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SCIENCE MEDICINES HEALTH

# EMA experience with paediatric PBPK

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# Disclaimer

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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



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)

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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

# Extrapolation in drug development

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The inference from the investigated population to the broader population or to subpopulations

# Paediatric dose selection strategies - pharmacology

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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

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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 workshop on modelling in paediatric medicines (2008)

  http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2009/11/event_detail_000029.jsp&mid=WC0b01ac058004d5c3

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

  http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2011/07/event_detail_000440.jsp&mid=WC0b01ac058004d5c3

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

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Lessons learned:

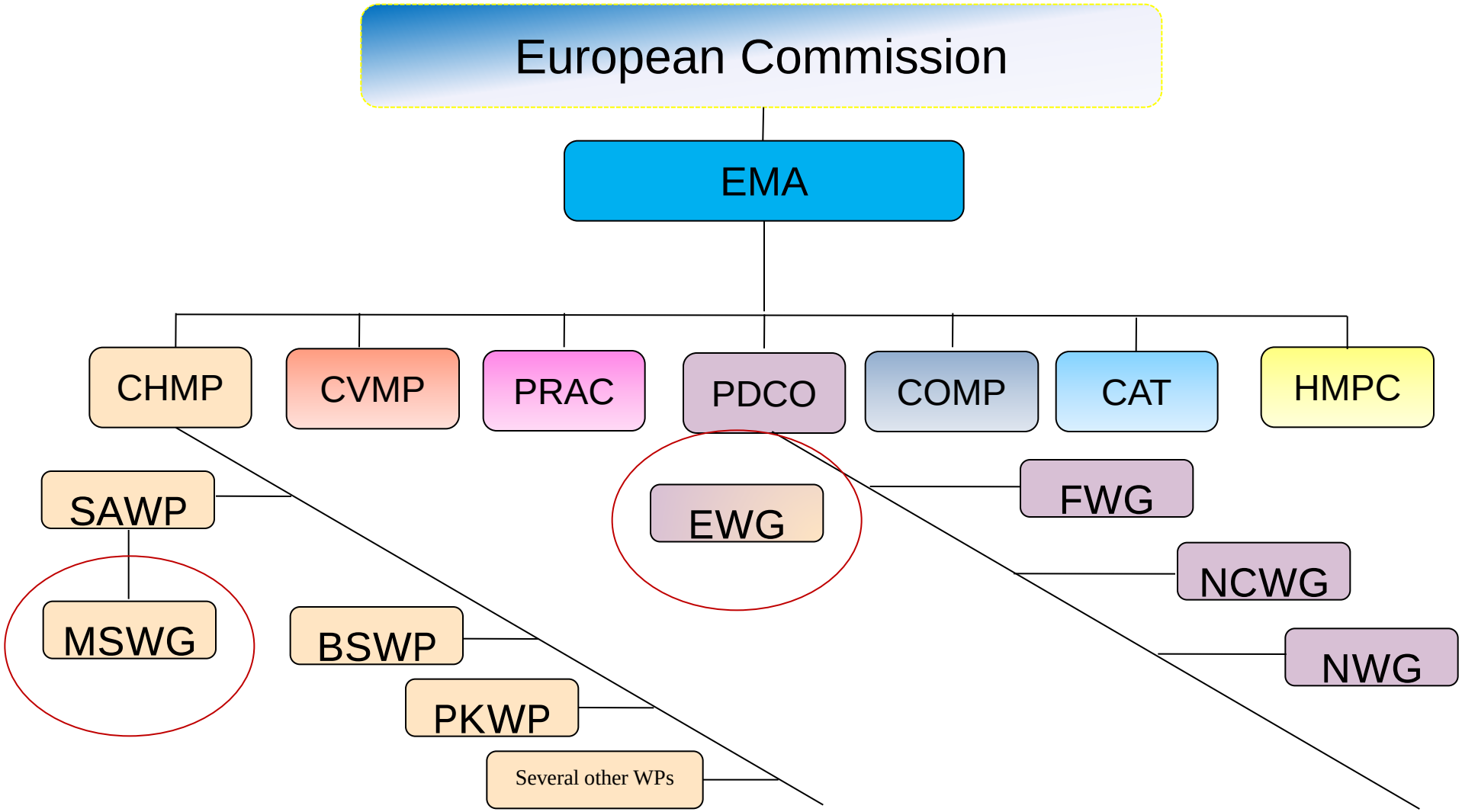
The need for a conceptual framework for all aspects of extrapolation


22 June 2012
EMA/129698/2012
Human Medicines Development and Evaluation

Concept paper on extrapolation of efficacy and safety in medicine development

Draft

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

# Regulatory view on M&S

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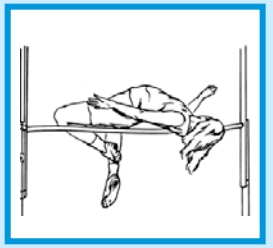
Impact of the M&S exercise on benefit-risk decision and level of regulatory scrutiny?

## High impact

Scientific Advice, Supporting Documentation, Regulatory Scrutiny } + + +

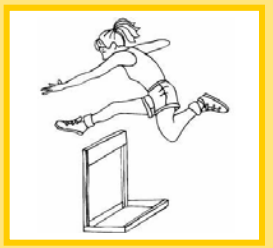
## Medium impact

Scientific Advice, Supporting Documentation, Regulatory Scrutiny } + +



## Low impact

Scientific Advice, Supporting Documentation, Regulatory Scrutiny } +



Impact on regulatory decision



Slide from T. Shepard, 2011

# Regulatory impact applied to PBPK applications

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**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

# Modeling and simulation in PIPs

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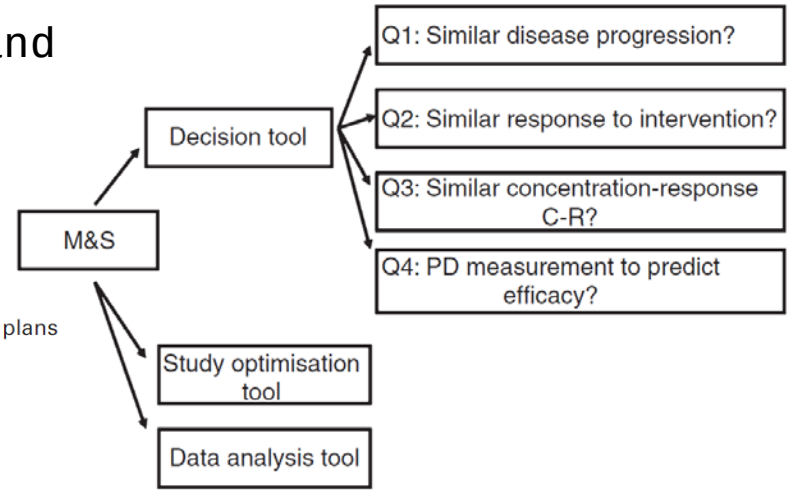
Based on the published research:
M&S abundant in PIP submissions, proposed for dose finding, study optimisation and analysis, not as a tool to navigate in the decision tree



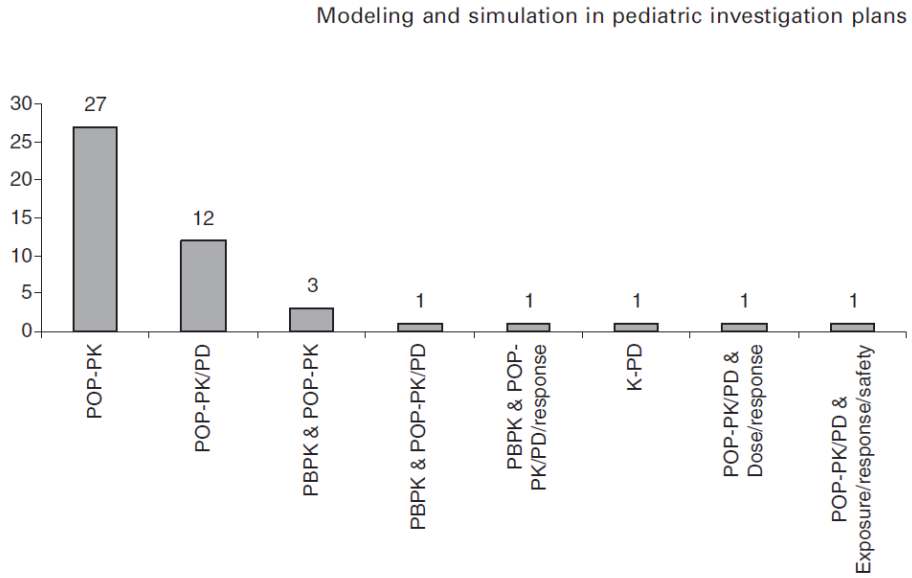




**Figure 3** M&S in positive PIP opinions (as of Jan 2010). Model types and the number of opinions with reference to the specific model types.

Paediatr Anaesth. 2011 Mar;21(3):214-21. doi: 10.1111/j.1460-9592.2011.03523.x. Epub 2011 Jan 18.

**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 i PIPs

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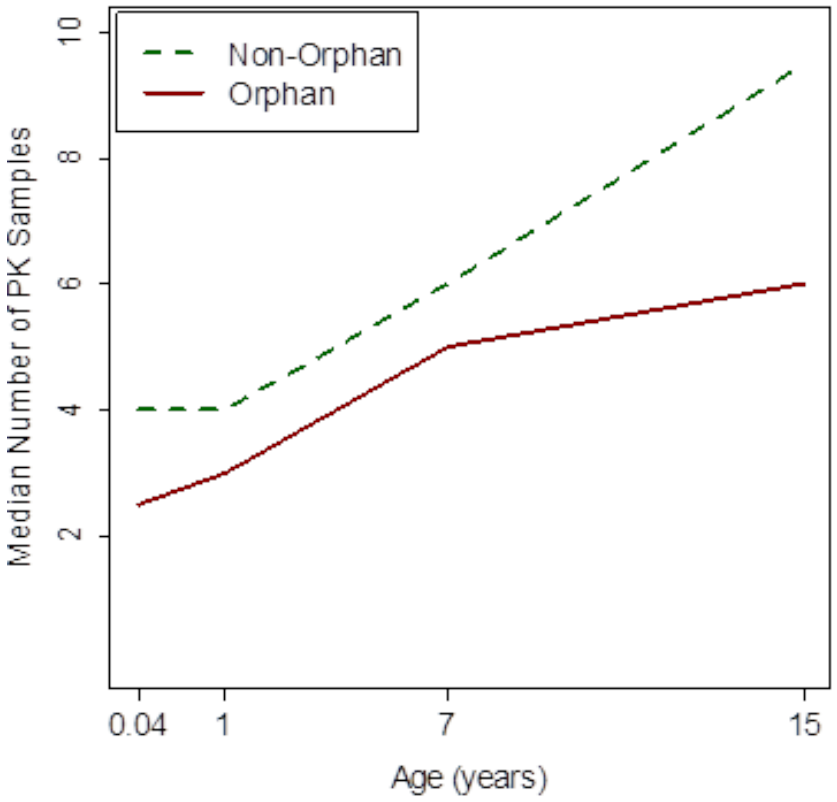
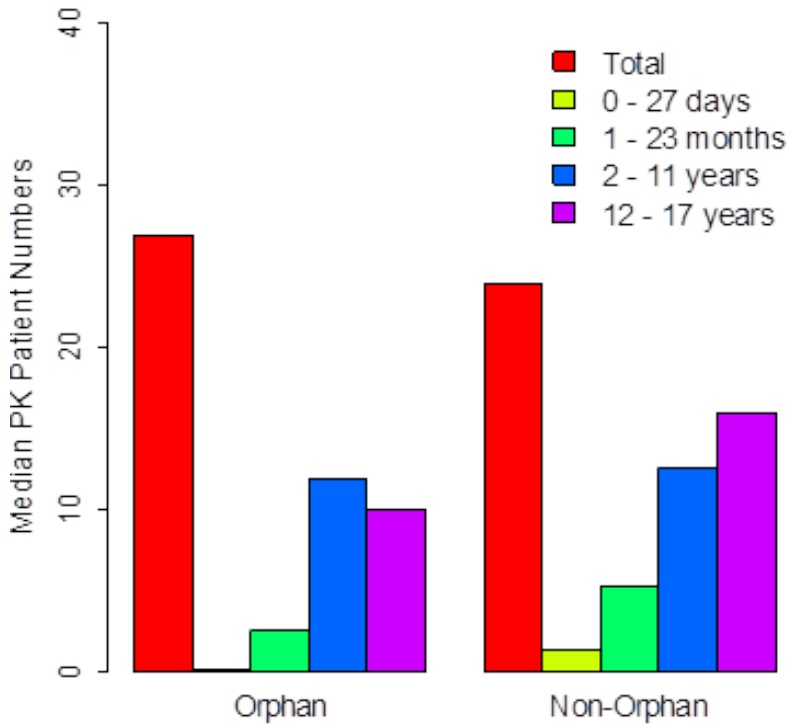
| Analysis technique | |
|---|---|
| Descriptive analyses<br>summary statistics including confidence intervals; graphics; summaries of PK or PD parameters | 73 (90.1%) |
| PK modelling<br>fixed effect or population PK models | 41 (50.6%) |
| PK-PD modelling<br>including exposure-response, PK-response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

**Br J Clin Pharmacol. 2014 Apr 10. doi: 10.1111/bcp.12402. [Epub ahead of print]**
**Bridging the gap: A review of dose-investigations in paediatric investigation plans.**
Hampson LV, Herold R, Posch M, Saperia J, Whitehead A.

# Dose-investigations i PIPs

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# Submissions – PBPK examples

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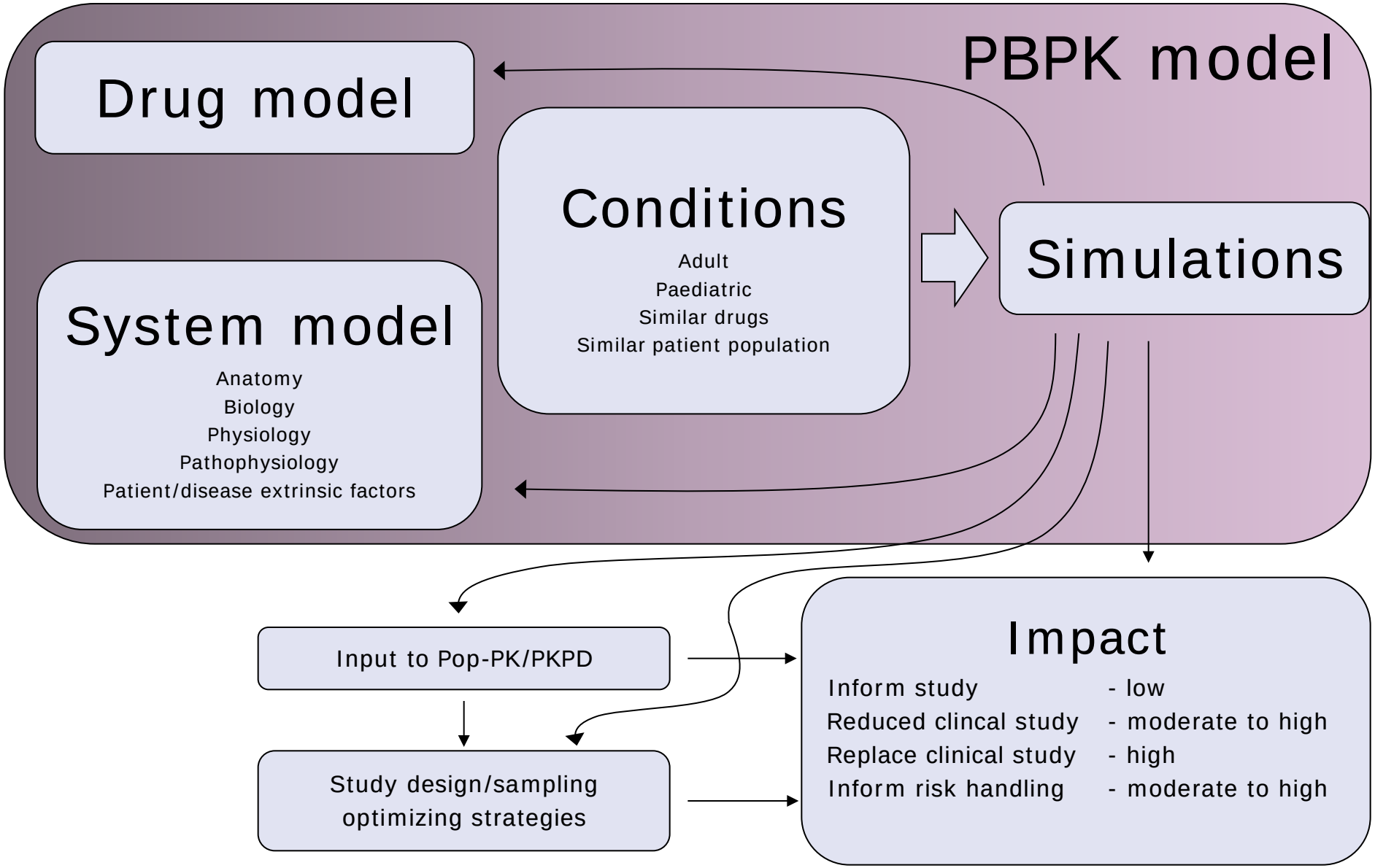
| Procedure (Committee / WP) Aim | n | Age groups | Status at assessment | Regulatory impact | Decision |
|---|---|---|---|---|---|
| **SA (SAWP / MSWG)** | 4 | | | | |
| Dose selection. Replace PK study | (1) | 0-18y | Planned | High to moderate | PK requested |
| Dose selection. Reduce PK study | (3)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

# PBPK in paediatric dose selection



# PBPK in paediatric dose selection

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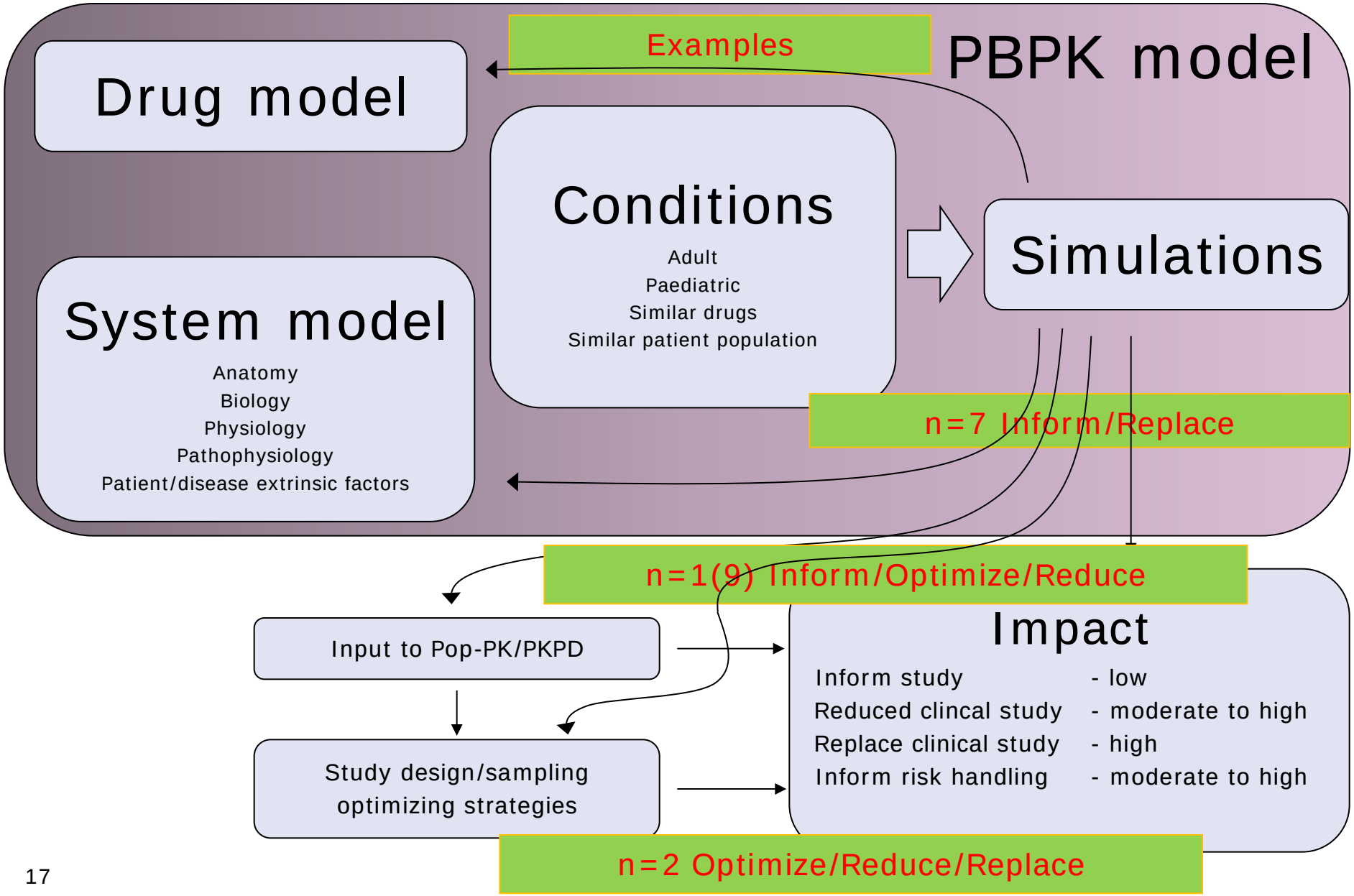

# Aspects of regulatory evaluation

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**Purpose and impact of extrapolation** in drug development and regulatory review

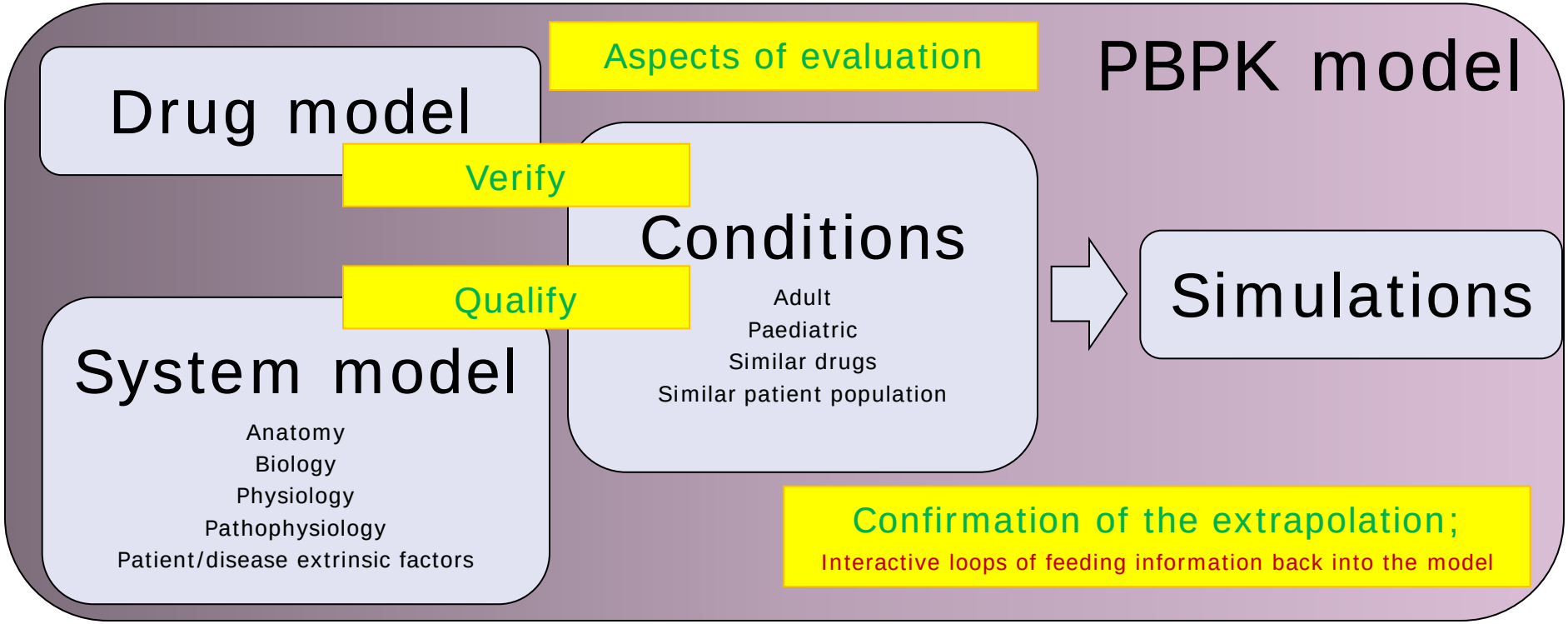
| | Domain | | | | |
|---|---|---|---|---|---|
| | Pharmacokinetics | Pharmacodynamics | Disease (progression) | Patient population | Statistical and design aspects |
| Assumption * | ▪ Exposure scalable by allometry<br>▪ Common metabolic pathways | ▪ Similar mechanism of action<br>▪ Clinical response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

CPT Pharmacometrics Syst Pharmacol. 2013 Feb 27;2:e28. doi: 10.1038/psp.2013.6.

**Modeling and simulation as a tool to bridge efficacy and safety data in special populations.**

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

# Aspects of regulatory evaluation




- Biological plausability
- 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 clincal study | - moderate to high |
| Replace clinical study | - high |
| Inform risk handling | - moderate to high |

# Aspects of regulatory evaluation



## 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

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## 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

## 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 peadiatric patients?
    - differences in/between paediatric age groups?

Confirmation that the paediatric PBPK models do predict paediatric PK data

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

# Acknowledgments

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