Integration of data using M&S can provide evidence for evaluation of efficacy-safety risks without the need for a separate study.

Regulatory perspective

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Background & Rationale

- What type of M&S on integrated data are we talking about

- Regulatory challenges in M&S of integrated data
  - What are elements that make it questionable
  - What is the added value

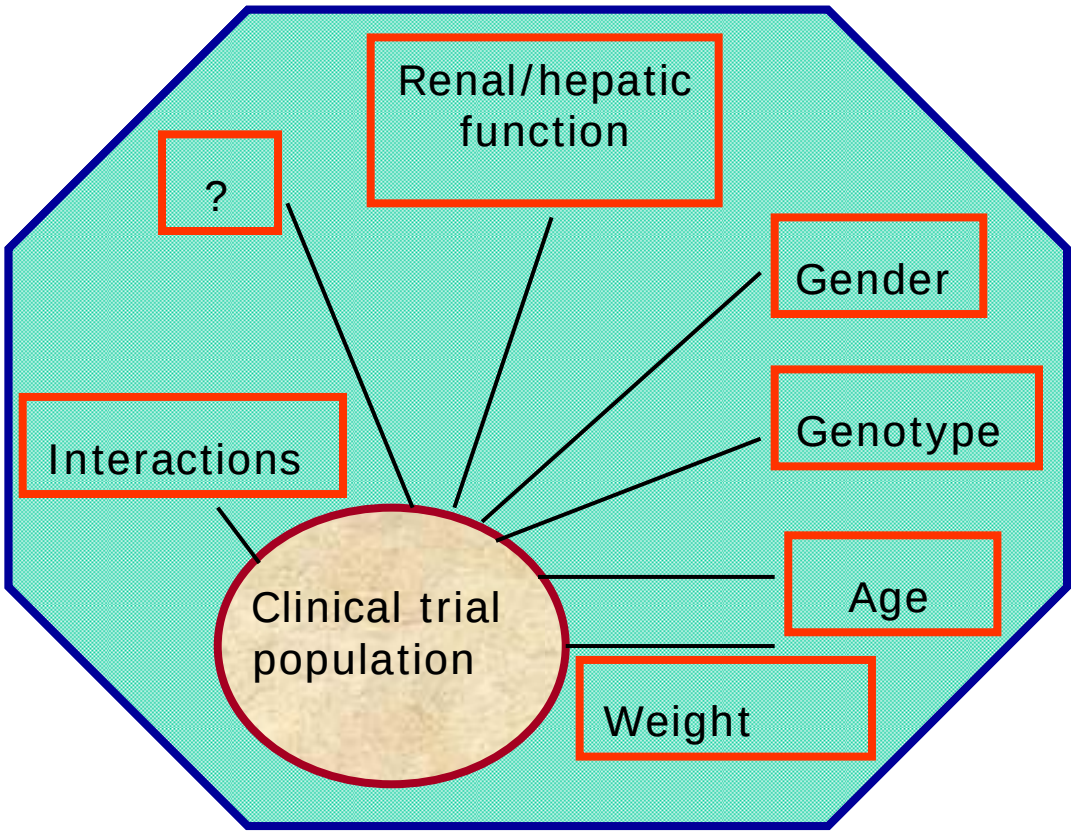
Type of M&S on integrated data, regulatory

- How can models and their simulation results be used in making regulatory decisions

- **Current approach**

- Sparse sampling in Phase III and population-PK modelling
- Support of final dose to be studied in Phase III
- Investigation of covariates for exposure variability, extrapolation to whole patient population:
- M&S can be used for multiple covariate analysis

M&S and PK: extrapolation to other populations



Assumption:
exposure-effect levels the same…

Type of M&S on integrated data, regulatory

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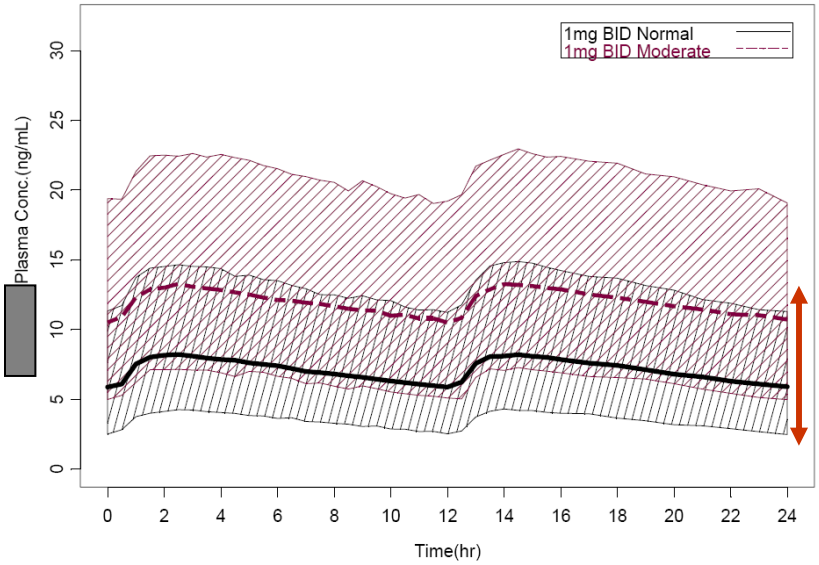
Type of M&S on integrated data, regulatory

- Content of a drug application file for NCE:
- Often contains **descriptive modelling** (pop-PK, pop-PK-PD)
- Sometimes **simulations**
- In case of drug-drug interactions:
  - simulations excluding a DDI are more easily accepted than modelling/simulation of DDIs that require a change in posology
  - In silico methods
  - Dose recommendations for situations that cannot (easily) be tested

Type of M&S on integrated data, regulatory

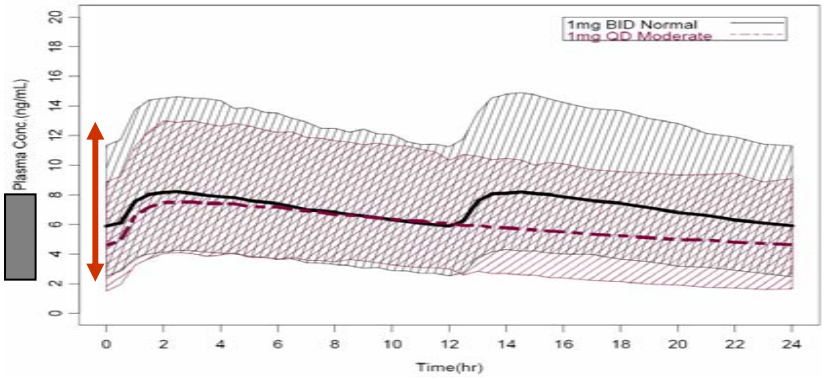
- Example simulation: Dose advice in renally impaired patients

- **Unadjusted** dose, 1 mg BID



Target level

- **Adjusted** dose, 1 mg OD



Acceptable use and quality of M&S

- Simulation acceptable, since pop-PK model was based on sufficient real PK data in renally impaired patients, was sufficiently validated, and predictive power was assessed.
- Supportive data: exposure target level was well determined based on Phase 2 data.

Regulatory challenges use and quality of M&S

- Justification of the model
- How far can we trust simulations beyond observations?
- How can we optimally make use of M&S?

Regulatory challenges use and quality of M&S

- **Justification of the model**
- **Assumptions made by modeller** should be made clear to the assessor
  - Assumptions reasonable and physiologically justified?
- **Validation** important, especially for poor datasets. Robustness and predictive performance
- **Sparse samples**: shrinkage to the mean risk
- **Report sufficiently detailed** to allow assessment

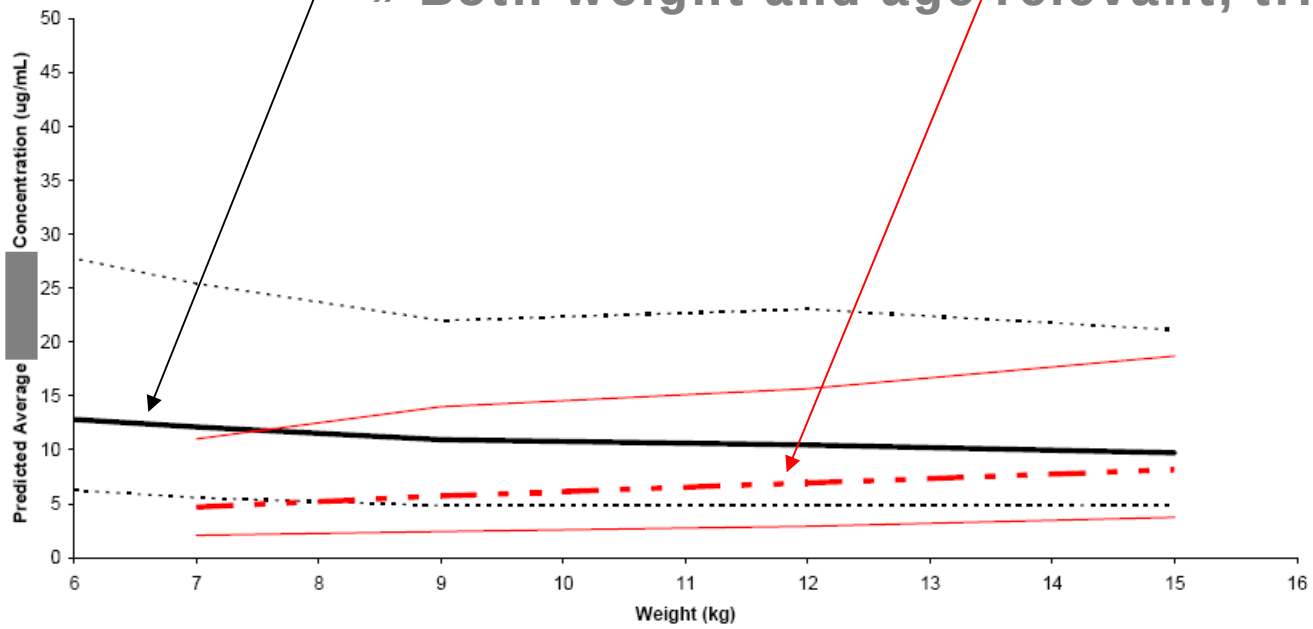
- **Quality of dataset**, e.g.,
  - Time between co-medication and investigational drug
  - Rich and/or sparse data as basis of the model
  - @@

Regulatory challenges use and quality of M&S

- How far can we **trust simulations beyond observations**?
  - Effect of weight
  - Effect age
  - Effect severe renal impairment outside range investigated in vivo
  - Effect polymorphisms, poor or ultrarapid metabolisers
- **Interpolation** (e.g. between severe and mild renal impaired, between poor metaboliser and extensive metaboliser) most trusted.
- **Translational models** (e.g. in-silico/in-vitro to clinical). As yet limited regulatory experience.
  - Mainly used for **excluding** relevant interactions. Not acceptable yet for specific dose-advice. Problem: validation

Simulation beyond observations

- Simulations based on data from children **<24 months**
- Simulations based on data from children **>24 months**
  - » **Both weight and age relevant, tricky**



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Regulatory challenges use and quality of M&S

- **How can we optimally make use of M&S?**
- Guard high quality dataset
- Clear communication, detailed study description available to assessors
- Not all issues may be resolved using modelling. Discuss modelling issues a prior with assessors (scientific advice)
- Continue optimising the model during the life-cycle of a product

- Note: In many drug development plans this is already the case.


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