European Federation of Pharmaceutical Industries and Associations

Model Informed Drug Discovery and Development (MID3) Good Practice: use of prior knowledge and setting up assumptions






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on behalf of the EFPIA MID3 Workgroup

EMA Extrapolation Workshop 17th & 18th May 2015

Outline

- **MID3 and DDMoRe:** constructing the quantitative framework
  - *Brief overview of these initiatives and how they come together*
- **Use of prior knowledge and setting up assumptions**
  - *MID3 Strategy Plan, assumptions in the learn and confirm cycle, assumption table*
- **Application of MID3 to Paediatrics – Lutz Harnisch**
  - *Paediatric MID3 examples: question, activities, assumptions & impact*
- **MID3 Perspective on Extrapolation Reflection Paper**
  - *Reflections on extrapolation reflection paper based on how the MID3 whitepaper evolved*
- **Summary**

CPT: Pharmacometrics & Systems Pharmacology
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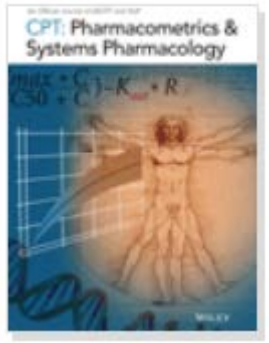

White Paper

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

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Good Practices in MID3 White Paper: Highlights

"Why" MID3 is important for decision makers

- Summary of the collated business value to-date based on available literature
- Compare and contrast different MID3 Modelling approaches
- Categorized review of 100 published case studies across Drug Discovery, Development and Life Cycle Management

"What" MID3 means for practitioners

- Premise of MID3 & Implementation strategy
- Challenges and opportunities at Pharma, Organization & Asset Levels
- EFPIA classification of MID3 Internal impact

"How" MID3 should be documented

- Basic standards in planning & reporting
- Risk Based QC/verification
- Documentation of assumptions, evaluation & impact assessment

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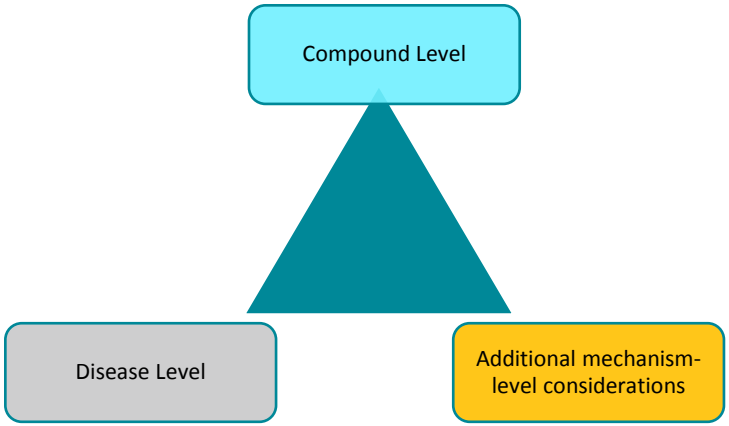
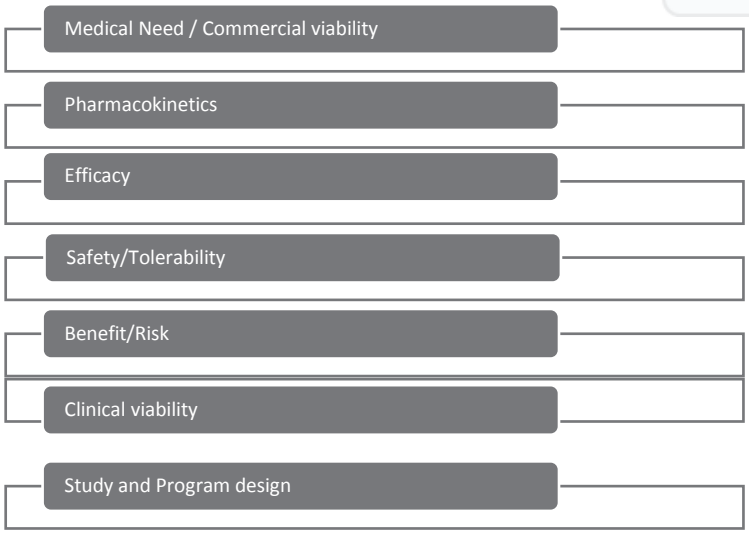
MID3 Strategic Plan: Constructed through consideration of pertinent R&D questions across level and theme ➡ Activity (Modelling approach)

- 3 Levels:



- 7 key themes:



- 5 Modelling approaches :

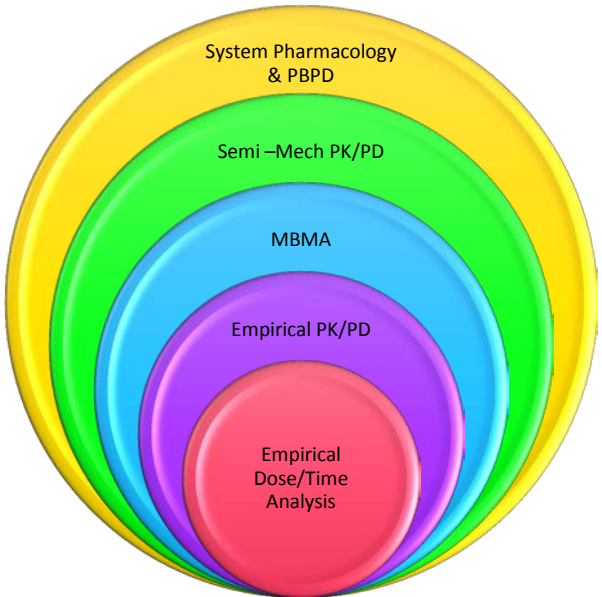


Illustration in Paediatrics

Key Themes	Disease Level		Compound Level		Additional mechanism-level considerations	
	Example questions or required knowledge?	Examples of proposed activities	Example questions or required knowledge?	Examples of proposed activities	Example questions or required knowledge?	Examples of proposed activities
Medical need/ Commercial viability						
PK	What is the impact of the disease on ADME processes in children?	PBPK model needs to include the pathophysiological link to ADME to be useful at the disease level	What is the predicted PK profile in children based on adult data?	PBPK model needs to include pathophysiological properties & translational ADME &/or Development of population PK model in adults adapted for allometric scaling & maturation of clearance processes	Based on prior compounds with a similar ADME profile, what DDI or genetic variations do we expect in children?	Use PBPK or semi-mechanistic extention to Pop PK model to investigate: i)potential for DDI based on prior in vitro data & ii) translation to DDI for other compounds with similar ADME profiles
Efficacy						
[…]						

EMA Regulatory Review of M&S

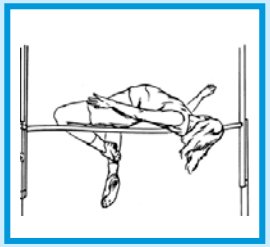
According to the impact on regulatory decision

High impact ← M&S to replace

Scientific Advice, Supporting Documentation, Regulatory Scrutiny +++

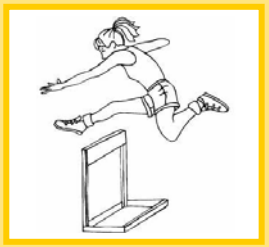
Medium impact ← M&S to justify

Scientific Advice, Supporting Documentation, Regulatory Scrutiny ++



Low impact ← M&S to describe

Scientific Advice, Supporting Documentation, Regulatory Scrutiny +



Impact on regulatory decision

Adapted from the framework proposed for M&S in regulatory review, presented at the EFPIA/EMA M&S Workshop 2011 by Terry Shepard (MHRA)

EFPIA Classification of MID3 Internal Impact

According to impact on R&D Decisions

HIGH CATEGORY IMPACT — replace –
MID3 approach provides inference which informs internal decisions without requiring additional experimental or trial data to be generated

MEDIUM CATEGORY IMPACT – inform –
MID3 approach provides inference which informs internal decisions

LOW CATEGORY IMPACT* – describe –
MID3 approach provides inference which has limited impact on internal decisions

Impact on Internal decision

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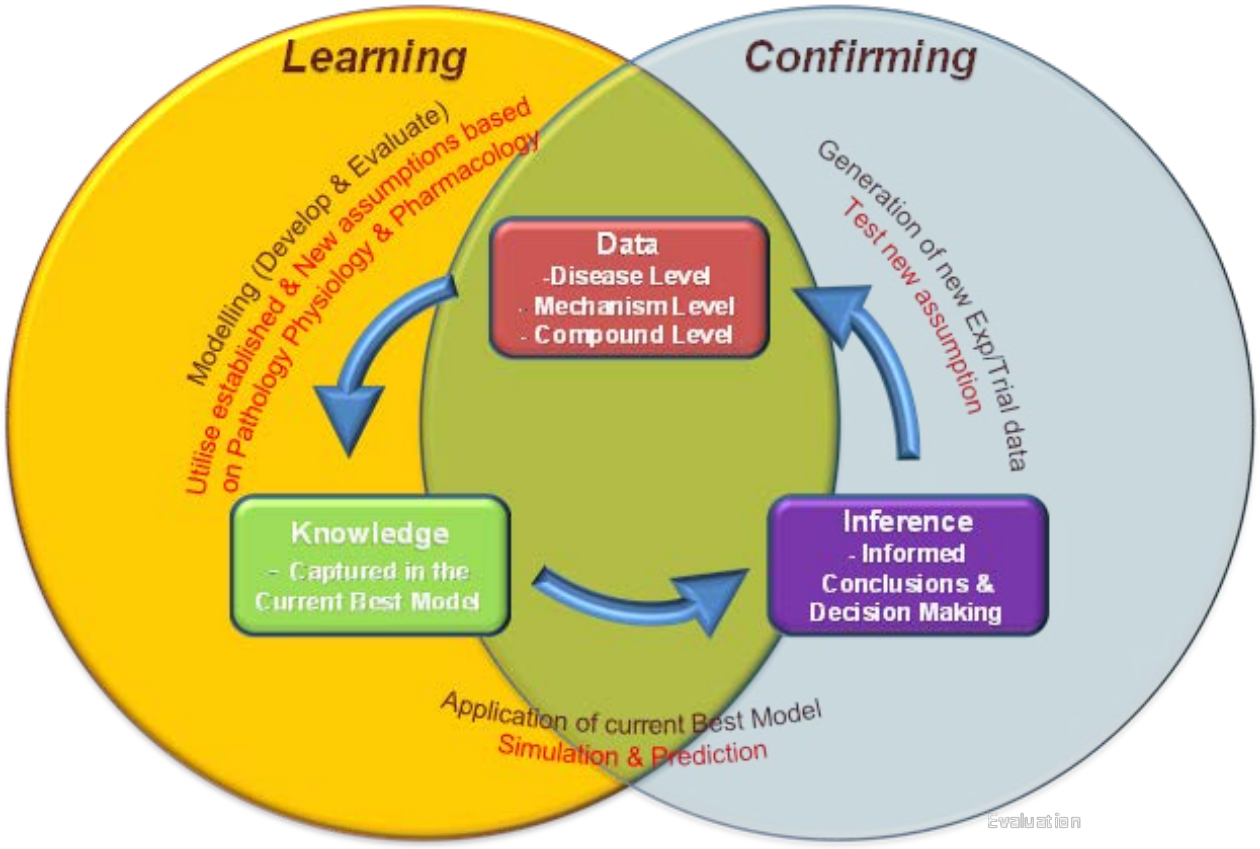
MID3: Assumptions in Learning & Confirming Cycle



''quantitative framework for prediction and extrapolation, centered on knowledge and inference generated from integrated models of compound, mechanism and disease level data and aimed at improving the quality, efficiency and cost effectiveness of decision making''

Coloured Boxes represent key steps in the "Learn and Confirm Cycle".
Arrows represent processes that link these key steps

1) Sheiner, L.B. Learning versus confirming in clinical drug development. Clin. Pharmacol.Ther. 61, 275–291 (1997).

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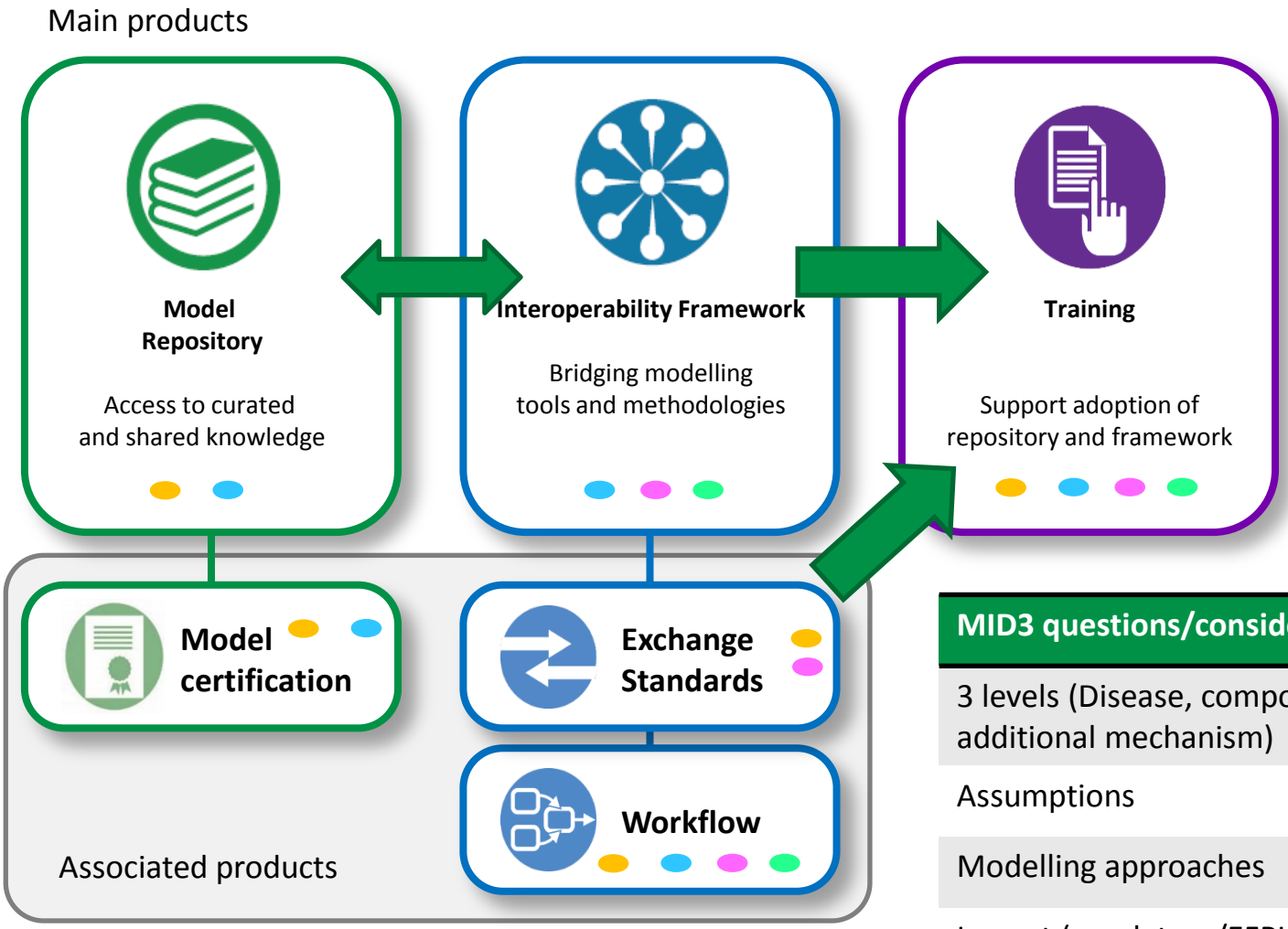
Assumption setting, evaluation, impact assessment and documentation

Important Assumptions	Justification	New/ Established	Testable/ Not-Testable	Test/Approach to assess impact	Evaluation
Pharmacological assumptions					
Physiological assumptions					
Disease assumptions-					
Data assumptions					
Mathematical and statistical assumptions					

Link between MID3 and IMI DDMoRe



MID3 questions/considerations:
3 levels (Disease, compound and additional mechanism)
Assumptions
Modelling approaches
Impact (regulatory/EFPIA)

MID3: Characterised Paediatric Examples

8 examples

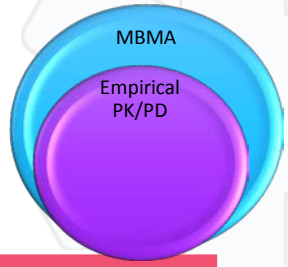
From	Disease	Compound	R&D stage
MID3	Venous thromboembolism	Rivaroxaban	Early Clinical Development
MID3	Epilepsy*	Topiramate	Late Clinical Development
MID3	Pulmonary Arterial Hypertension (PAH)*	Revatio	Late Clinical Development
MID3	Systemic Juvenile Idiopathic Arthritis (sJIA)*	Tocilizumab	Late Clinical Development
MID3	Schizophrenia	Paliperidone	Approval Phase
MID3	sugammadex-mediated reversal of rocuronium-induced neuromuscular blockade	Sugammadex/rocuronium	Life Cycle Management & Therapeutic Use
MID3	HIV	Vitamin D3	Life Cycle Management & Therapeutic Use
MID3	Schizophrenia and bipolar disorder	Quetiapin	Life Cycle Management & Therapeutic Use

*EMA/EFPIA M&S WS 2011 Break out session BOS

Source: EFPIA MID3 workgroup: Good Practices in Model-Informed Drug Discovery and Development (MID3): Practice, Application and Documentation in preparation

Revatio (Sildenafil) in PAH

Building Supporting Evidence for Paediatric Dose-Response Characterization



Strategic Question: Can the label in children with PAH be based on available children and adult data without the need for further studies?

- Orphan Indication Pulmonary Arterial Hypertension (PAH)
  - Progressive life-threatening, prevalence 2-20:1M
- Sildenafil (REVATIO®), 20 mg TID, received approval for the treatment of adult PAH in the US based on improvement in exercise capacity (6MWD) data in 2005
  - Primary EP: 6MWD, secondary EP: PVRI/hemodynamic …, PK
- Paediatric PAH trial, dose ranging (3 wt based treatment cohorts), plc controlled, 1-17 yrs old
  - Primary EP: pVO2 at week 16 (only available in 7-17 yrs)
    - 6MWD not feasible in children
  - Secondary EP: PVRI (available in all children from 1-17 yrs)
  - Pop PK to confirm scaling from adult to paediatric exposure

	Sildenafil Dose, mg		
Body Weight, kg	Low	Medium	High
≥8 to 20	NA†	10†	20
>20 to 45	10	20	40
>45	10	40	80

- Aim: Assessment of Sildenafil efficacy **and** dose selection in children with PAH
- Challenges: Clinical EP is different in children (pVO2 ~ 6MWD ?) and is not available in younger population, i.e. <7 yrs (PVRI ~ CPX ?)

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Lutz Harnisch (Pfizer) EMA/EFPIA M&S WS 2011 BOS3 http://www.emea.europa.eu/docs/en_GB/document_library/Presentation/2011/11/WC500118284.pdf

Revatio (Sildenafil) in PAH

Building Supporting Evidence for Paediatric Dose-Response Characterization

Assumption setting, evaluation, impact assessment and documentation

Important assumptions	Justification	New/ established	Testable/ not-testable	Test/approach to assess impact	Evaluation
Disease assumption: **(CPX~HD)paed= (CPX~HD)adult**	Linkage between HD changes and exercise capacity assumed to be the same in adults	New	Testable	Comparison of existing adult and paediatric data	•The relationship is similar, HD can be used for dose selection •Justify bridging of CPX~HD EPs between populations

CPX: cardio pulmonary exercise testing as measured by 6MWD in adults and pVO2 in children
HD: hemodynamics as measured by PVRI

Revatio (Sildenafil) in PAH

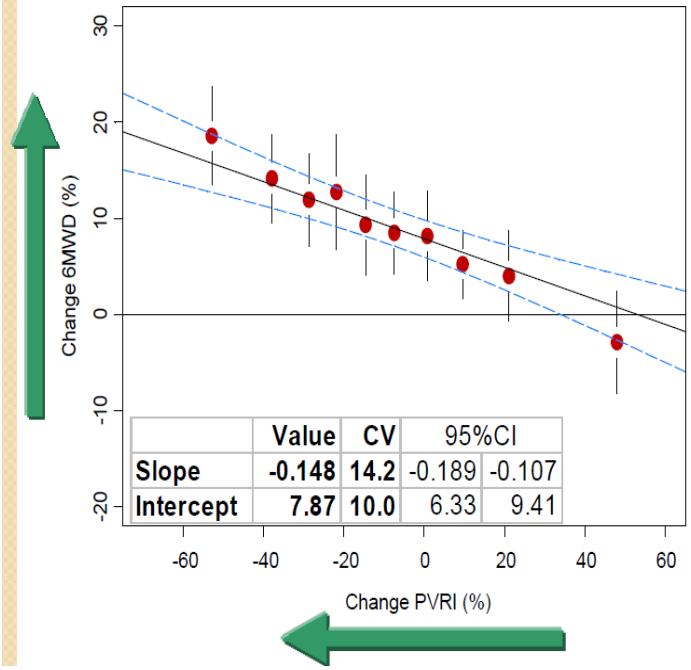
Building Supporting Evidence for Paediatric Dose-Response Characterization

MBMA

- Comparison of Sildenafil data with FDA model demonstrates adult data is consistent
- In children, pVO2 has similar relationship with PVRI

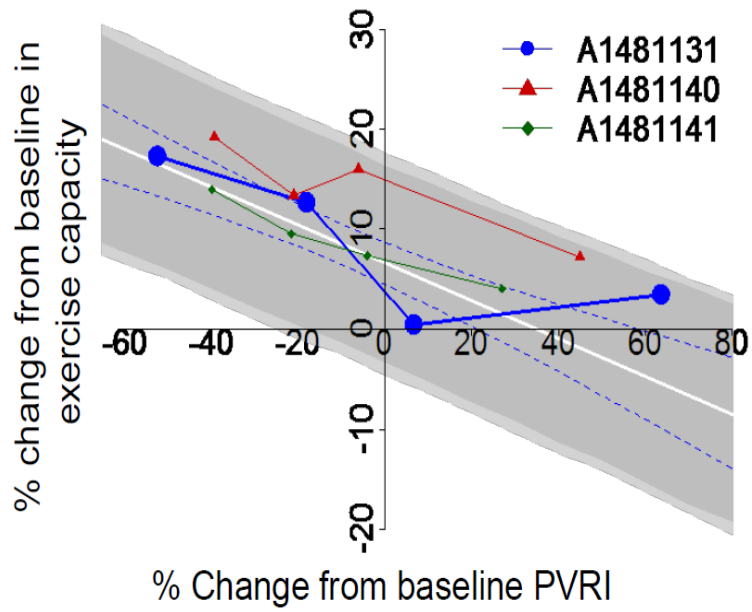
Adults

Univariate Regression of %Δ6MWD vs. %ΔPVRI for Pooled Analysis



Adults & Children

FDA based prediction interval + Sildenafil



n=30/bin (dark grey)
n=24/bin (light grey)

Source: FDA-CDER-CDRAC, 29th July 2010, Satjit Brar, Pharm.D., Ph.D., Division of Pharmacometrics, "Use of Change in PVRI for Dosing Recommendations of Adult-Approved Drugs in Pediatric PAH Patients"

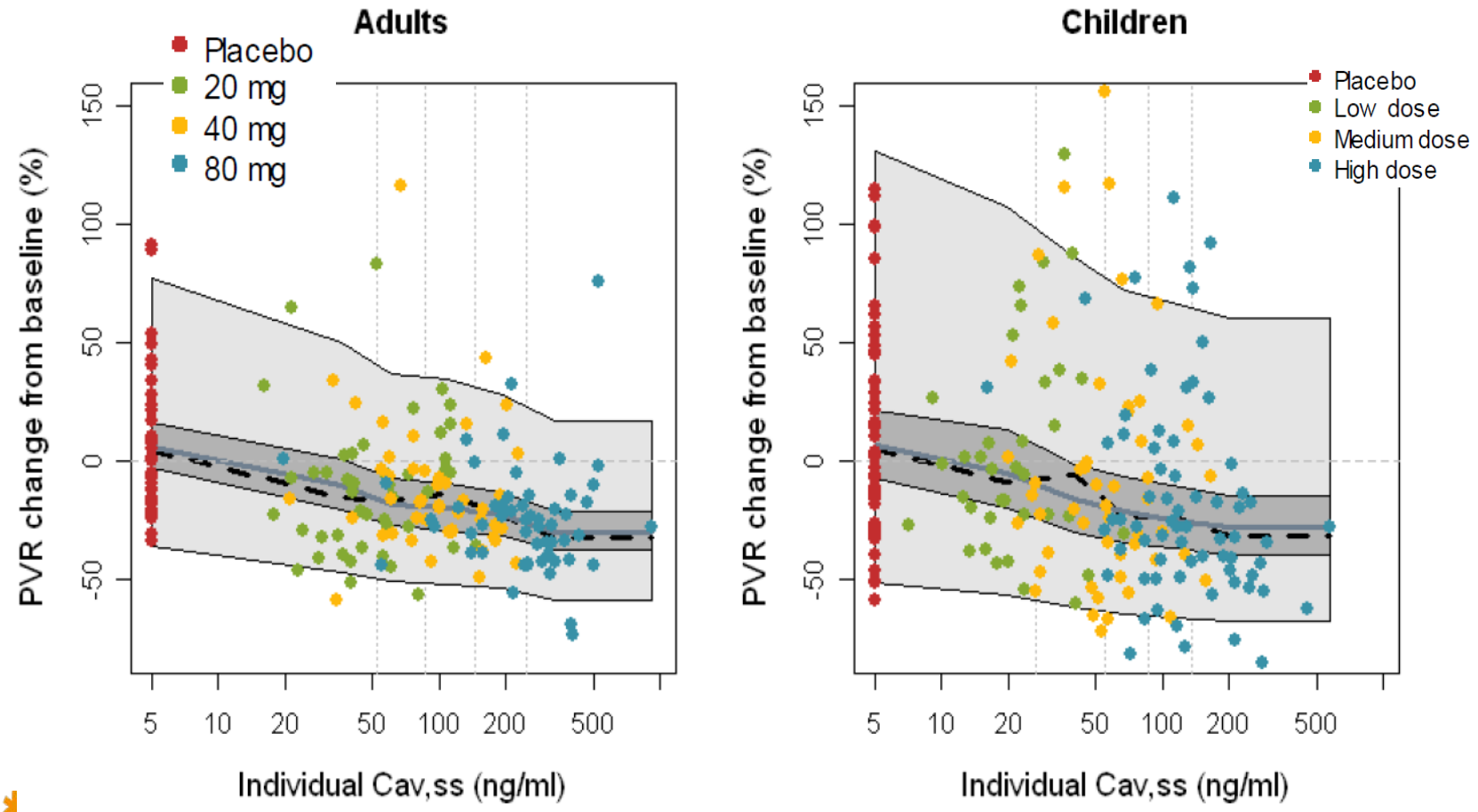
Lutz Harnisch (Pfizer) EMA/EFPIA M&S WS 2011 BOS3 http://www.emea.europa.eu/docs/en_GB/document_library/Presentation/2011/11/WC500118284.pdf

Revatio (Sildenafil) in PAH

Building Supporting Evidence for Paediatric Dose-Response Characterization

Empirical PK/PD

- Similar exposure-response relationship in adult and children for PVRI



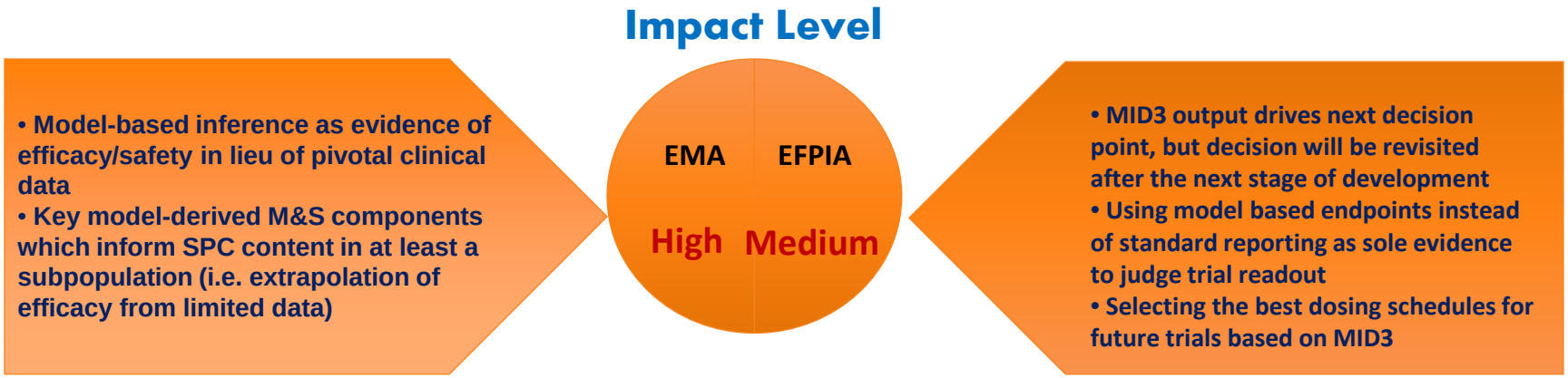
Barst et al Circulation 2012; 125:324-334

Lutz Harnisch (Pfizer) EMA/EFPIA M&S WS 2011 BOS3 http://www.emea.europa.eu/docs/en_GB/document_library/Presentation/2011/11/WC500118284.pdf

Revatio (Sildenafil) in PAH

Building Supporting Evidence for Paediatric Dose-Response Characterization

- Model based approach addressed efficacy evaluation of sildenafil in paediatric PAH population
- Labelled dose is model based. This analysis was central to the submission package and was deemed as important in the evaluation of the totality of the evidence.
- M&S could alleviate the risk of violating some assumptions on translational EPs
  - Integration of adult and paediatric data with historic data for the same indication (FDA model)
- MID3 approach provided regulatory agencies sufficient evidence to approve dose recommendations



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Summary MID3 Paediatric Examples

	Disease	Compound	R&D stage	Level	Assumptions e.g	Modelling Approach	EMA Impact	EFPIA Impact
1	Venous thromboembolism	Rivaroxaban	Early Clinical Development	Compound	Physiological	Mechanistic PKPD/PBPK	Medium	Medium
2	Pulmonary Arterial Hypertension (PAH)	Revatio	Late Clinical Development	Compound/ Disease	Disease	Model Based Meta Analysis (MBMA)	High	Medium
3	Systemic Juvenile Idiopathic Arthritis (sJIA)	Tocilizumab	Late Clinical Development	Compound	Data	Empirical PKPD	High	High
4	Schizophrenia and bipolar disorder	Quetiapin	Life Cycle Management & Therapeutic Use	Compound	Physiological, Disease	Mechanistic PKPD/PBPK	High*	High

Assumption setting, evaluation, impact assessment and documentation: Paediatrics

Important assumptions	Justification	New/ established	Testable/ not-testable	Test/approach to assess impact	Evaluation
Pharmacological **The PK/PD relationship of Tocilizumab is independent of body weight and the lower efficacy in BW<30kg is due to a lower PK exposure**	No evidence that the IL-6 signalling pathway and the IL6-R expression would differ in low body weight kids	New	Testable	Test in phase III a higher dose selected by using a PK/PD modelling approach.	Using phase III data
Physiological assumption: **Renal clearance via GFR**	Population assumed to be the same as that used to develop the equation: $GFR = \left(\left(\frac{PMA^{Hill}}{TM_{50}^{Hill} + PMA^{Hill}} \cdot (1 - GFR_{premat}) \right) + GFR_{premat} \right) \cdot Volume_{Kidney} \cdot GFR_{mat}$	Established from literature	Non-testable	NA	NA
Disease assumption: **(CPX~HD)paed= (CPX~HD)adult** **HD: hemodynamic endpoint** **CPX: cardio pulmonary exercise**	Linkage between HD changes and exercise capacity assumed to be the same as adults	New	Testable	Comparison of existing adult and paediatric data	The relationship is similar, HD can be used for dose selection Justify bridging of CPX~HD EPs between populations
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

EFPIA MID3 Perspective on Extrapolation Reflection Paper:
Covered, Emerging or Gap

"Why" Extrapolation in Paediatrics is important for All stakeholders ?

Aspect	Activity	Proposal
Value to Stakeholders	Physicians /Patients - ↑ Confidence in treatments Regulators- ↑ Confidence in decisions Pharma- ↑ Confidence in efficiency	Development of "value" proposition for all stakeholder
Approaches to extrapolation	Comparison and contrast of different approaches to extrapolation	Determine factors which govern acceptability of different approaches
Exemplify Good practice	Need categorised exemplifying case studies : MID3 (8)++	Need examples covering cycles of learning and confirming : Extrapolation Concept to Extrapolation Plan to Validation /Extrapolation to Further Validation

EFPIA MID3 Perspective on Extrapolation Reflection Paper:

Covered, Emerging or Gap

"What" Extrapolation means for Practitioners?

Aspect	Activity	Proposal
Premise	Clarity of Extrapolation Concept for Paediatrics	Agree a standard definition for the extrapolation framework and set of rationales
Implementation	Development of extrapolation concept plan of activities	Utilise MID3 style "Strategic Plan -Question based approach" with considerations extracted from Table 1
Implementation	Balancing the present aspirational goal against the likely probability of success	Stepwise practical implementation & reflection at future points in time
Challenges and opportunities for Pharma & Regulators	Identify the hurdles in order to return value to all stakeholders	Joint EFPIA/EMA group to identify and address challenges, opportunities and solutions leading up to implementation
Process to gain alignment between Pharma & Regulators	Align on key questions, activities, assumptions & impact assessment	Agree actions to progress at end of workshop

EFPIA MID3 Perspective on Extrapolation Reflection Paper:

Covered, Emerging or Gap

"How" Extrapolation should be Documented?

Aspect	Activity	Proposal
Standards in planning & reporting	Recommend MID3 standards in planning & reporting are used	Make linkage to MID3 good practice clear in further rollout. Consider specifics for extrapolation
QC/QA	MID3 Risk Based QC/verification applies	Use MID3 construct and look to DDMoRe for further evolution to reproducible research
Model Evaluation & qualification/ validation	Assumptions: Documentation, evaluation & impact assessment	Utilise MID3 assumption table in plans and reports Extent & evaluation of sensitivity analysis

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Summary

- **Application of** MID3 concepts key for paediatric drug discovery and development (EMA/EFPIA Impact Med to High)
- **PIP**: requires sharing and alignment on MID3 strategic plan between sponsors and regulatory authorities
  - MID3 tools e.g. assumption table and documentation standards will help increase the transparency and facilitate regulatory review of future PIPs
- **EFPIA MID3 Perspective on Extrapolation Reflection Paper**
  - "Why" – Generally covered but gaps in value for Pharma & need for examples across L&C cycles of extrapolation
  - "What"-Premise covered but gaps in the implementation- MID3 strategic plan approach is provided as a proposal
  - "How"- Generally covered by MID3 good practice

Objectives of Session 2

- Showcase the methods available for evidence synthesis
- Showcase how to build confidence in clinical decision making based on these methods and how to communicate/document the numerical approaches to clinicians and regulators and vice versa
- Setting up the assumptions and manage the uncertainties in decision making

Points to be addressed are:

- How can we communicate/document the
  - strength of the synthesised evidence?
  - implication of uncertainties?
- What do we need to set-up explicit predictions of differences in PK, PK/PD across different age ranges, the nature of disease (manifestation, severity, progression, etc.), and clinical response to treatment in the target population as compared to the source population?
- Can we include in the trials endpoints the objective to investigate similarity of disease, beyond confirmation of efficacy and safety?
-

Implementation of Extrapolation Framework
(High level “Agreements” identified from Sessions 2 /6)

- Associated MID3 & statistical approaches and qualitative or semi-quantitative integration activities should be based on agreed strategic questions utilising MID3 terminology and overarching considerations from Table 1 of extrapolation framework document
- Alignment and debate between regulators and pharma should centre on the key strategic question, associated activity, assumptions and intended inference
- Implementation of extrapolation framework require a clear, efficient, transparent and consistently implementable process to gain this alignment
- A staged manner of implementation is recommended in order to learn and adapt process and requirements
- Publically available examples showing evolution in terms of learning and confirming across the extrapolation roadmap will be required
- Identify and openly address/harness upfront both the challenges and opportunities for EFPIA and EMA with respect to framework implementation

EFPIA MID3 proposed rationale, definitions and “agreements”

Goal (Overall Objective)

"To facilitate rapid access to safe and effective Paediatric medicines through integration of all relevant prior knowledge, subsequently informed by optimal designed /analysed studies/experiments utilising the most appropriate quantitative approaches, which implement established or appropriately evaluated assumptions to maximise efficiency in learning phase and provide replacement confirmatory level inference when necessary and /or appropriate."

Definition of Extrapolation Framework
(Adapted from the reflection Paper)

- Utilises both statistical and/or physiologically/ pharmacologically based models to provide inference and extrapolate with respect to drug action in both partial studied and unstudied situations with the aim of informing treatment for Paediatric patients
  - MID3 approaches with in a wider statistical framework

- May utilise more qualitative or semi-quantitative integration approaches to extract knowledge from KOLs (e.g. elicited priors) or literature (e.g. systematic review), particular with respect to similarity of disease or standard of Care treatment

Rationale for Extrapolation Framework (High level "Agreements" from session 1)

- There is a **clear need** from the point of view of patients, physicians, regulators and pharma to utilise an extrapolation framework in development and labelling of medicines for Children.
- It is inefficient, sometimes unethical or indeed impossible to conduct trials and experiments to gather independent evidence to answer all associated drug development questions
- Model based inference from an adequately qualified/ validated model based on established assumptions or sufficiently evaluated new assumptions should be used to inform further trials or experiments or partially or fully replace the need for them.
- A wide variety of quantitative analytical tools are currently available in order to implement the extrapolation framework. New and established methodological approaches will continue to be developed.
- Dedicated approaches to ensure integration of knowledge & abilities across disciplines in the regulatory authorities and across Pharma is required for successful implementation, e.g. clinicians, statisticians and clinical pharmacologists/Pharmacometricians etc etc working together

Objective of Extrapolation Framework
(High level "Agreements" from Sessions 2-5)

To allow:

- Efficient Design of Paediatric trials and related preclinical experiments
- Efficient Analysis of emerging data using estimation approaches and/or approaches informed by prior knowledge
- Informed decision-making in the interpretation and knowledge extraction from generated data
- Derive inference based directly on estimated model parameters or via subsequent simulations to both partial studied and unstudied situations
  These inference include but are not limited to:
  1) Appropriate dose choice in the various age groups
  2) Conclusion on Efficacy and safety and the benefit-risk balance in the target population.

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