Use of quantitative tools for study planning purposes and study design optimisation

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Interests in pharmaceutical industry	NO	Current	From 0 to 3 previous years	Over 3 preavious years
DIRECT INTERESTS:				
1.1 Employment with a company: pharmaceutical company in an executive role	X	☐	☐	☐ mandatory
1.2 Employment with a company: in a lead role in the development of a medicinal product	X	☐	☐	☐ mandatory
1.3 Employment with a company: other activities	X	☐	☐	☐ optional
2. Consultancy for a company	X	☐	☐	☐ optional
3. Strategic advisory role for a company	X	☐	☐	☐ optional
4. Financial interests	X	☐	☐	☐ optional
5. Ownership of a patent	X	☐	☐	☐ optional
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6. Principal investigator	X	☐	☐	☐ optional
7. Investigator	X	☐	☐	☐ optional
8. Grant or other funding	X	☐	☐	☐ optional
9. Family members interests	X	☐	☐	☐ optional

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OUTLINE

- M&S within the EU extrapolation framework
- Opportunity to optimize a pediatric development
- M&S can help to address PAH uncertainties
- Case study 1: sildenafil
- Case study 2: bosentan
- Conclusion

ROLE OF M&S WITHIN THE EMA EXTRAPOLATION FRAMEWORK

According to the model complexity, quality of data, previous knowledge of a compound, quantitative tools of analysis can be used to support an extrapolation approach in EU on three dimensions (3Rs)*:

1. Refine Clinical Trials
2. Reduce Clinical Trials
3. Replace Clinical Trials

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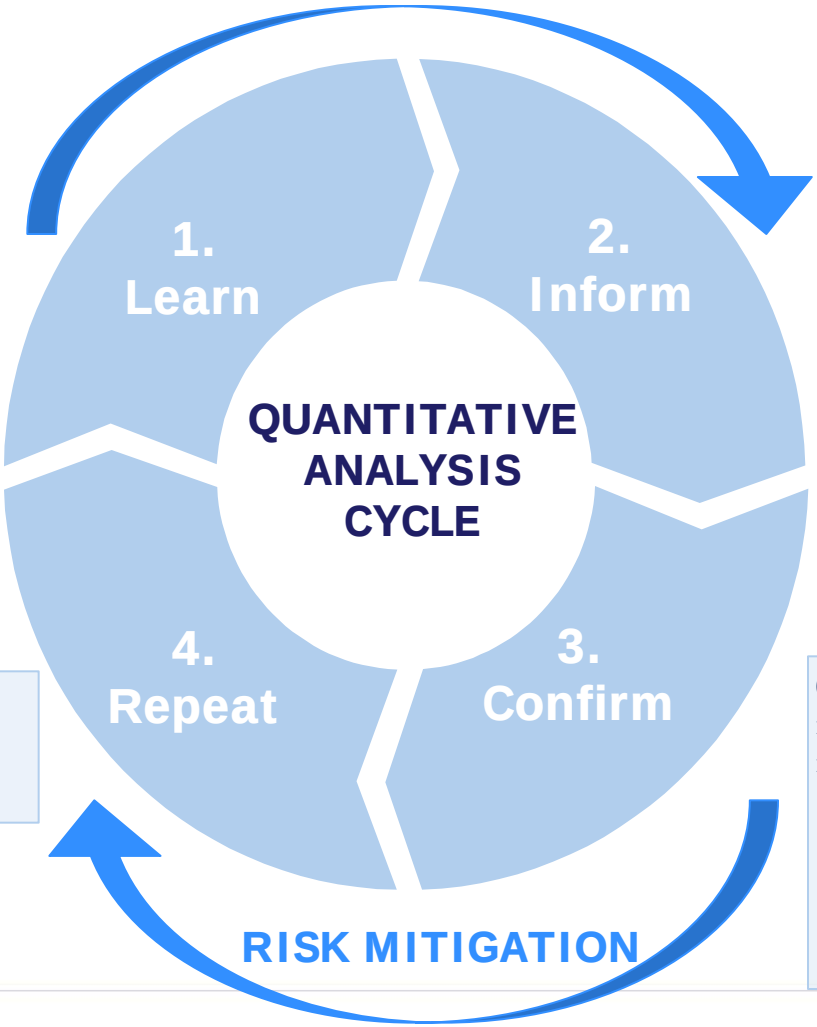
* Avicenna Roadmap

EMA EXTRAPOLATION FRAMEWORK

Extrapolation concept
- Definition extrapolation target and scenarios
- Systematic synthesis of existing data
- Quantitative predictions on the degree of similarity between source and target population in 1) medicine disposition and effects, 2) disease progression, 3) clinical response
- Quantification of confidence in prediction



Extrapolation plan
- Identify gaps in knowledge
- Plan optimized studies in target population in accordance with predicted degree of similarity defined in the extrapolation concept
- Identify follow-up measures to produce data required by the extrapolation concept
- Assess impact assumptions violation/worst case scenarios via risk minimisation measures in the RMP

Mitigating uncertainty and risks
- Additional follow-up data (pre or post MA

Confirmation & extrapolation
- No extrapolation vs extrapolation
- Confirmation or adaptation of the extrapolation concept by relevant emerging data using M&S in the planning and analysis of pediatric studies

BENEFITS OF M&S TO PEADIATRIC CTs

1. STUDY OPTIMIZATION TOOL

- Bridge the available knowledge (PK, PK/PD, response to treatment..)
- Guide clinical trial design
  - sample sizes, choice of trial design
  - dose optimization
  - sampling schemes
  - sensitivity of endpoints/appropriate times for measuring endpoints
  - avoid unnecessary studies

2. DATA ANALYSIS TOOL

- Integrate and analyse of sparse and unbalanced data
- Detect variability in the clinical outcome
- Identify covariates affecting exposure

M&S CAN ADDRESSES PAH GAPS

PAEDIATRIC INTRINSIC OR EXTRINSIC FACTORS	SOLUTION
Developmental growth	PBPK
Metabolism	PBPK
DDIs in children	PBPK
Comorbidities	PoPPK
Weight/age/sex	PoPPK, PBPK
Disease progression Pathophysiology	Health data, including registry data
MoA	Network disease model /causal cohesive genotype-pheneotype models

POTENTIAL ISSUE	SOLUTION
Dose	PoPPK, PBPK, DER
Study designs	Clinical trial simulation/ *in silico* trials
Efficacy, extrapolation	Future disease models
Adverse events	Future disease models

PEADIATRIC PAH TREATMENTS IN EU

Medicine Name	Active Substance	Peadiatric Indication	Orphan	Pediatric Formulation
Adcirca	tadalafil	no	no	no
Adempas	riociguat	no	yes	no
Opsumit	macitentan	no	yes	no
Revatio	sildenafil	yes in 4.1 children >1 year (E&S data)	no	powder for oral suspension
Tracleer	bosentan	dose recom. in 4.2 children >1 year (PK data)	no	dispersible tablets
Uptravi	selexipag	no	no	no
Volibris	ambrisentan	no	yes	no

CASE STUDY: SILDENAFIL

Sildenafil clearance

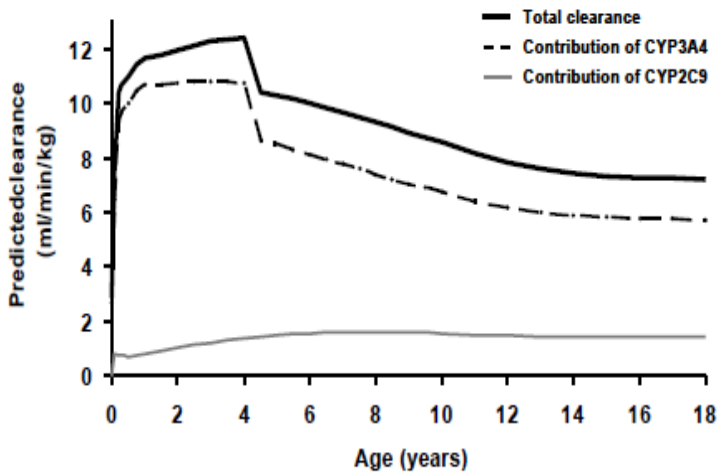


Figure 12: Predicted age-dependent sildenafil hepatic clearance across the different paediatric ages based on the clearance scaling module in PK-Sim®

L. Hsien, 2010

Time varying physiology in a PBPK model

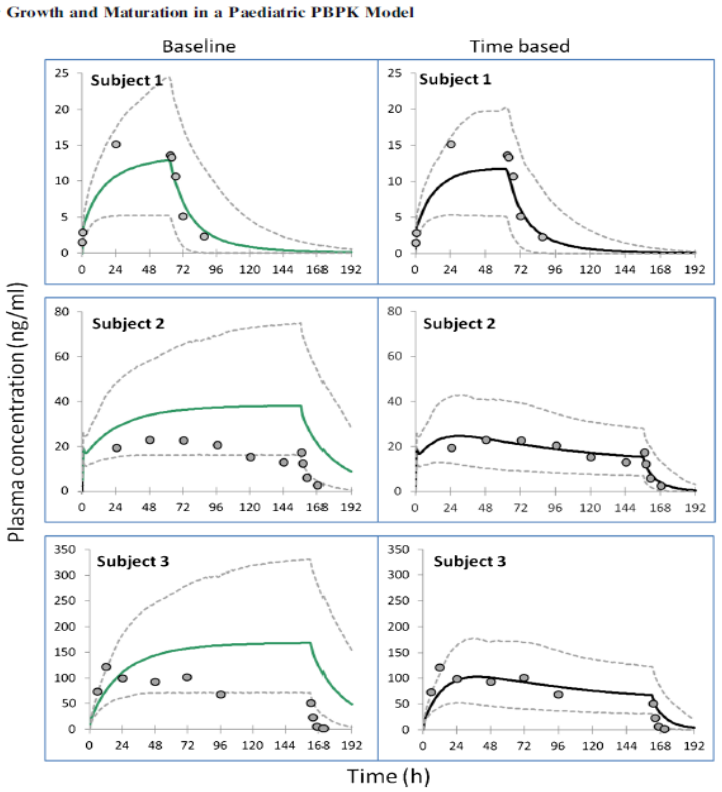


Fig. 4. Simulated mean (*solid lines*) and 95% predictive interval values (*dashed lines*) of sildenafil plasma concentration over time for three representative subjects using both baseline and time-based changing physiology in the p-PBPK model. *Filled circles* are the observations from each subject as reported in Mukherjee *et al.* 2009

K. Abduljalil et al., 2010

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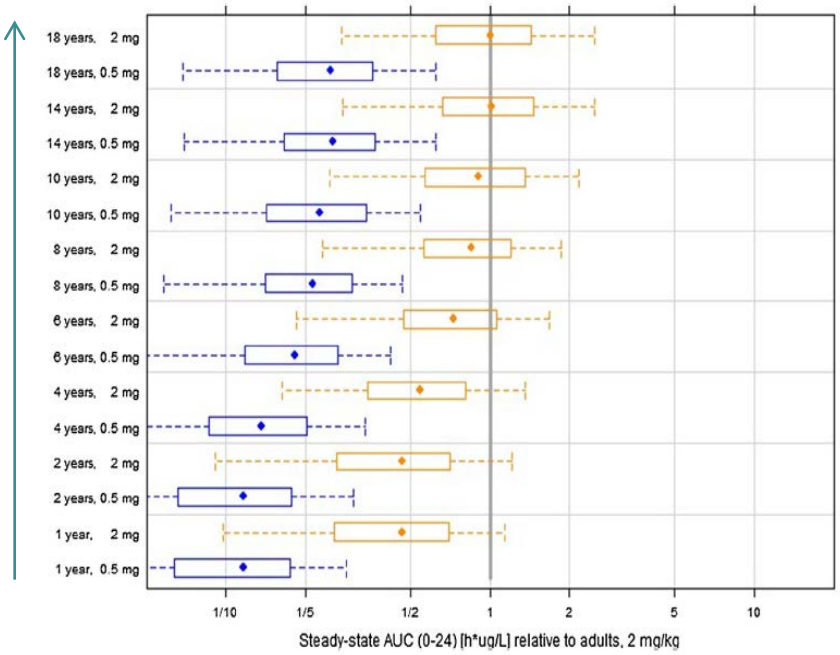
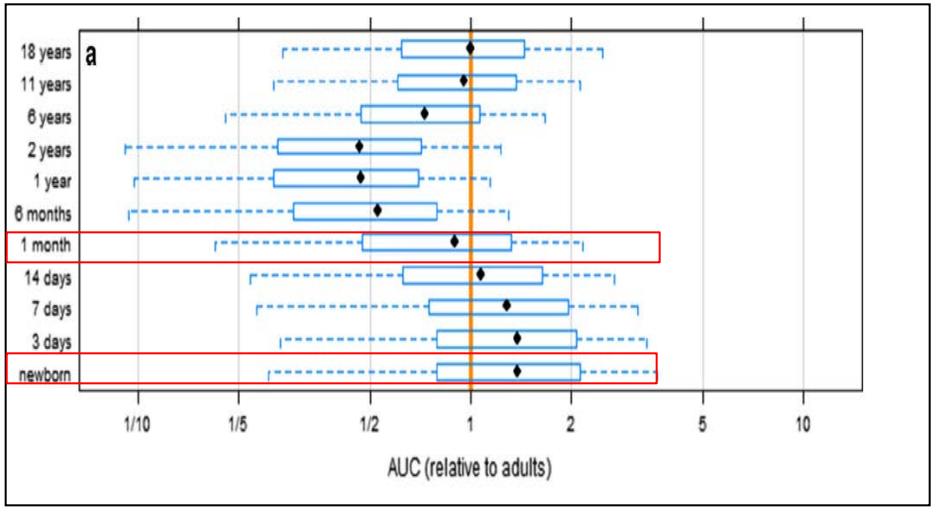
CASE STUDY: BOSENTAN



Comparison of exposure at steady state after bosentan 0.5 or 2 mg/kg twice daily in a pediatric population simulated from the PBPK model stratified by age



a) Age-dependence of AUC 0-inf

J. Zisowsky et al., 2017

CONCLUSION

- Safety should be investigated in the target population to confirm estimates and detect unforeseen age-specific AEs
- What endpoint allow a comparison between adult and children? And in children less than 2 years?
- How *similar* is enough?
- Interdisciplinary effort

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