ICH E11 Revisions and Pediatric Model Informed Drug Development and Simulation

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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

ICH Harmonised Tripartite Guideline

Clinical Investigation of Medicinal Products in the Pediatric Population E11

Current Step 4 version
dated 20 July 2000

15 years later

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 5
Jan. 2001

Step 4
Aug. 2017
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
"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

- Identify new targets
- Characterization of target mechanism
- Early projection of efficacious dose to select clinical candidates
- Determination of minimum anticipated biological effect level
- Prediction of performance of formulations
- Prediction of H2H trials
- Assessing QT liability
- Predicting long term outcome from early clinical studies
- Increase efficiency of (pre)-clinical studies
- Extrapolation from HV to Patients
- Reduce costs for (pre)-clinical trials
- Dose and schedule selection
- Dose adjustments in subpopulations

Primarily internal decision making

- Reduce costs for (pre)-clinical trials
- Extrapolation from HV to Patients
- Increase efficiency of (pre)-clinical studies
- Assessing QT liability
- Predicting long term outcome from early clinical studies
- Predictions of benefit/risk
- Determination of minimum anticipated biological effect level
- Prediction of performance of formulations

Both internal and regulatory decision making

- Identify new targets
- Characterization of target mechanism
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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

Barriers for use in the regulatory context

- Resistance to MIDD use from clinical groups within companies
- Variation in MIDD use based on philosophy of company leadership
- Low availability of skilled MIDD personnel
- High resource requirements for development and maintenance of MIDD groups

- Variation in acceptance of MIDD across different FDA divisions
- Unclear standards for model qualification in regulatory decisions
- Lack of an established process to meet with the FDA on model design early in development
- In EU, experience is scattered (MSWG)
- Beyond EU and the US, expertise is more limited
THE EFPIA MID3 WORK GROUP – the journey

Marylore Chenel (Servier)
Nicolas Frey (Roche)
Lutz Hamisch (Pfizer)
Scott Marshall (Pfizer)*
Peter Milligan (Pfizer)*
Alexander Staab (Boehringer-Ingelheim)*
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James Yates (AZ)
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Dinko Rekic (AZ)

2011
EMA/EFPIA workshop on M&S

Feb. 2013
Outputs published in CPT/PSP Journal

Dec. 2014
EMA D-E-R workshop Paper approved by CPT in March 2017

March 2016
MID3 White paper published in CPT Journal

May 2016
EMA workshop on Paediatric Extrapolation
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

<table>
<thead>
<tr>
<th>Opportunities</th>
<th>Key Challenges</th>
<th>Actions</th>
<th>Progress</th>
</tr>
</thead>
</table>
| Robust informed R&D decision making - Improve R&D efficiency | • MID3 - underutilized & undervalued by Pharma  
• Communication gap between modellers & non-modellers | • Develop **Common understanding** in terms of the practice, application and **value** of MID3 | • Good Practices in MID3 White Paper: Why, What & Challenges /Opportunities for Pharma. companies |
| Robust informed R&D regulatory assessment  
• Inform Risk Benefit assessment  
• Greater acceptance in extrapolation and other medium & high impact Regulatory Decisions | • Heterogeneity of MID3 reporting in submissions | • EFPIA to agree basic documentation standards for submissions | • Good Practices in MID3 White Paper: How (Documentation) |
| • Variable readiness of EMA & other agencies to evaluate MID3: staff & lack of guidelines | • EMA to form and evolve MSWG  
• Develop guidelines | • MSWG Formed 2013  
• Activity reports **2013, 2014, 2015, 2016**  
• Development of MID3 regulatory guideline planned via ICH | • Workshop held Dec 2014- EFPIA/EMA Report, publications  
• Review templates to be updated  
• Formation of expert group to drive outputs |
| • Misperception that dose response is only company risk | • Host workshop and evolve Dose Response practice & Review | • Extrapolation Workshops (EMA Sept 2015, EMA/EFPIA May 2016)  
• PBPK WS (EMA/EFPIA Nov. 2016)  
• Qualification Procedures x3 with Key M&S component | |
| • Communication gap between modellers & non-modellers | • Host workshops involving multifunctional group | • IMI DDMoRe (2016) / Access to Clinical Trial Data | |
| • Data Sharing | • Strengthen data sharing initiatives | | |
Scope of M&S in regulatory submission as experienced by MSWG

MSWG was established in 2013
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)
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
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)
### Paediatric Application - Examples in the literature

<table>
<thead>
<tr>
<th>From</th>
<th>Disease</th>
<th>Compound</th>
<th>R&amp;D stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>MID3</td>
<td>Venous thromboembolism</td>
<td>rivaroxaban</td>
<td>Early Clinical Development</td>
</tr>
<tr>
<td>MID3</td>
<td>Epilepsy</td>
<td>topiramate</td>
<td>Late Clinical Development</td>
</tr>
<tr>
<td>MID3</td>
<td>Pulmonary Arterial Hypertension (PAH)*</td>
<td>Revatio</td>
<td>Late Clinical Development</td>
</tr>
<tr>
<td>MID3</td>
<td>Systemic Juvenile Idiopathic Arthritis (sJIA)</td>
<td>tocilizumab</td>
<td>Late Clinical Development</td>
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<tr>
<td>MID3</td>
<td>Schizophrenia</td>
<td>paliperidone</td>
<td>Approval Phase</td>
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<tr>
<td>MID3</td>
<td>sugammadex-mediated reversal of rocuronium-induced neuromuscular blockade</td>
<td>sugammadex/rocuronium</td>
<td>Life Cycle Management &amp; Therapeutic Use</td>
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<tr>
<td>MID3</td>
<td>HIV</td>
<td>vitamin D3</td>
<td>Life Cycle Management &amp; Therapeutic Use</td>
</tr>
<tr>
<td>MID3</td>
<td>Schizophrenia and bipolar disorder</td>
<td>quetiapine</td>
<td>Life Cycle Management &amp; Therapeutic Use</td>
</tr>
</tbody>
</table>

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


- 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)

<table>
<thead>
<tr>
<th>300mg dose Minimal PBPK</th>
<th>AUC0-24 (ng/ml/h)</th>
<th>Cmax (mg/ml)</th>
<th>tmax (h)</th>
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<tbody>
<tr>
<td>IR</td>
<td>XR</td>
<td>XR/IR</td>
<td>IR</td>
</tr>
<tr>
<td>Adult</td>
<td>2464</td>
<td>2570</td>
<td>1.04</td>
</tr>
<tr>
<td>10 – 17y</td>
<td>3316</td>
<td>3738</td>
<td>1.13</td>
</tr>
<tr>
<td>13 – 17y</td>
<td>2974</td>
<td>2986</td>
<td>1.0</td>
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<tr>
<td>10 – 12y</td>
<td>3958</td>
<td>4227</td>
<td>1.07</td>
</tr>
</tbody>
</table>

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

In vitro DMPK
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
Recently published in CPT/PSP Journal - July 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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