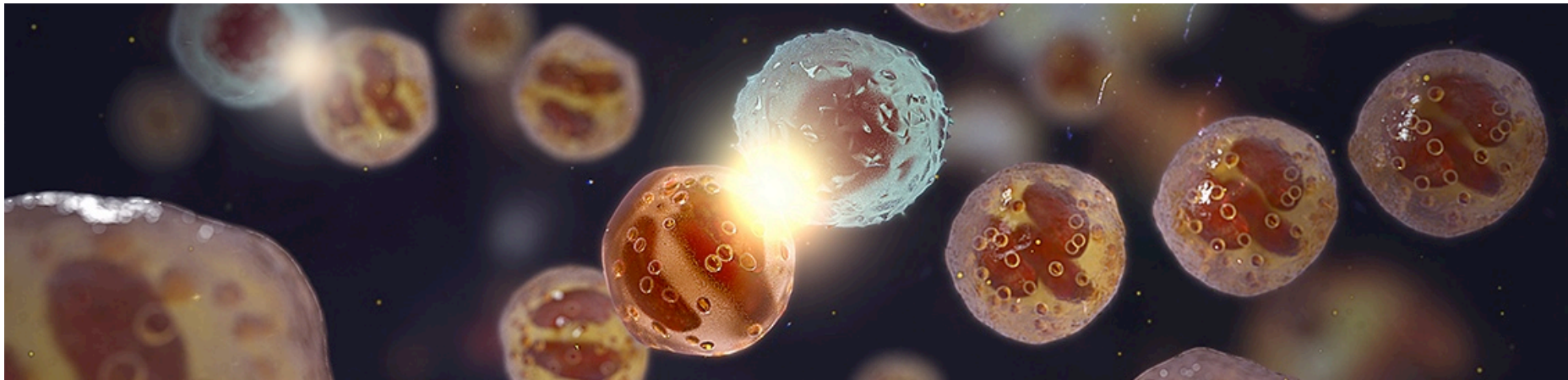


ICH E11 Revisions and Pediatric Model Informed Drug Development and Simulation

Solange Corriol-Rohou, MD

FDA Workshop: Pediatric Trial Design and Modeling: Moving into the next decade

8 September 2017



Content

- Revision of the ICH E11 guideline
 - Why a section on M&S?
- EFPIA MID3 work group
 - The MID3 white paper
 - MID3 and paediatric drug development - examples
- Conclusion & Next steps



ICH E11 – the journey



US – BPCA/PREA



EU – Regulation 1901/2006

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL
REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN
USE

ICH HARMONISED TRIPARTITE GUIDELINE

CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS
IN THE PEDIATRIC POPULATION
E11

Current *Step 4* version
dated 20 July 2000

Step 5
Jan. 2001

15 years later

INTERNATIONAL COUNCIL ON HARMONISATION OF TECHNICAL
REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

ADDENDUM TO ICH E11: CLINICAL INVESTIGATION OF
MEDICINAL PRODUCTS IN THE PEDIATRIC
POPULATION

E11 (R1)

Current *Step 3* version
dated 20 July 2017

Step 4
Aug. 2017

ICH E11 CP



June 2014



Scope

E11(R1) addendum supplements the current E11 guideline in several areas, reflecting various progress in paediatric drug development, especially in extrapolation, modelling and simulation, and trial methodology

E11 and E11(R1) include consideration points for planning and executing paediatric drug development in several specific areas of timing of development, types of studies, age categories, and ethical consideration

Contents of E11(R1) addendum

- INTRODUCTION
- ETHICAL CONSIDERATIONS
- **COMMONALITY OF SCIENTIFIC APPROACH FOR PEDIATRIC DRUG DEVELOPMENT PROGRAMS**
- AGE CLASSIFICATION AND PEDIATRIC SUBGROUPS, INCLUDING NEONATES
- **APPROACHES TO OPTIMIZE PAEDIATRIC DRUG DEVELOPMENT**
 - **The Use of Extrapolation**
 - **The Use of Modelling and Simulation**
- PRACTICALITIES IN THE DESIGN AND EXECUTION OF PAEDIATRIC CLINICAL TRIALS
- PAEDIATRIC FORMULATIONS

APPROACHES TO OPTIMIZE PAEDIATRIC DRUG DEVELOPMENT

The Use of Extrapolation in Paediatric Drug Development

“Paediatric Extrapolation” defined as an approach to providing evidence in support of effective and safe use of drugs in the paediatric population when it can be assumed that **the course of the disease and the expected response to a medicinal product** would be **sufficiently similar in the paediatric and reference population** (adult or other paediatric).

Paediatric extrapolation will be addressed further in a future ICH guideline as endorsed by the ICH Assembly.

APPROACHES TO OPTIMIZE PEDIATRIC DRUG DEVELOPMENT

The Use of M&S in Paediatric Drug Development

- Advancement in clinical pharmacology and quantitative M&S techniques has enabled progress in utilising model-informed approaches in drug development.
- M&S can help quantify available information and assist in defining the design of paediatric clinical studies and/or the dosing strategy.
- Considering the limited ability to collect data in the paediatric population, M&S can be a tool to address knowledge gaps.

The Use of M&S in Paediatric Drug Development Approach

- The incorporation of M&S into paediatric drug development should be based on a strategic plan through multidisciplinary discussions.
- Several points should be considered, including the intended use of the model itself, the quality and the extent of the existing data, and the assumptions made.
- Important to consider the maturation of organ systems, acknowledging that data from older subgroups may not necessarily be informative for the younger subgroups.
- Risk assessment of clinical and statistical consequences of a specific approach should be discussed with experts.
- Risks associated with accepting the M&S assumptions should be assessed and managed prospectively.

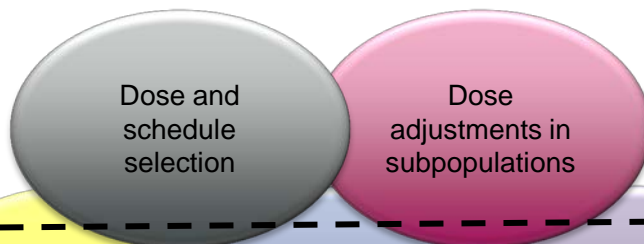
Terminology

- MIDD (Model Informed Drug Development) is in use in the US
- MID3 (Model Informed Drug Discovery and Development) is in used in Europe
- M&S (Modelling & Simulation) is in use in Japan

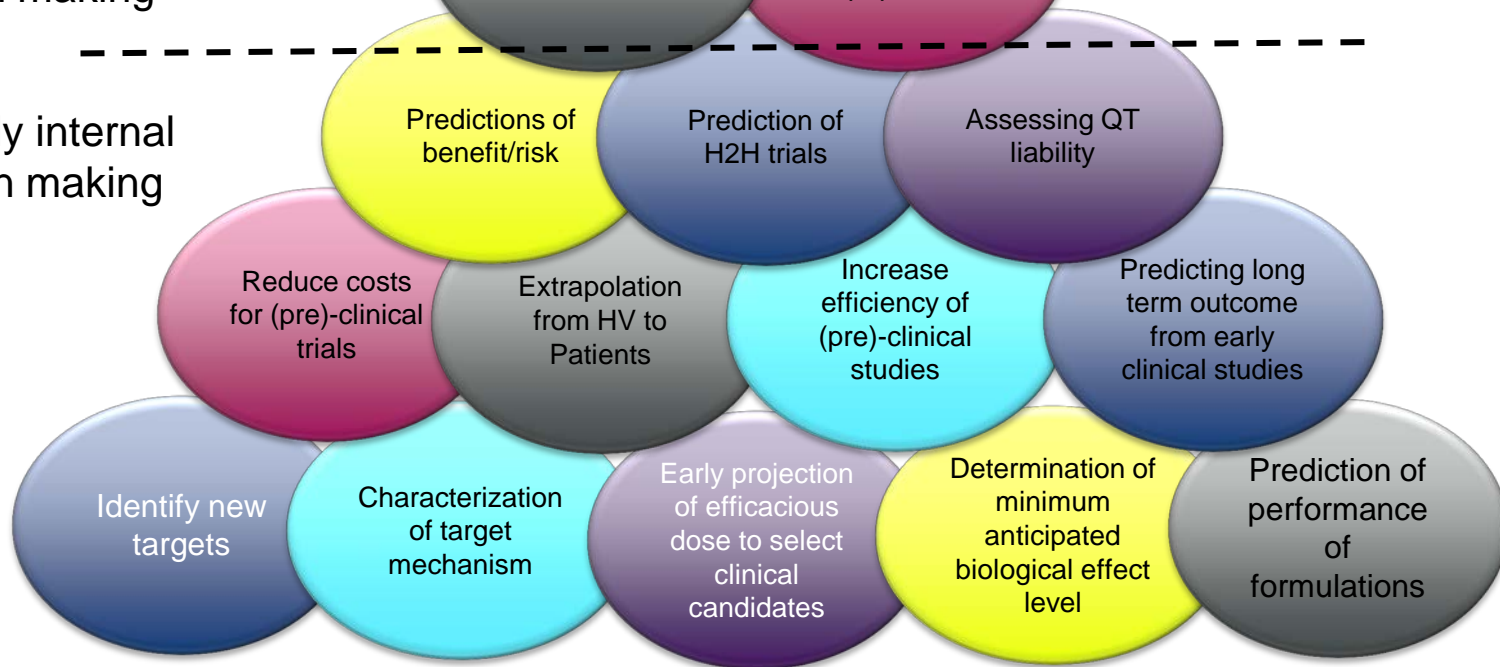


Applications of MID3 for internal and regulatory decision making

Both internal and regulatory
decision making

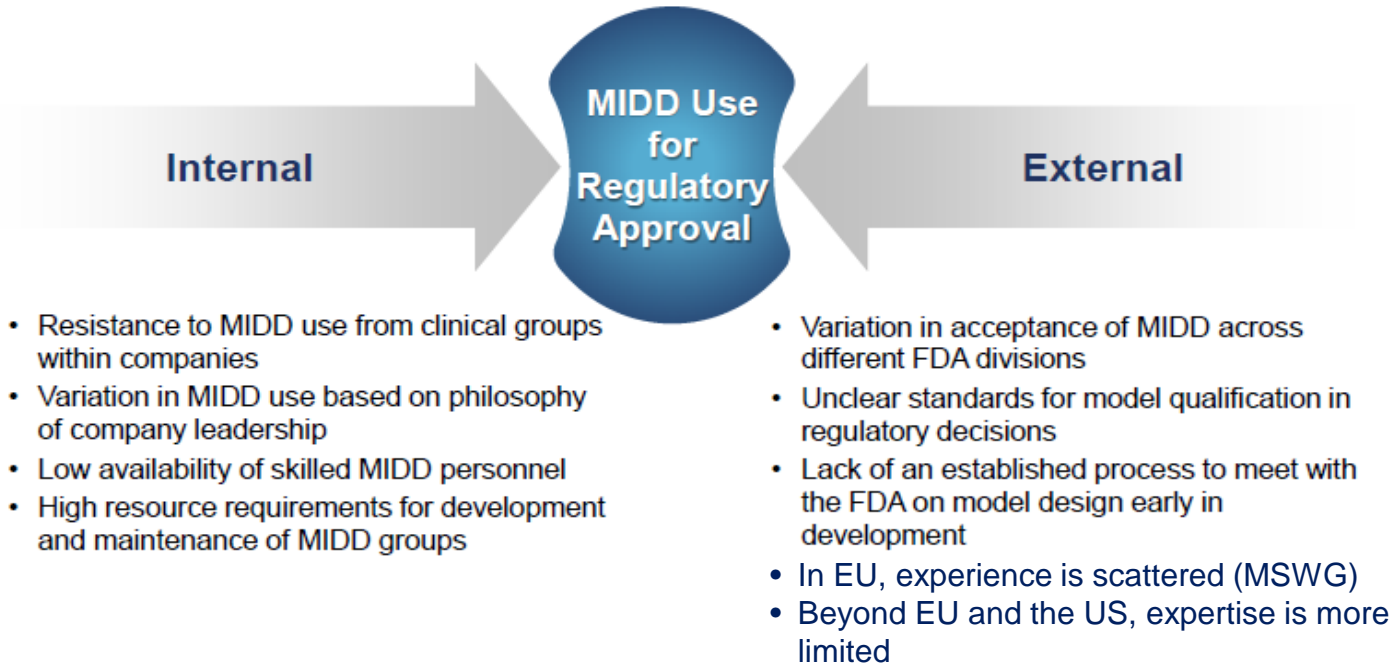


Primarily internal
decision making



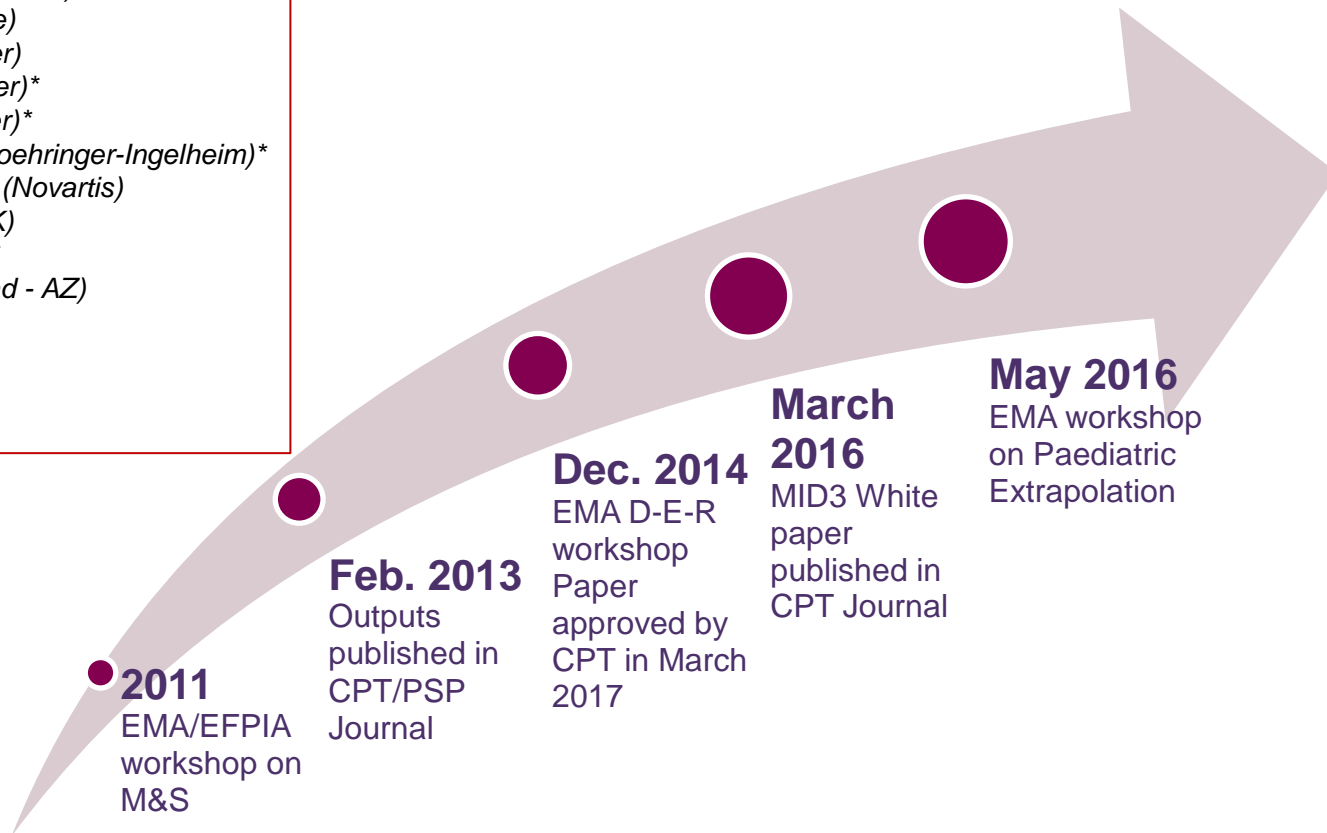
Barriers for use in the regulatory context

Lack of organisation-wide acceptance of M&S inside member companies
and uncertainty about regulators' comfort level
which limit industry's use of M&S in regulatory submissions



THE EFPIA MID3 WORK GROUP – the journey

Marylore Chenel (Servier)
Nicolas Frey (Roche)
Lutz Harnisch (Pfizer)
Scott Marshall (Pfizer)*
Peter Milligan (Pfizer)*
Alexander Staab (Boehringer-Ingelheim)*
Jean-Louis Steimer (Novartis)
Sandra Visser (GSK)
Anne Chain (MSD)*
Solange Rohou (lead - AZ)
Amy Cheung (AZ)
James Yates (AZ)
Bengt Hamrén (AZ)
Dinko Rekic (AZ)



The EMA/EFPIA M&S WORKSHOP (Dec. 2011)

Objectives

- Discuss the role and scope of M&S in drug-development from both the developer's and the regulator's perspectives
- An opportunity for industry, academia and regulators:
 - To learn from each other
 - Create greater awareness
 - Share experiences
 - Identify gaps and future opportunities



Outputs



Opportunities identified in Dec. 2011 and progress so far

Opportunities	Key Challenges	Actions	Progress
Robust informed R&D decision making - Improve R&D efficiency	<ul style="list-style-type: none"> MID3 - underutilized & undervalued by Pharma Communication gap between modellers & non-modellers 	<ul style="list-style-type: none"> Develop Common understanding in terms of the practice, application and value of MID3 	<ul style="list-style-type: none"> Good Practices in MID3 White Paper: Why, What & Challenges /Opportunities for Pharma. companies
Robust informed R&D regulatory assessment <ul style="list-style-type: none"> Inform Risk Benefit assessment Greater acceptance in extrapolation and other medium & high impact Regulatory Decisions 	<ul style="list-style-type: none"> Heterogeneity of MID3 reporting in submissions 	<ul style="list-style-type: none"> EFPIA to agree basic documentation standards for submissions 	<ul style="list-style-type: none"> Good Practices in MID3 White Paper: How (Documentation)
	<ul style="list-style-type: none"> Variable readiness of EMA & other agencies to evaluate MID3: staff & lack of guidelines 	<ul style="list-style-type: none"> EMA to form and evolve MSWG Develop guidelines 	<ul style="list-style-type: none"> MSWG Formed 2013 Activity reports 2013, 2014, 2015, 2016 Development of MID3 regulatory guideline planned via ICH
	<ul style="list-style-type: none"> Misperception that dose response is only company risk 	<ul style="list-style-type: none"> Host workshop and evolve Dose Response practice & Review 	<ul style="list-style-type: none"> Workshop held Dec 2014- EFPIA/EMA Report, publications Review templates to be updated Formation of expert group to drive outputs
	<ul style="list-style-type: none"> Communication gap between modellers & non-modellers 	<ul style="list-style-type: none"> Host workshops involving multifunctional group 	<ul style="list-style-type: none"> Extrapolation Workshops (EMA Sept 2015, EMA/EFPIA May 2016) PBPK WS (EMA/EFPIA Nov. 2016) Qualification Procedures x3 with Key M&S component
	<ul style="list-style-type: none"> Data Sharing 	<ul style="list-style-type: none"> Strengthen data sharing initiatives 	<ul style="list-style-type: none"> IMI DDMoRe (2016) / Access to Clinical Trial Data



Scope of M&S in regulatory submission as experienced by MSWG

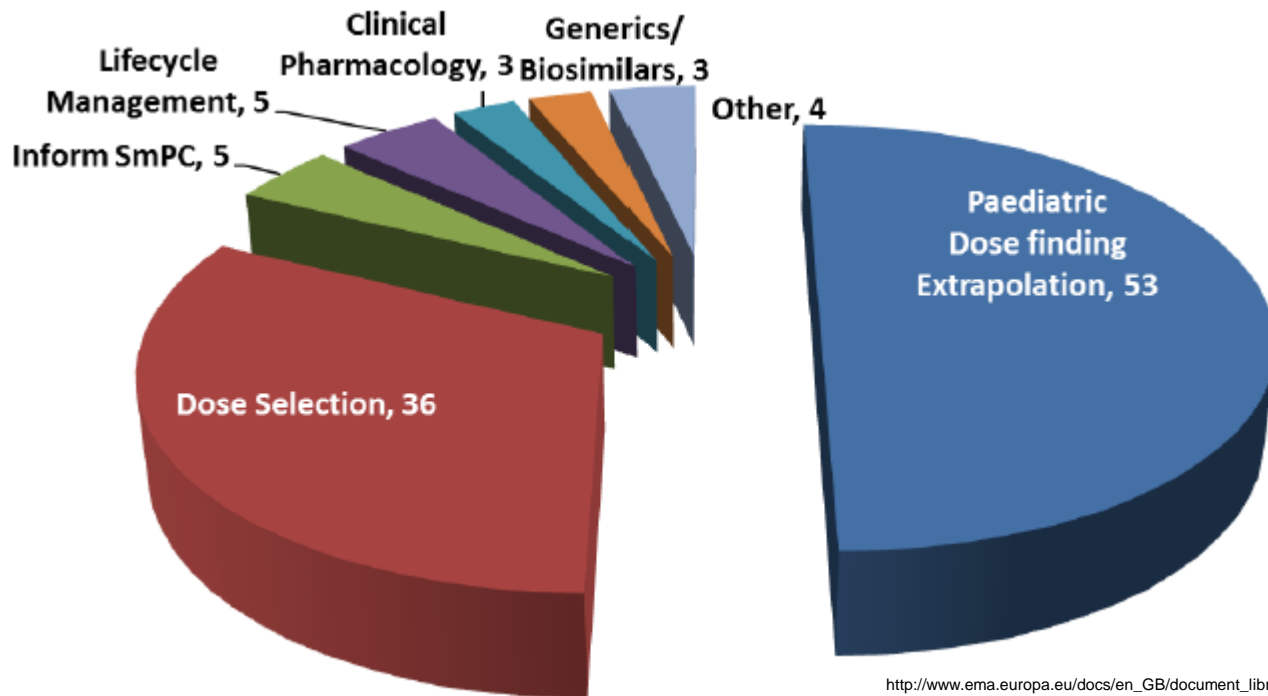
MSWG was established in 2013



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

December 2016
EMA/800956/2016

2016 Activity report of the Modelling and simulation working group (MSWG)



WHITE PAPER

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

EFPIA MID3 Workgroup: SF Marshall^{1*}, R Burghaus², V Cosson³, SYA Cheung⁴, M Chenel⁵, O DellaPasqua⁶, N Frey³, B Hamrén⁷, L Harnisch¹, F Ivanow⁸, T Kerbusch⁹, J Lippert², PA Milligan¹, S Rohou¹⁰, A Staab¹¹, JL Steimer¹², C Tornøe¹³ and SAG Visser¹⁴

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)

And CHMP members:

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

Abstract:

<http://onlinelibrary.wiley.com/doi/10.1002/psp4.12049/abstract>

Paper:

<http://onlinelibrary.wiley.com/doi/10.1002/psp4.12049/pdf>

Supplemental info:

<http://onlinelibrary.wiley.com/doi/10.1002/psp4.12049/supinfo>

Podcast:

[http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2163-8306/homepage/podcasts.htm](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

- 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



Summarizing: MID3 Strategy, Plans & Documentation

- **Strategic level**

- key questions
- Key themes

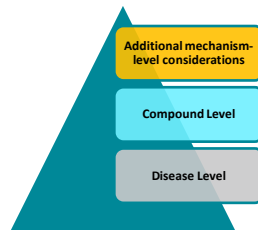
- **Assumptions**

- **Modelling Approach**

- **Impact Level**

- EMA & EFPIA
- Describe/Justify/Replace

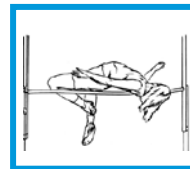
- **Documentation**



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
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Analysis plan	Simulation plan	Report
<ul style="list-style-type: none"> • Introduction • Objectives • Data plan • Data exploration • Methods • Assumptions 	<ul style="list-style-type: none"> • Introduction • Objectives • Additional information • Methods • Assumptions 	<ul style="list-style-type: none"> • Synopsis • Introduction • Objectives • Data • Methods • Assumptions • Results • Applications (prediction/simulation) • Discussion • Conclusions • Appendix



Applications of MID3 in public domain

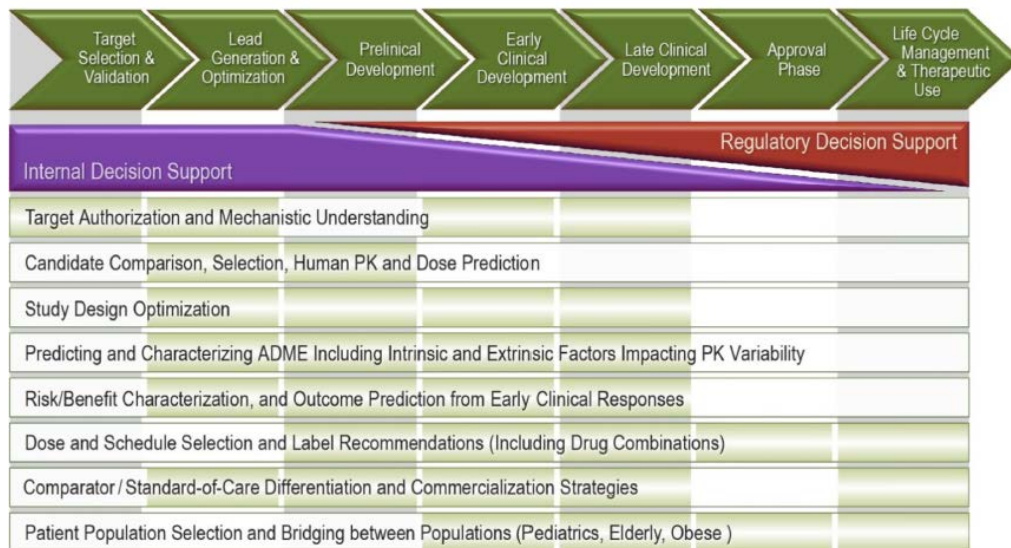
- **About 100 case studies arranged by Application Type and R&D stages**

- ~30 exemplified in document

- **Summarised by:**

- Key themes
- Activities levels
- Modelling approach
- R&D questions
- Internal impact and decision making

- ▶ Sourced from PUBMED and the EMA/EFPIA M&S workshop
- ▶ Does not pretend to be an exhaustive overview of each application



Source: EFPIA MID3 workgroup: Good Practices in Model-Informed Drug Discovery and Development (MID3)
<http://onlinelibrary.wiley.com/doi/10.1002/psp4.12049/supinfo>



Paediatric Application - Examples in the literature

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	quetiapine	Life Cycle Management & Therapeutic Use



Paediatric Case study - Development of PBPK model to evaluate the relative systemic exposure to quetiapine after administration of IR and XR formulations to adults, children and adolescents

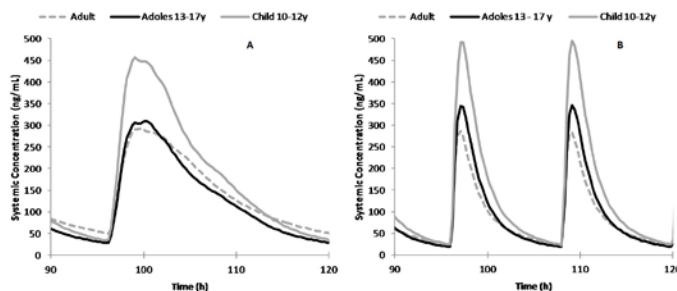
Johnson T, Bui K, Zhou D. Biopharm. Drug Dispos. 2014;5:341–352

- FDA WR: new dosage form (May 2011)
- Use simulation to replace bioequivalent study in paediatrics

Impact:

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

300mg dose Minimal PBPK	AUC ₀₋₂₄ (ng/ml/h)			C _{max} (mg/ml)			t _{max} (h)		
	IR	XR	XR/ IR	IR	XR	XR/ IR	IR	XR	XR/ IR
Adult	2464	2570	1.04	254	249	0.98	1.42	4.3	3.0
10 – 17y	3316	3738	1.13	393	447	1.14	1.61	4.5	2.8
13 – 17y	2974	2986	1.0	344	342	0.99	1.67	4.4	2.6
10 – 12y	3958	4227	1.07	517	523	1.01	1.65	4.6	2.8

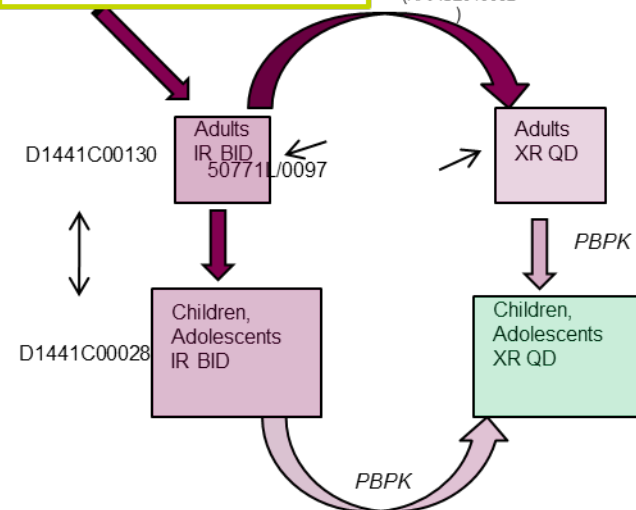


High Impact



DDI inhibition with ketoconazole (Study 1)
DDI induction with carbamazepine (Study 2)
Phys. Prop.
In vitro DMPK

IV/VC
(RAASZ049082)



MID3 Good Practice White Paper

Next steps: Share, Evolve & Implement

Share

- PAGE & ACOP (2015, 2016 and 2017)
- PSI/ EFSPi special interest group for M&S (2016), & ASA Best Practice in Modelling and Simulation (2016)
- DIA meeting (2015), EMA Extrapolation workshop (2016), TOPRA (2016)
- External communications in Japan & China, via congresses and ICH
- Colleagues continue to create awareness within and across companies (via EFPIA, and PhRMA)
- Interactions with Health Canada are planned

Evolve

- Continue to discuss good practices, terminology and improve understanding across pharma & other relevant stakeholders, e.g. Decision Makers, Clinicians, Statisticians and Clin Pharmacologists
- Continue to review ongoing MID3 practice with EMA MSWG
- Enhanced integration e.g via IMI [DDMoRe](#)

Implement

- Update to internal companies guidelines to meet good practice and aligned regulatory guidelines
- EMA endorsement: Jan (F2F meeting) & May (Paeds. Extrapolation workshop) 2016, and in March 2017
- EMA D-E-R (Dec. 2014), PBPK Qualification workshop (Nov. 2016)
- OCP FDA (Guideline Development) June 2016 discussions
- ICH: E11 (R1) addendum and future Paediatric Extrapolation guideline
- MID3 section in upcoming IQ paper on paediatric extrapolation



Commentary on the MID3 Good Practices Paper

Elthymios Manolis^{1,2*}, Jacob Brogren^{2,3}, Susan Cole^{2,4}, Justin L. Hay^{2,4}, Anna Nordmark^{2,3}, Kristin E. Karlsson^{2,3}, Frederike Lentz^{2,5}, Norbert Benda^{2,5}, Gaby Wangorsch^{2,6}, Gerard Pons^{2,7}, Wei Zhao^{2,8,9}, Valeria Gigante^{2,10}, Francesca Serone^{2,10}, Joseph F. Standing^{2,11}, Aris Dokoumetzidis^{2,12}, Juha Vakkilainen^{2,13}, Michiel van den Heuvel^{2,14}, Victor Mangas Sanjuan^{2,15}, Johannes Taminiau^{2,16}, Essam Kerwash^{2,4}, David Khan^{2,3}, Flora Tshinanu Musuamba^{2,17} and Ine Skottheim Rusten^{2,18}, on behalf of the EMA Modelling and Simulation Working Group

During the last 10 years the European Medicines Agency (EMA) organized a number of workshops on modeling and simulation, working towards greater integration of modeling and simulation (M&S) in the development and regulatory assessment of medicines. In the 2011 EMA – European Federation of Pharmaceutical Industries and Associations (EFPIA) Workshop on Modelling and Simulation, European regulators agreed to the necessity to build expertise to be able to review M&S data provided by companies in their dossier. This led to the establishment of the EMA Modelling and Simulation Working Group (MSWG). Also, there was agreement reached on the need for harmonization on good M&S practices and for continuing dialog across all parties. The MSWG acknowledges the initiative of the EFPIA Model-Informed Drug Discovery and Development (MID3) group in promoting greater consistency in practice, application, and documentation of M&S and considers the paper is an important contribution towards achieving this objective.

CPT Pharmacometrics Syst. Pharmacol. (2017) 6, 416–417; doi:10.1002/psp4.12223; published online 27 June 2017.

**Recently published in
CPT/PSP Journal -
July 2017**

PERSPECTIVE

Quantitative Modeling and Simulation in PMDA: A Japanese Regulatory Perspective

M Sato*, Y Ochiai, S Kijima, N Nagai, Y Ando, M Shikano and Y Nomura

In Japan in October 2016, the Pharmaceuticals and Medical Devices Agency (PMDA) began to receive electronic data in new drug applications (NDAs). These electronic data are useful to conduct regulatory assessment of sponsors' submissions and contribute to the PMDA's research. In this article, we summarize the number of submissions of quantitative modeling and simulation (M&S) documents in NDAs in Japan, and we describe our current thinking and activities about quantitative M&S in PMDA.

CPT Pharmacometrics Syst. Pharmacol. (2017) 6, 413–415; doi:10.1002/psp4.12203; published online 1 June 2017.



MID3 - to summarise

- MID3 is essential for paediatric drug development
- Use of MID3 can optimise the development of medicines to fulfil unmet medical needs across different therapeutic areas
- Use of MID3 allows quantitative decision making
- Use of MID3 requires advance evaluation and sharing of MID3 plan between sponsors and regulatory authorities
- Various paediatric examples with different impact levels in the literature
- High interest of regulators WW → a specific ICH guideline would be useful to align best practices



**With special
acknowledgments**



The ICH E11 Expert Work Group

The EFPIA MID3 work group

Amy Cheung, Senior Clinical Pharmacometrician, AZ



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