European Federation of Pharmaceutical Industries and Associations

Session 2: Qualification of the PBPK platform for the Intended Purpose: EFPIA comments overview






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on behalf of EFPIA and EFPIA MID3 Working Group

EMA workshop on qualification and reporting of physiologically-based pharmacokinetic (PBPK) modelling and simulation

21 November 2016

EMA questions

- How would you qualify a PBPK platform for an intended purpose, as outlined in the Guideline? (Preferably with examples).
  Focus should be on a high impact application.

- Are the 3 practical qualification processes suitable?

- What problems and benefits can you see with the outlined qualification approach in the guideline?

- In a constructive way - what changes would you propose?

Overview

- EMA questions
- EFPIA MID3 good principles
- Examples of qualification
- Suitability of qualification routes
- Problems and benefits of the Guidance
- Proposed improvements to guidance

Citation: CPT Pharmacometrics Syst. Pharmacol. (2016) 00, 00; doi:10.1002/psp4.12049

WHITE PAPER

Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation

EFPIA MID3 Workgroup: SF Marshall[1]*, R Burghaus[2], V Cosson[3], SYA Cheung[4], M Chenel[5], O DellaPasqua[6], N Frey[3], B Hamrén[7], L Harnisch[1], F Ivanow[8], T Kerbusch[9], J Lippert[2], PA Milligan[1], S Rohou[10], A Staab[11], JL Steimer[12], C Tornøe[13] and SAG Visser[14]

Objectives:

- To promote "Good Practices" with regards to the planning conduct & documentation
- To include illustrative examples to demonstrate their use, impact & value
- To promote Model Informed Drug Discovery & Development (MID3)

Review and Input from MSWG:

- Efthymios Manolis (EMA/MSWG)
- Terry Shepard (MHRA/MSWG))
- Ine Skottheim-Rusten (NMA/MSWG/PDCO)

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- Tomas Salmonson (MPA/CHMP chair)
- Rob Hemmings (MHRA/CHMP/SAWP)

Abstract:
http://onlinelibrary.wiley.com/doi/10.1002/psp4.12049/abstract
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Podcast:
http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2163-8306/homepage/podcasts.htm

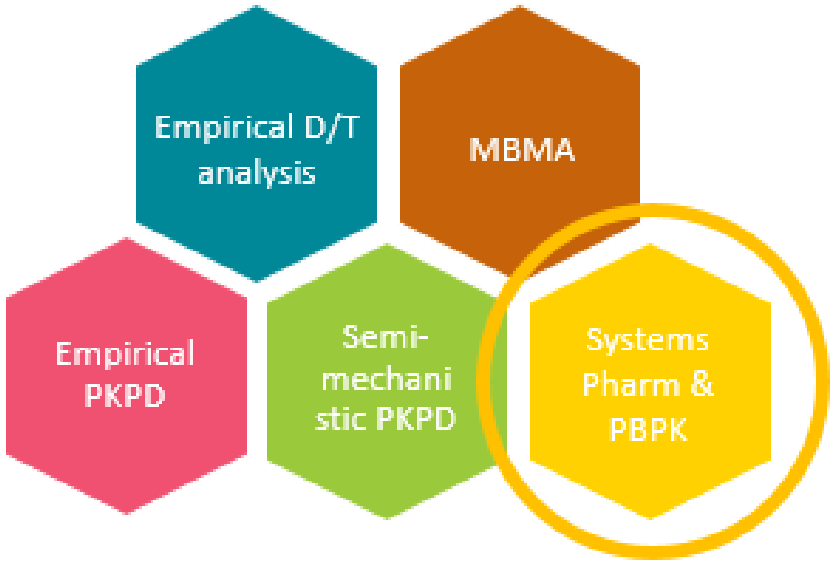
Good Practices in MID3 White Paper Highlights

“Why” MID3 is important for decision makers

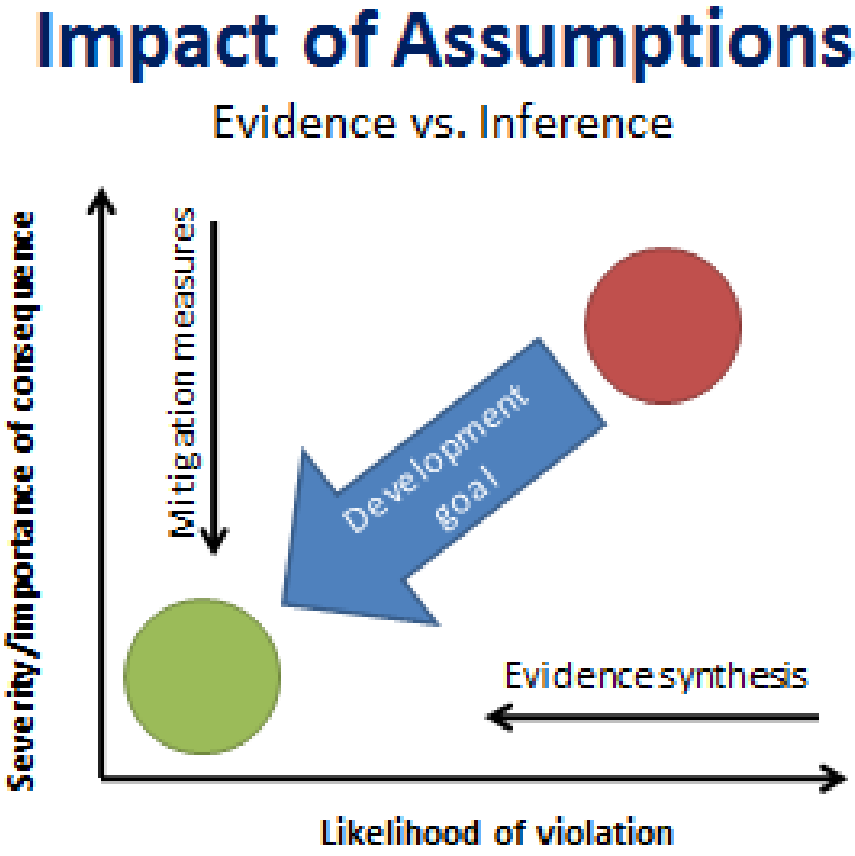
“What” MID3 means for developers

“How” MID3 should be documented

MID3 Paper describes applications of PBPK published in the literature.



MID3 Assumption setting, evaluation, impact assessment



Qualification should:

- List of assumptions
- approaches to qualify /test /assess as per MID3 assumption table:
  - Important assumptions
  - Justification
  - New/established
  - Testable/non-testable
  - Test/approach to assess impact
  - Evaluation

See Table 5 in white paper: http://onlinelibrary.wiley.com/doi/10.1002/psp4.12049/pdf

MID3 paper outlined qualification

- As "***part of both the model development and evaluation process and the inference step … current data (internal qualification)*** *…" and "* ***data not used in the model building*** *(****external qualification****)."*
- With ***precise criteria to assess the quality of the model*** *with respect to its* ***intended purpose****."*
- *"…****The degree of qualification will depend on the use and their importance to the subsequent decision****. …".*
- *"****Sensitivity analysis*** *… explore the* ***impact of limitations on the results****."*
- *"The model-building process …* ***qualification may lead to changes in the methodology*** *…"*

Extrapolation of Quetiapine (Seroquel) XR formulation to paediatric

- FDA Granted paediatric labelling for SEROQUEL and SEROQUEL XR
- Fulfilled WR – 6 months exclusivity
- Avoid unnecessary paediatric trial (ethical, cost and time)

Phys. Prop.data
In vitro DMPK data
DDI inhibition results with ketaconazole (Study 1)
DDI induction results with carbamezapine (Study 2)

High impact

Study 6 IVIVC

Study 3 (PK)

Adults IR BID

Study 5

Adults XR QD

PBPK extrapolation

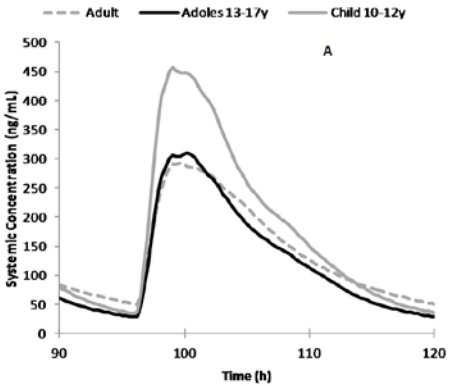
Study 4 (PK)

Children, Adolescents IR BID

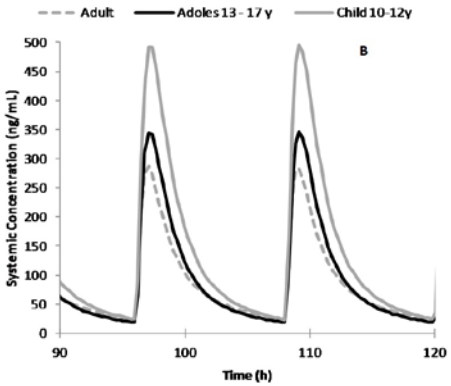
Children, Adolescents XR QD

PBPK extrapolation

The last of five daily doses of the 300mg XR formulation



150mg b.i.d. IR formulation



PBPK model predicted that children and adolescents are likely to achieve a similar exposure following administration of either the XR formulation once daily or the IR formulation twice daily at similar total daily doses

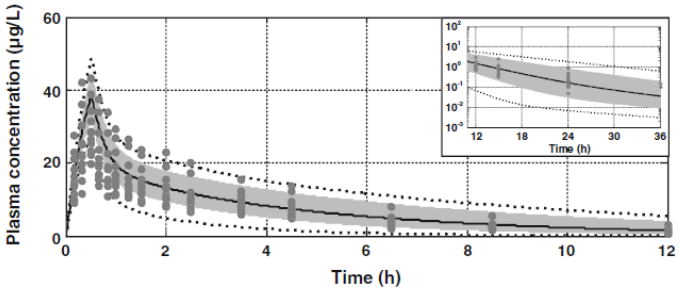
Johnson TN, Zhou D, Bui KH. Biopharm Drug Dispos. 2014 Sep;35(6):341-52

Development of a paediatric PBPK model of rivaroxaban

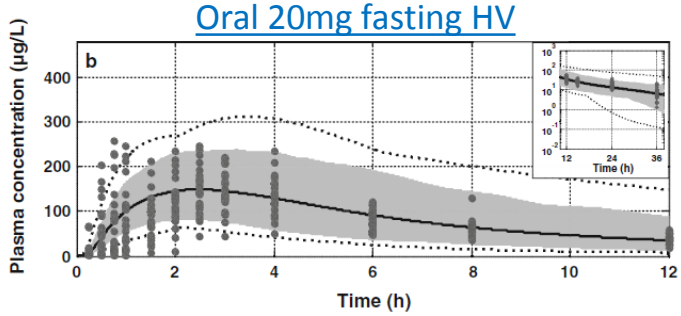
a and c are for the 10mg/70kg dosing regimen

Adult PBPK model qualification:

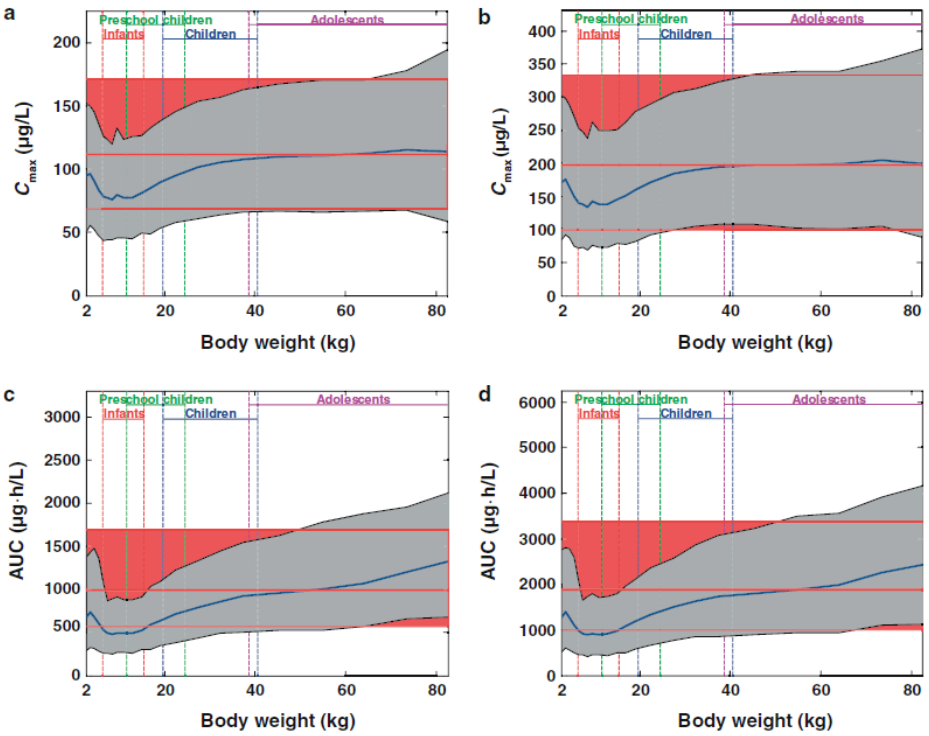
iv 1 mg HV



Oral 20mg fasting HV



Paediatric PBPK model of Rivaroxaban:



Zhao et al, 2011 Clin. Pharm. Ther

b and d are for the 20mg/70kg dosing regimen

Medium impact

Willmann S et al Clin Pharmacokinet. 2014 Jan;53(1):89-102.

Are the 3 proposed qualification processes suitable?

- **Process 1:**

  CHMP qualification

  (EMA/CHMP/SAWP/72894/2008/Rev.3)

- **Process 2:**

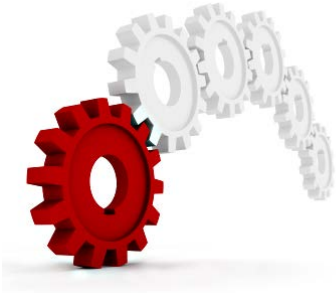
  Qualification included in the application

- **Process 3:**

  Through e.g. learned societies

Are the 3 proposed qualification processes suitable?

- The PBPK platform and compound level information can be qualified separately.
  - EFPIA companies consider platform qualification and drug libraries are the vendors' responsibility.
  - New chemical entity (NCE) data is the responsibility of the sponsor.
- How would the CHMP 6 months lead time for this process work with software version renewal?
  - How often qualification should be repeated for a new platform version?
  - What about small addition of code?



Are the 3 proposed qualification processes suitable?

- Range of physiochemical and pharmacokinetic properties tested in platform qualification define degree of interpolation and extrapolation for an NCE.
- What if there are no known examples of other compounds undergoing a particular route of metabolism? This increases degree of extrapolation.
- For sponsor's tailored made PBPK platform, is qualification via pre-specified analysis plan an option?
- Who are the learned societies and what could be their motivation to undertake qualification on behalf of industry and regulators?
- What qualification/ validation information (including a PIP) to provide to regulators?

What are potential benefits and problems with the qualification approach outlined in the guideline?

Benefits:

- Understanding of regulatory expectations
- Potential harmonisation across industry, vendors and agencies
- Easier review of the submission

Problems:

- Restricts the applications of PBPK that are submitted to the agencies: obscures the internal decision process
- Restricts the scientific development to the prescribed applications
- Encourage reliance on commercial platforms over bespoke model building
- Who ultimately has responsibility for qualification of PBPK platform?
- PBPK refers to a broad family of models so there is risk for ambiguity and inconsistency

In a constructive way - what changes to propose?

- Define the concepts of predictive performance and adequate precision
  - Is this intended use and impact dependent?
  - Is this dependent on novelty of assumptions?
- Clarify whether the qualification procedure has to be pre-specified.
  - Can pre-specification work with the iterative data integration paradigm of PBPK?
- More clarity on other common uses of PBPK.
  - Biowaivers, extrapolation to special populations, food effect
- Provide information on medium and low impact applications and consequences associated with the software qualification
- Qualified commercial platforms should be made publically
- Linkage to existing guidance and white paper

Summary

We welcome the guidance and are keen to work with EMA to put appropriate practice in place and that our constructive feedback indicates the companies willingness to work with EMA on developing a practice that works well for all parties

Acknowledgements

- EFPIA members companies
- EFPIA MID3 workgroup

Thank you.

Backup

In a constructive way - what changes to propose?

Backup

- A discussion of where iv. dosing data might be necessary for orally dosed drug
- Is the guidance applicable to parent drug only or (active) metabolites?
- Provide a clear definition of a PBPK model versus other types of modelling
- Define the term “external data”
- Clarify how many compounds should be included in a qualification

- Clarify how good prediction for DDI involving an enzymes express at multiple sites in the body should be demonstrated

In a constructive way - what changes to propose?

Backup

- PBPK is a method of extrapolation so reference to other guidance documents is important for consistency:
  - Reflection Paper on Extrapolation of Efficacy and Safety in Paediatric Medicine Development (EMA/199678/2016)
  - ICH-E11 guidance

- Also links should connect with other guidance and white papers:
  - Guideline On Reporting The Results Of Population Pharmacokinetic Analyses
  - In decreased renal function (CHMP/EWP/225/02) or hepatic function (CPMP/EWP/2339/02)
  - PBPK white paper by Jones et al 2015 and MID3 White paper by Marshall et al 2016

Assumption setting, evaluation, impact assessment: examples

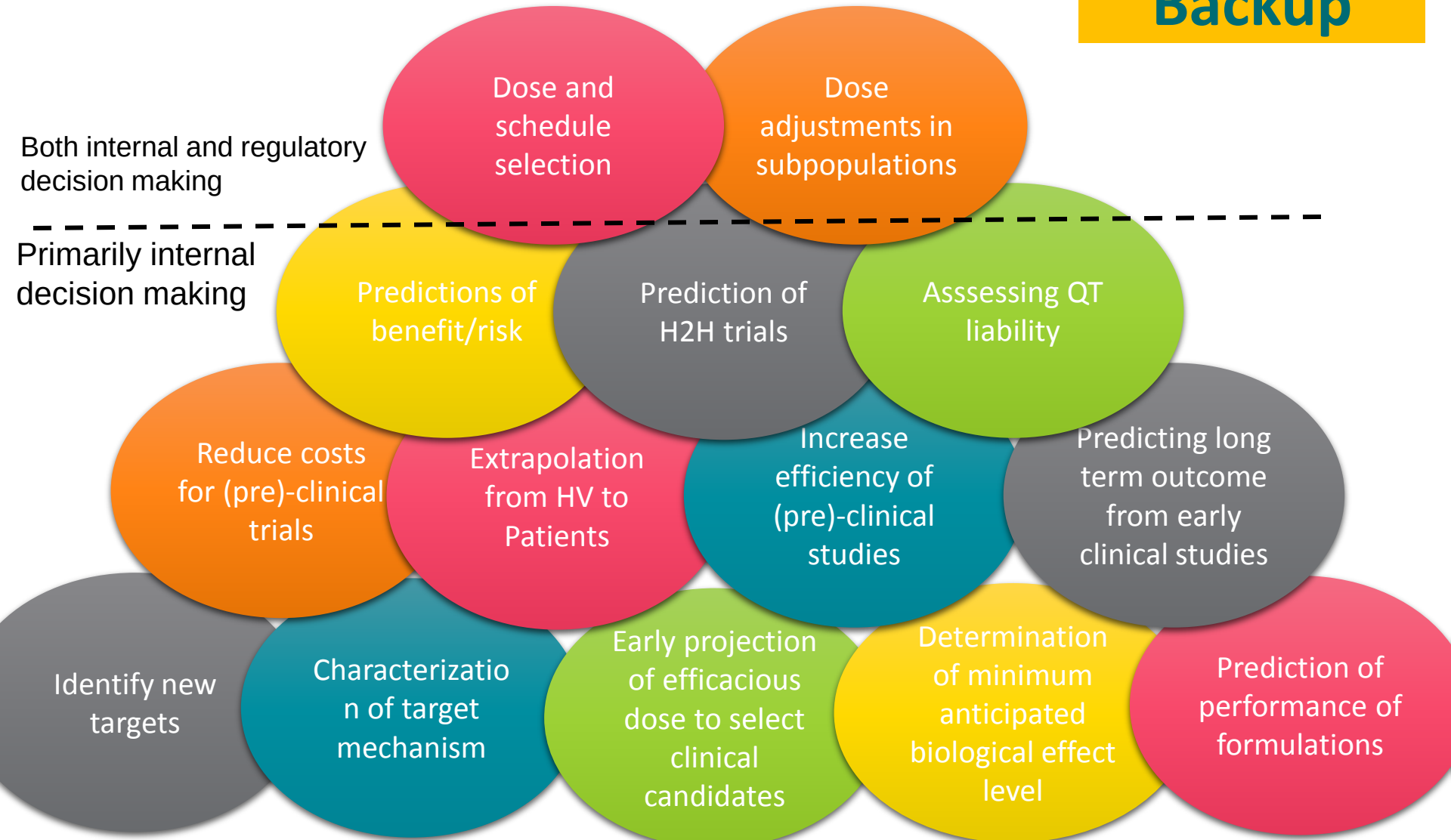
Backup

Important assumptions	Justification	New/ established	Testable/ not-testable	Test/approach to assess impact	Evaluation
Pharmacological assumption Emax model fixed to 100% is a more physiological description of the data compared to a linear model.	Emax model is not better than linear model; however, for this drug class, Emax of 100% is more realistic	New	Testable with a wider range of concentrations (external/ future study).	Comparison of simulated metrics of interest between the two competing models.	To achieve a 90% response (assumed to be clinically meaningful) requires a twofold higher dose using the Emax model compared to the linear model. ➔ Test doses suggested by Emax model in Phase 2.
Physiological assumption No difference in clearance between healthy subjects and patients.	Patients with major depression disorders are considered as healthy subjects (in regard of ADME/PK features) once age and weight are taken into account.	Established	Testable by pooling healthy subjects and patient data, assuming that all other qualities across the pooled trials are exchangeable.	Combined analysis with healthy subjects and patients.	Combined analysis found only a 10% lower clearance in patients. ➔ No dose adjustment necessary for PK reasons
Disease assumption: Linear progression of disease with a slope of X/year	Cannot be estimated directly from the dataset, but supported by literature review	Established	Not testable with the present dataset	Sensitivity analysis changing the value of the slope for disease progression from X to Y	Varying the slope by X and Y will not change the selected dose for P3 ➔ Selected dose for P3 can be implemented Varying the slope by X and Y will change the selected dose for P3 drastically ➔ Three different doses should be tested
Data assumption: Data below limit of quantification (BLQ) have no impact on analysis results	There are <20% BLQ concentrations after treatment	New	Testable	Run final model with BLQ using M3 method (Beal 2001[82]) and compare to model without BLQ	Negligible changes in parameter estimates ➔ Final model excluding BLQ observations selected
Mathematical and/or statistical assumption Similar variability in clearance between adults and children	Physiological and PK knowledge	New	Not testable at the stage of predictions but can be evaluated with data from children	Sensitivity analysis on the variance value of clearance	If variance is 2-fold, children would be still with the highest dose in the safety range established for adults? ➔ Suggested dosing can be used in Children

See Table 5 in white paper: http://onlinelibrary.wiley.com/doi/10.1002/psp4.12049/pdf

Applications of MID3 for internal and regulatory decision making

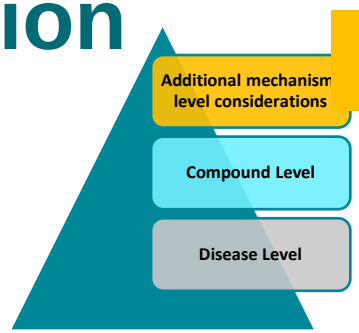
Backup



Summarizing: MID3 Strategy, Plans & Documentation

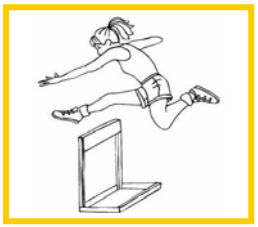
Backup

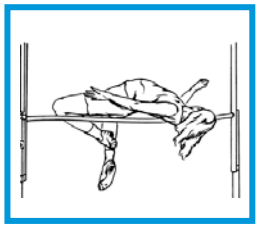
- **Strategic level**
  - key questions
  - Key themes
- **Assumptions**
- **Modelling Approach**
- **Impact Level**
  - EMA/EFPIA
- **Documentation**



Type of Assumptions
• Pharmacological
• Physiological
• Disease
• Data
• Mathematical and statistical

Empirical dose/time analysis	Empirical PK/PD	Model-based meta-analysis	(Semi) mechanistic PK/PD (PBPK)	Systems pharmacology modelling





Analysis plan	Simulation plan	Report
• Introduction	• Introduction	• Synopsis
• Objectives	• Objectives	• Introduction
• Data plan	• Additional information	• Objectives
• Data exploration	• Methods	• Data
• Methods	• Assumptions	• Methods
• Assumptions		• Assumptions
		• Results
		• Applications (prediction/simulation)
		• Discussion
		• Conclusions
		• Appendix

Development of physiologically based pharmacokinetic model to evaluate the relative systemic exposure to quetiapine after administration of IR and XR formulations to adults, children and adolescents

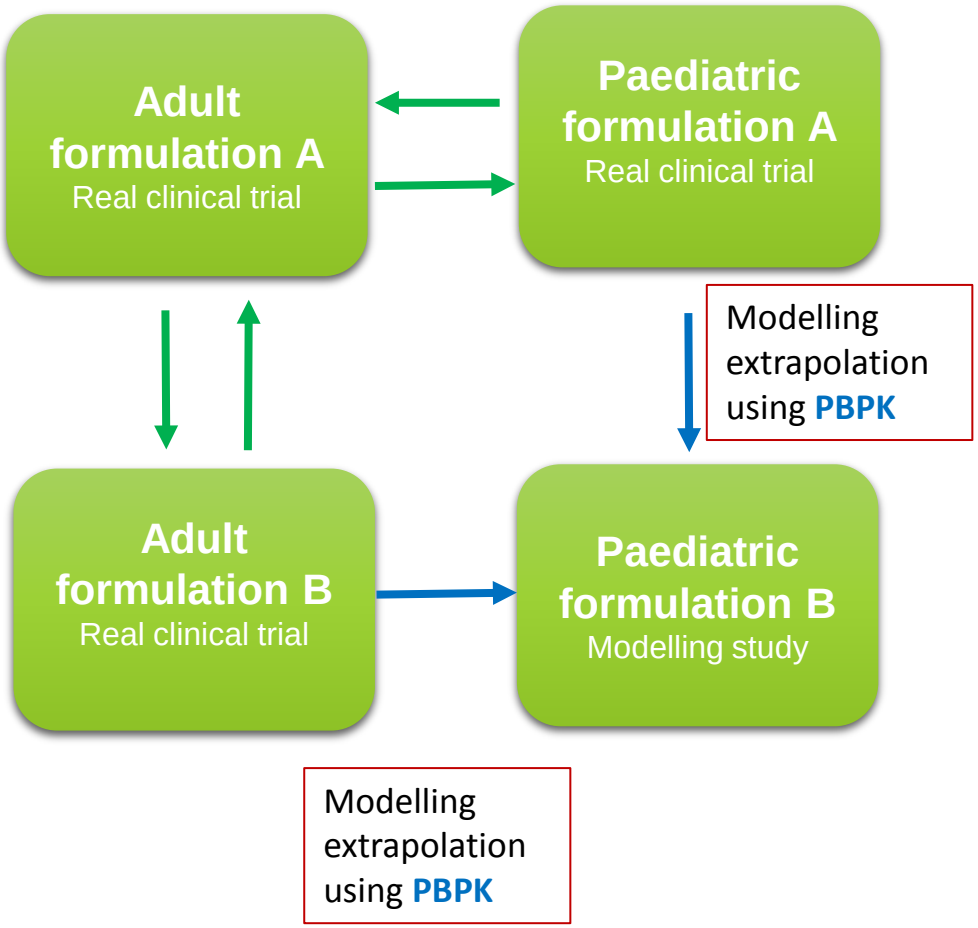
Backup

Paediatric formulation extrapolation

Assumptions:
Similar disease/progression
Similar response to treatment

Validate in adult in two formulations in **PBPK** model
Adult & Paed. PBPK Comparing PK parameters:
- •Absorption, CL/f, V
- •AUC/Cmax

Allow investigation of DDI aspects, CYPs, transporter and UGT
Ethical to avoid unnecessary trial & increase for other paediatric development



Development of a paediatric PBPK model of rivaroxaban

Backup

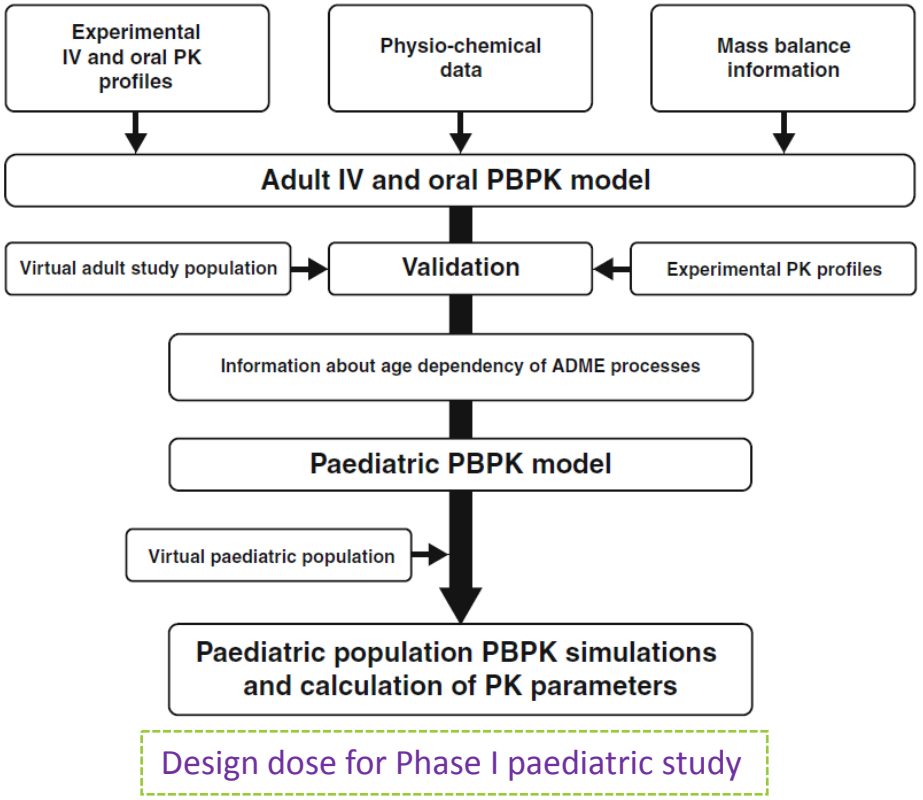
Paediatric Dose Recommendation

PBPK model (using PKsim):

- Anthropometric & physiological info.
  - Maturation and ontogeny taken into account
- 8 Phase I adult PK (HV male)
  - IV
  - Oral suspension data (10 mg and 20 mg)
  - Food effect data
  - Mass balance safety data
  - Absolute bioavailability data

Assumption & values on PBPK model:

- CYPs, GFR, the kidney P-gp transporter,
- Gastric emptying time in the fasted and the fed state
- Transit times of the small and the large intestine
- Effective surface area of intestinal sections



Willmann S et al Clin Pharmacokinet. 2014 Jan;53(1):89-102.