EMA experience with paediatric PBPK

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Member of PDCO and MSWG, EMA
The opinions expressed during this presentation are those of the speaker, and not necessarily those of the Norwegian Medicines Agency, the EMA or one of its committees or working parties.
The paediatric regulation was introduced in Europe in 2007 in order to:

- Improve the health of children
  - Increase high quality, ethical research into medicines for children
  - Increase availability of authorised medicines for children
  - Increase information on medicines

Achieve the above
- Without unnecessary studies in children
- Without delaying authorisation for adults
Paediatric investigation plan (PIP)

Intended to support a potential indication (‘paediatric use”) in all subsets of the paediatric population

Data on efficacy, safety and age-appropriate formulation

Timelines for start and completion of trials

Binding EMA decision on the development plan

Waivers possible if

- Potentially harmful or ineffective
- No significant therapeutic benefit expected in children
- Disease to be treated does not occur in children
The inference from the investigated population to the broader population or to subpopulations.
### Sources of prior data
- Adult data
- Paediatric data in other indications
- Adult and/or paediatric data for similar substances
- Animal data
- In vitro data
- ...

### Strategies for analysis
- Pop-PK/PKPD
- Bayesian analysis
- Frequentist multivariate regression
- Allometric scaling (<?y)
- PBPK
- Combination of methods
- ...

### Optimizing study design
- CTS
- Optimal sampling
- ...
- What criteria to set for determining PK(/PD) endpoints?
- How to proceed if PK(/PD) is not as expected?
The place for PBPK in drug development

Expanding use the last decades

- from use in environmental tox to
- scaling from animals to humans and now
- extensive use in pharmaceutical drug development
  - drug formulation development
  - DDIs
  - subpopulations such as paediatrics

The advantage being the mechanistic basis
which, when scientifically well founded, allows
greater confidence in extrapolation outside
the studied population.
The use of extrapolation, when **adequately justified and adequately reported** is encouraged by the EMA.

Several means taken to encourage the use and increase the quality of extrapolation

  

- European Medicines Agency-European Federation of Pharmaceutical Industries and Associations modelling and simulation workshop (2011)


- Specific tables within the Summary Report and opinion to be completed when PBPK are suggested or requested by the PDCO.
Lessons learned:

The need for a conceptual framework for all aspects of extrapolation

The **objective** of this concept paper is to develop a framework for an explicit and systematic approach which sets out i) when, ii) to what extent, and iii) how extrapolation can be applied
European Commission

EMA

CHMP
CVMP
PRAC
PDCO
COMP
CAT
HMPC

SAWP
MSWG

BSWP
PKWP

Several other WPs

EWG

FWG
NCWG
NWG
Impact of the M&S exercise on benefit-risk decision and level of regulatory scrutiny?

**High impact**

Scientific Advice, Supporting Documentation, Regulatory Scrutiny

+++  

**Medium impact**

Scientific Advice, Supporting Documentation, Regulatory Scrutiny

++  

**Low impact**

Scientific Advice, Supporting Documentation, Regulatory Scrutiny

+
Regulatory impact applied to PBPK applications

High
To support waiver of an in vivo study for substrate of CYP enzymes.

Medium to high
To predict optimal doses in different age and weight categories of children.

Low
To provide quantitative evidence of the plausibility of mechanisms important for the disposition of the drug.

High
To support waiver of an in vivo study for inhibitor of CYP enzymes.

High
To support SmPC statements regarding the need to adjust dosage for drug combinations not tested.

Key points:
Impact ≠ Value
Certainty ≠ Value

Slide from T. Shepard, 2014
Based on the published research:
M&S abundant in PIP submissions, proposed
for dose finding, study optimisation and
analysis, not as a tool to
navigate in the decision tree


Role of modeling and simulation in pediatric investigation plans.
Manolis E, Osman TE, Herold R, Koenig F, Tomasi P, Vamvakas S, Saint Raymond A.

Slide from E. Manolis, 2014
## Dose-investigations in PIPs

<table>
<thead>
<tr>
<th>Analysis technique</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Descriptive analyses</strong></td>
<td>73 (90.1%)</td>
</tr>
<tr>
<td>summary statistics including confidence intervals; graphics; summaries of PK or PD parameters</td>
<td></td>
</tr>
<tr>
<td><strong>PK modelling</strong></td>
<td>41 (50.6%)</td>
</tr>
<tr>
<td>fixed effect or population PK models</td>
<td></td>
</tr>
<tr>
<td><strong>PK-PD modelling</strong></td>
<td>17 (21.0%)</td>
</tr>
<tr>
<td>including exposure-response, PK-response models</td>
<td></td>
</tr>
<tr>
<td><strong>Dose-response modelling</strong></td>
<td>10 (12.3%)</td>
</tr>
<tr>
<td>including dose-PD (eg, ANCOVA model), dose-toxicity, dose-PK-PD models</td>
<td></td>
</tr>
<tr>
<td><strong>Physiologically-based PK modelling</strong></td>
<td>3 (3.7%)</td>
</tr>
<tr>
<td><strong>Dose-exposure modelling</strong></td>
<td>3 (3.7%)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>22 (27.2%)</td>
</tr>
<tr>
<td>Formal hypothesis testing on efficacy or PD endpoints; non-parametric time-to-event analyses; other types of models not captured above</td>
<td></td>
</tr>
</tbody>
</table>


Bridging the gap: A review of dose-investigations in paediatric investigation plans.

Hampson LV, Herold R, Posch M, Saperia J, Whitehead A.
Dose-investigations in PIPs


Bridging the gap: A review of dose-investigations in paediatric investigation plans.

Hampson LV, Herold R, Posch M, Saperia J, Whitehead A.
## Submissions - PBPK examples

<table>
<thead>
<tr>
<th>Procedure (Committee/WP)</th>
<th>n</th>
<th>Age groups</th>
<th>Status at assessment</th>
<th>Regulatory impact</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SA (SAWP/MSWG)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose selection. Replace PK study</td>
<td>4</td>
<td>0-18y</td>
<td>Planned</td>
<td>High to moderate</td>
<td>PK requested</td>
</tr>
<tr>
<td>Dose selection. Reduce PK study</td>
<td>(3)</td>
<td>5-11y/12-18y/12-18y</td>
<td>Planned/ Preliminary results/ Performed</td>
<td>High to moderate/Moderate/Moderate</td>
<td>PK requested/ Endorsed/ Endorsed</td>
</tr>
<tr>
<td><strong>PIPs (PDCO/MSWG)</strong></td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose selection. Replace PK study</td>
<td>(1)</td>
<td>0-18y</td>
<td>Planned</td>
<td>High</td>
<td>Described in the PIP</td>
</tr>
<tr>
<td>Dose selection. Reduce PK study</td>
<td>(1)</td>
<td>0-18y</td>
<td>Planned</td>
<td>High</td>
<td>Key binding in the Opinion</td>
</tr>
<tr>
<td>Dose selection.</td>
<td>(10)</td>
<td>0-18y</td>
<td>Range of Suggested - Considered – Planned - Performed</td>
<td>Range of Low - Moderate to low - Moderate to high</td>
<td>Described in the PIP or key binding in the Opinion</td>
</tr>
<tr>
<td><strong>MAA/indication (CHMP)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Support the dose, inform co-variables</td>
<td>2</td>
<td>0-18y, in particular 1-2y</td>
<td>Performed</td>
<td>Low</td>
<td>Variation accepted</td>
</tr>
<tr>
<td>Support the dose</td>
<td>(1)</td>
<td>0-18y</td>
<td>Performed</td>
<td>High</td>
<td>Active procedure</td>
</tr>
</tbody>
</table>
PBPK in paediatric dose selection

Input to Pop-PK/PKPD

System model
- Anatomy
- Biology
- Physiology
- Pathophysiology
- Patient/disease extrinsic factors

Drug model

Conditions
- Adult
- Paediatric
- Similar drugs
- Similar patient population

Simulations

Impact
- Inform study: low
- Reduced clinical study: moderate to high
- Replace clinical study: high
- Inform risk handling: moderate to high
PBPK in paediatric dose selection

Drug model

System model

Anatomy
Biology
Physiology
Pathophysiology
Patient/disease extrinsic factors

Conditions

Adult
Paediatric
Similar drugs
Similar patient population

Simulations

Input to Pop-PK/PKPD

Study design/sampling optimizing strategies

Examples

n=2 Optimize/Reduce/Replace

n=1(9) Inform/Optimize/Reduce

n=7 Inform/Replace

Impact

Inform study - low
Reduced clinical study - moderate to high
Replace clinical study - high
Inform risk handling - moderate to high
## Purpose and impact of extrapolation in drug development and regulatory review

<table>
<thead>
<tr>
<th>Domain</th>
<th>Pharmacokinetics</th>
<th>Pharmacodynamics</th>
<th>Disease (progression)</th>
<th>Patient population</th>
<th>Statistical and design aspects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assumption</td>
<td>Exposure scalable by allometry</td>
<td>Similar mechanism of action</td>
<td>Similar etiology across different conditions</td>
<td>Comparable baseline characteristics</td>
<td>Nature of parameter distribution</td>
</tr>
<tr>
<td>Probability to violate (uncertainty in assumption)</td>
<td></td>
<td></td>
<td></td>
<td>Definitely / Likely / Unlikely / Improbable</td>
<td></td>
</tr>
<tr>
<td>Clinical consequence(s) if assumptions are violated</td>
<td>Minor / Major / Unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Skepticism scale”</td>
<td>Weight given to the assumptions underpinning the extrapolation or inferences</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implications for evidence synthesis</td>
<td>No additional evidence required</td>
<td>More evidence required from small subset (bridging study)</td>
<td>More evidence required from a large trial</td>
<td>Agree on risk mitigation for acceptable risks, if further evidence gathering is unfeasible</td>
<td>Restrict label, if risk is unacceptable</td>
</tr>
<tr>
<td>Impact of Modeling and simulation on the development programme</td>
<td>Reduce trial burden (e.g., sparse sampling)</td>
<td>Use of biomarkers as predictors of response</td>
<td>Stratification by severity</td>
<td>Estimation of covariate effects</td>
<td>Reduced sample size</td>
</tr>
<tr>
<td></td>
<td>Assessment of metabolic maturation in children</td>
<td>Characterization of phenotypical differences due to ontogeny and maturation processes.</td>
<td>Different dosing recommendation</td>
<td>Identification of groups at risk (e.g., polymorphisms)</td>
<td>Eliminate the need for additional study</td>
</tr>
</tbody>
</table>

*Harnisch L, Shepard T, Pons G, Della Pasqua O.*


Modeling and simulation as a tool to bridge efficacy and safety data in special populations.
Aspects of regulatory evaluation

**Drug model**
- Verify

**System model**
- Qualify
  - Anatomy
  - Biology
  - Physiology
  - Pathophysiology
  - Patient/disease extrinsic factors

Aspects of evaluation

PBPK model

**Conditions**
- Adult
- Paediatric
- Similar drugs
- Similar patient population

**Simulations**

Confirmation of the extrapolation;
Interactive loops of feeding information back into the model

**Biological plausibility**

- Assumptions – justify and validate
- System/drug variability – define and quantify
- Uncertainty and risk – sensitivity analysis and worst case scenario assessments

**Impact**
- Inform study - low
- Reduced clinical study - moderate to high
- Replace clinical study - high
- Inform risk handling - moderate to high
In summary, requirements for paediatric PBPK would include

- the PBPK model developed and qualified/verified/refined in adults

- further qualification with model drugs needed if new data (enzymes/transporters etc) are included in the model

- systematically list and justify assumptions

- evaluate the impact of the major assumptions (sensitivity analysis, worst/best case scenarios)

Address impact of the M&S

- How are the data planned to be used?
  - Replace/reduce/optimize/inform
  - If confirmation of the extrapolation needed
    - Study design/optimal sampling scheme/sample size
    - How to proceed if the observed data do not confirm the M&S?
EMAs regulatory activity on PBPK

Guidelines

Reporting of PBPK

Draft Concept paper on Qualification and Reporting of PBPK modelling and analyses

Extrapolation

Concept paper on extrapolation of efficacy and safety in medicine development

Interactions

Guideline on the Investigation of Drug Interactions

Renal impairment

Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function

Further advice

• Central scientific advice/protocol assistance or qualification advice/opinion by SAWP (involvement of PDCO and MSWG)

• Presubmission meeting with the Paediatric sector

• During the PIP review procedure
Challenges and potential solutions

What is needed to increase confidence?

• Update/publish models/results
  • what works?
  • what are the shortcomings?
    • differences in the metabolic pattern in small children versus adult?
    • differences in co-variate correlations between adults and pediatric patients?
    • differences in/between pediatric age groups?

• System and drug data
  • Biology
    • Ontogony (metabolizing enzymes phase I+II, transporters (liver, GI, tissues))
    • Patophysiology of the various pediatric populations
    • Patient intrinsic/extrinsic factors
  • Methotological work

Confirmation that the pediatric PBPK models do predict pediatric PK data
Acknowledgments

EMA Paediatric Committee
EMA Modelling and Simulation Working Group

Particularly thanks to
Ralf Herold
Efthymios Manolis
Anna Nordmark
Theresa Shepard
Siri Wang