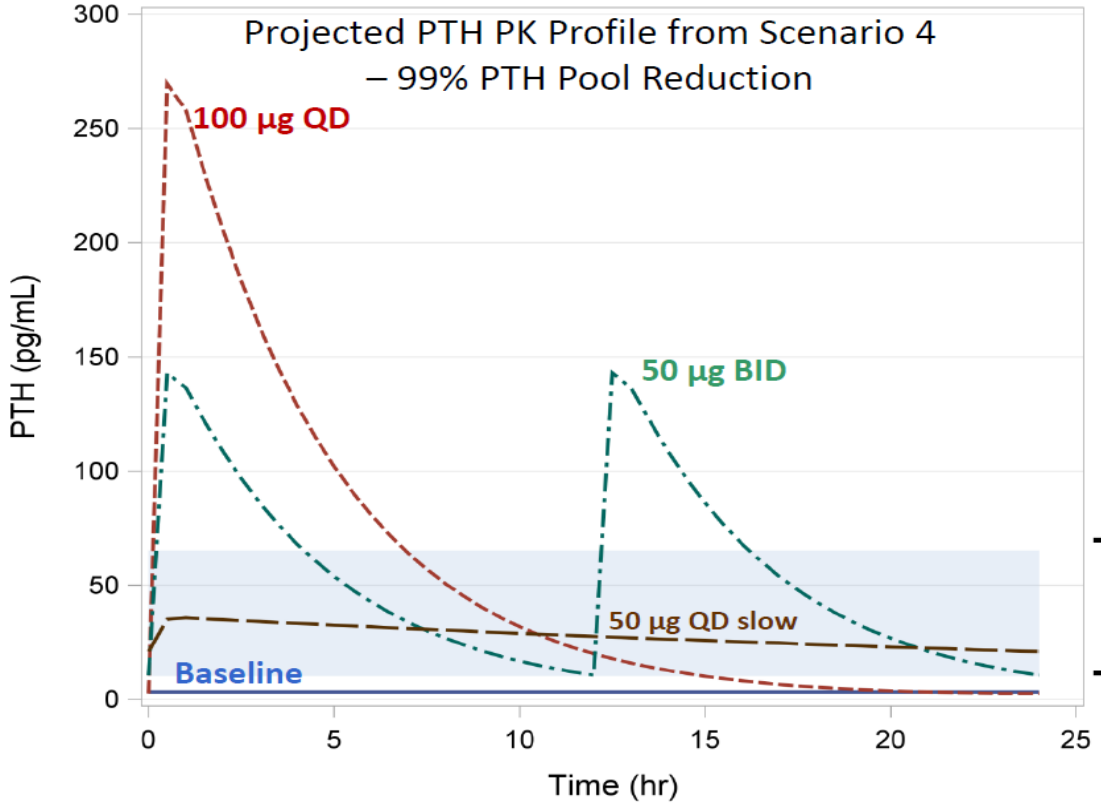
# In the scope of MSWG regulatory submissions




Source: MSWG activity report, 2016

# Altering Regimen (QD to BID) or Release Profile Bring PTH Levels Close to the Physiological Levels




Normal Physiological range
(10 -65 pg/mL)*



Source = FDA slides for Endocrinologic and Metabolic Drugs Advisory Committee Meeting, September 12, 2014, Natpara

# Paediatric development

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

Slide from Ine Skottheim Rusten, NOMA

# Scaling approaches of Dose-Exposure to children

The standard methods to account for developmental changes in PK

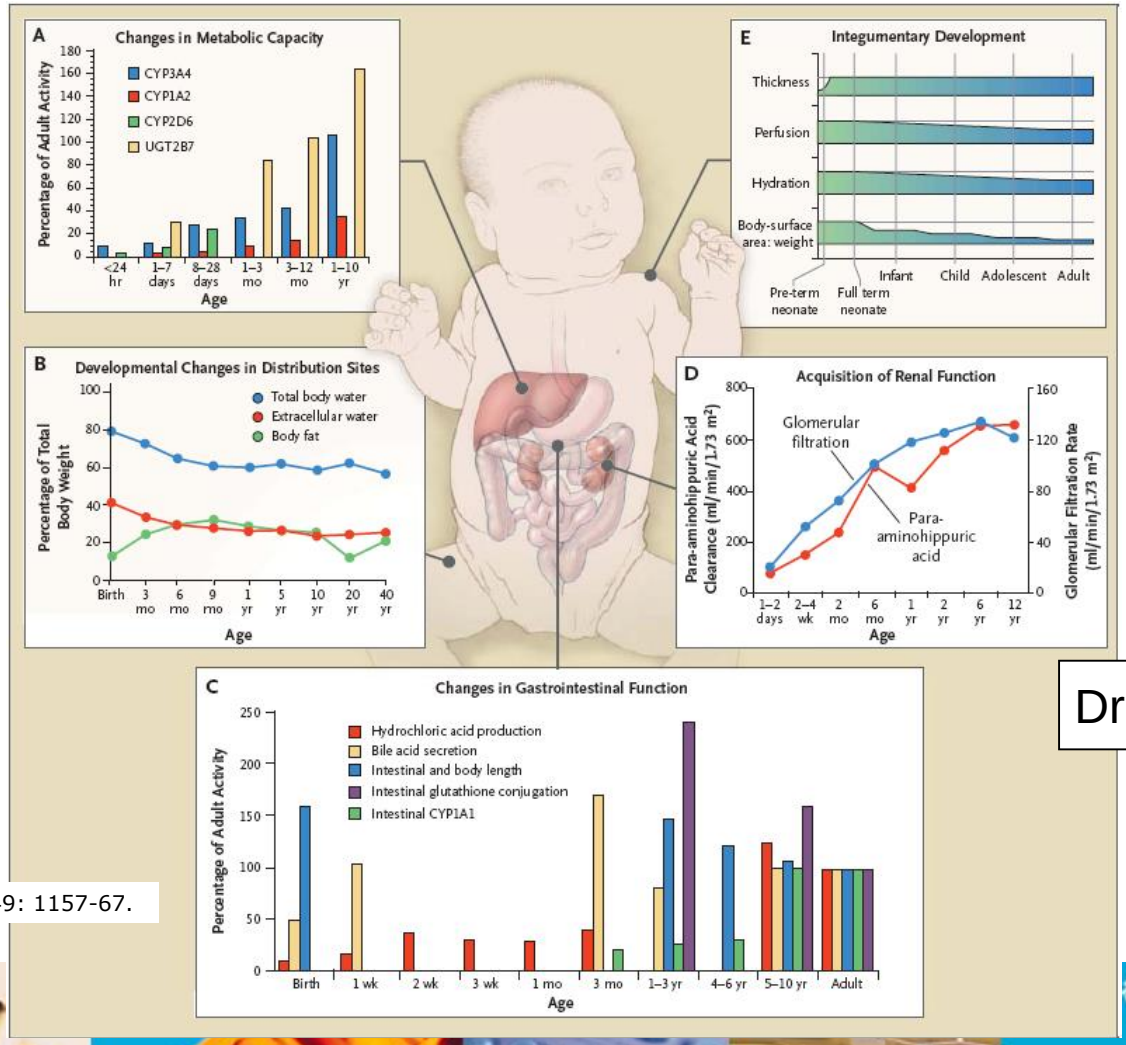
- **Size**
  - Weight
  - Allometric scaling
- **Maturation**
  - Organ function
  - Maturation functions
- **Co-variates**
  - Disease
  - Co-medication (DDIs)
  - Nutrition
  - Formulation
  - Pharmacogenetics
  - Ethnicity
  - …

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

Slide from Ine Skottheim Rusten, NOMA

# PBPK for extrapolation of PK across populations

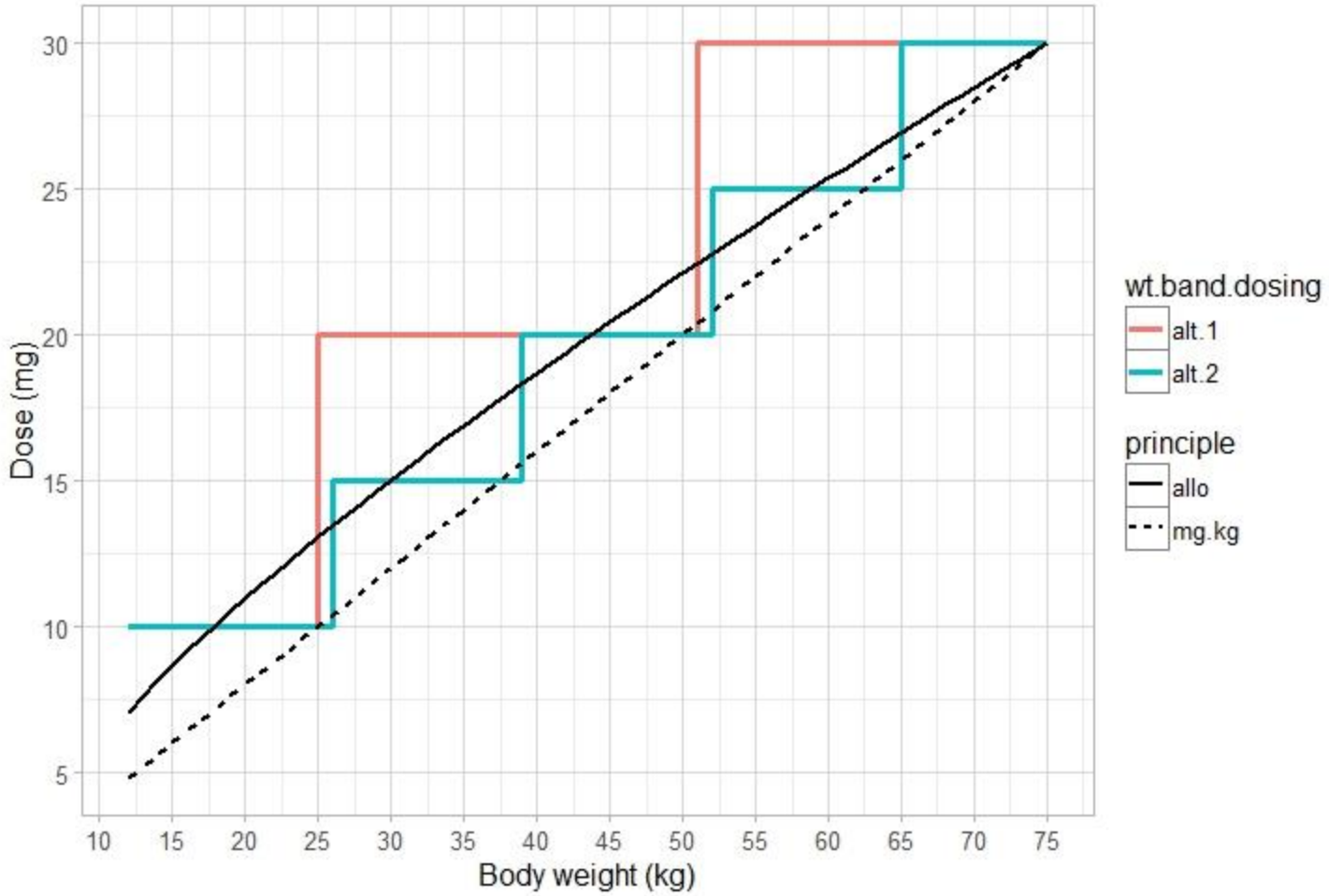
How do populations vary? Children versus adults.




Drug-independent!

Kearns et al. 2003. N Eng J Med. 349: 1157-67.

# Population Model to optimise dosing in children




# EMA Guidelines relevant to dose selection

- Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal product (**EMEA/CHMP/SWP/28367/07 Rev. 1**)
- Guideline on clinical development of fixed combination medicinal products (**EMA/CHMP/158268/2017**)
- Population Exposure: The Extent of Population Exposure to Assess Clinical Safety (**CPMP/ICH/375/95**)
- Dose Response Information to Support Drug Registration (**CPMP/ICH/378/95**)
- Guideline on reporting the results of population pharmacokinetic analyses (**CHMP/EWP/185990/06**)
- Guideline on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation (**EMA/CHMP/458101/2016**)
- Guideline on the investigation of drug interactions (**CPMP/EWP/560/95/Rev. 1 Corr. 2**)**
- Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (**EMA/CPMP/EWP/280/96 Corr1**)
- Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products (**EMA/CHMP/37646/2009**)

# Conclusions

- Modification of dose regimen and/or formulation might be necessary to achieve optimal dosing in the target population.
- Several tools available to support this challenging task.
- We are open to the use of various statistical and pharmacometric techniques.
- We developed specific guidelines for support.
- Additionally, we are available to provide you with scientific advice at any stage.

MHRA

# THANK YOU