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Regulatory Model-Informed Drug Development in EU

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Currently I am Chair of the EMA Modelling and Simulation Party, and Regulatory Chair of the ICH MIDD discussion group as well as a member of the ICH E11A Pediatric Extrapolation expert group.

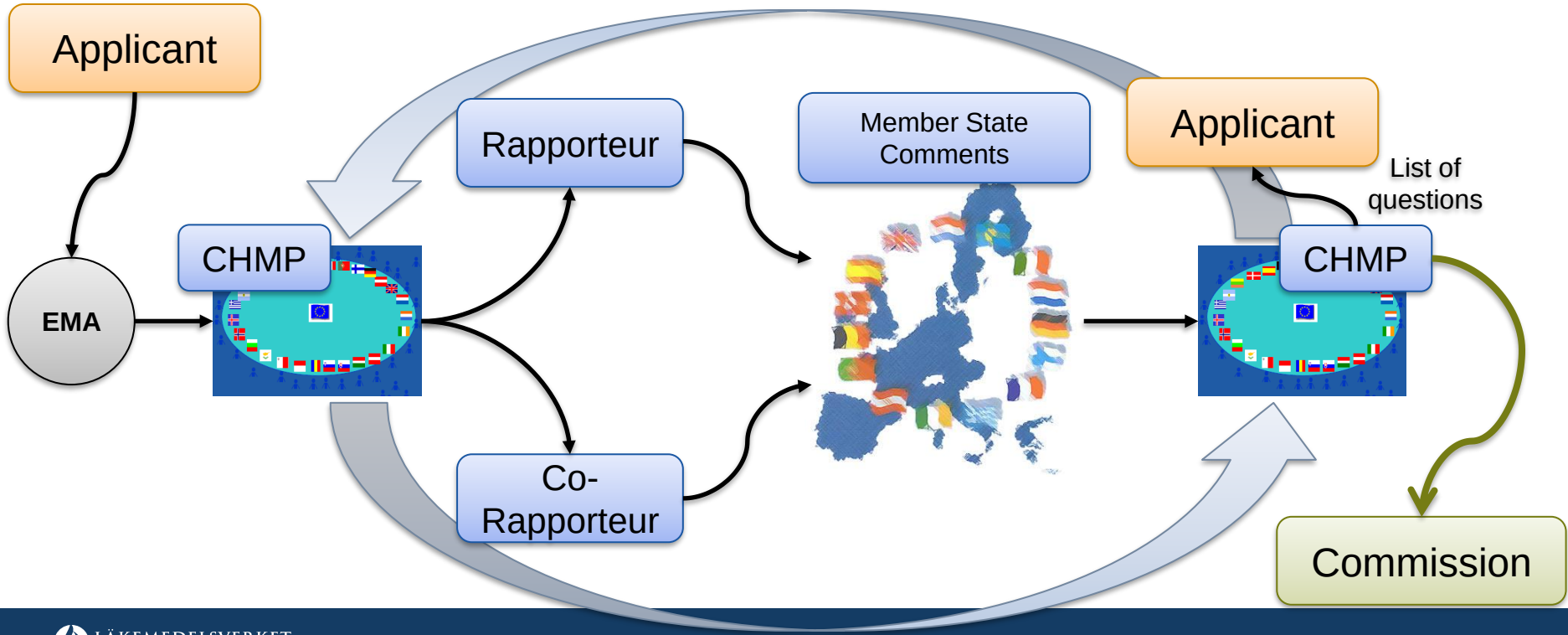
Disclaimer

The views expressed in this presentation are those of the speaker, and are not necessarily those of MPA or EMA.

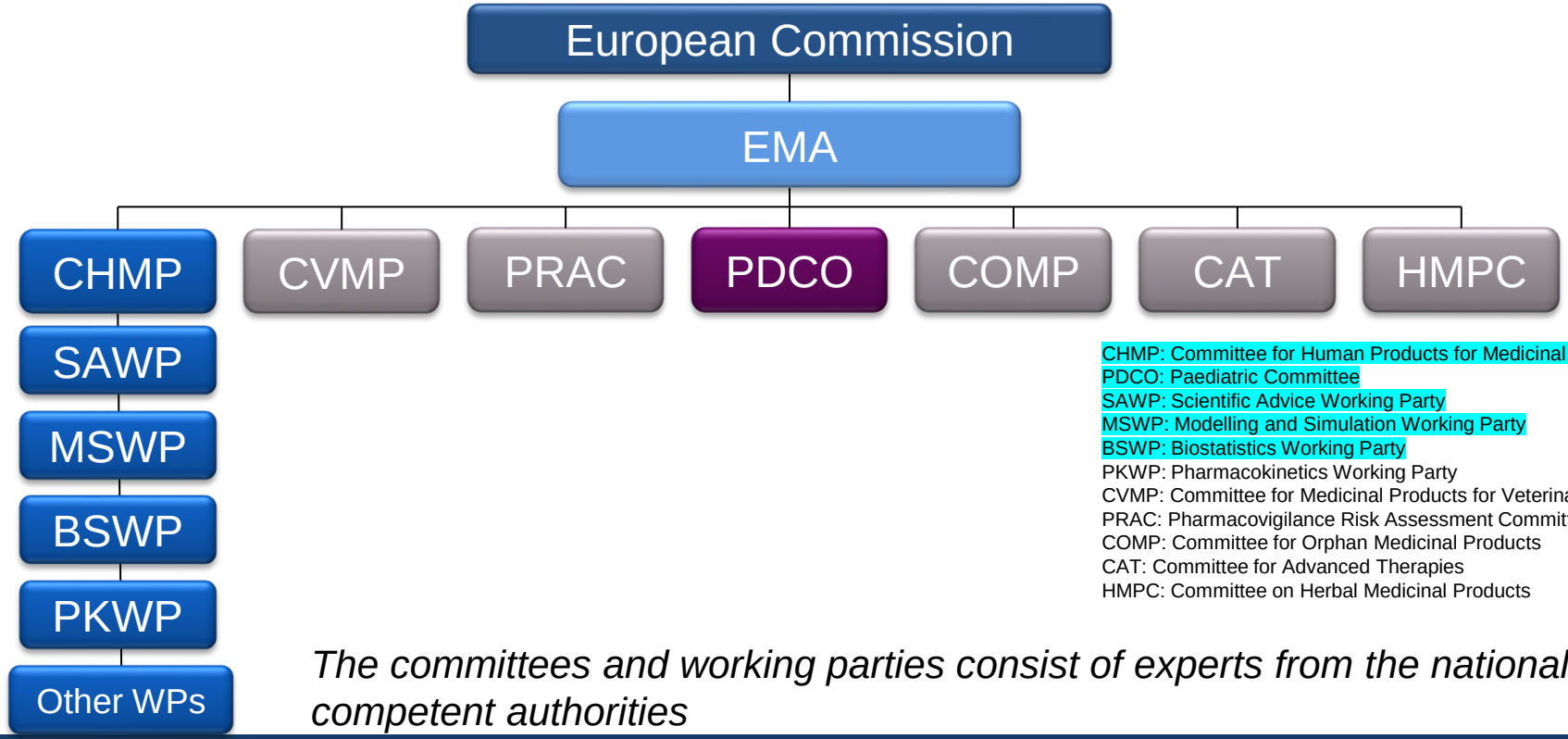
Outline

- Overview of the regulatory proccess in EU
- Regulatory value of MIDD
- Interacting with regulators in EU
- Reporting and presentation of MIDD analyses
- Guidance documents
- Summary

Procedure for assessment of marketing authorisation applications



EMA framework



CHMP: Committee for Human Products for Medicinal Use
PDCO: Paediatric Committee
SAWP: Scientific Advice Working Party
MSWP: Modelling and Simulation Working Party
BSWP: Biostatistics Working Party
PKWP: Pharmacokinetics Working Party
CVMP: Committee for Medicinal Products for Veterinary Use
PRAC: Pharmacovigilance Risk Assessment Committee
COMP: Committee for Orphan Medicinal Products
CAT: Committee for Advanced Therapies
HMPC: Committee on Herbal Medicinal Products

The committees and working parties consist of experts from the national competent authorities

EMA Regulatory Science to 2025
Published in 2020

Strategic goals and core recommendations - Human medicines[1]	
2. Driving collaborative evidence generation – improving the scientific quality of evaluations	▸ Leverage non-clinical models and 3Rs principles[¥] ▸ **Foster innovation in clinical trials** ▸ **Develop the regulatory framework for emerging clinical data generation** ▸ **Expand benefit-risk assessment and communication** ▸ Invest in special populations initiatives ▸ **Optimise capabilities in modelling, simulation and extrapolation** ▸ Exploit digital technology and artificial intelligence in decision making

EMA Regulatory Science to 2025 (europa.eu)

EMA Regulatory Science to 2025

Published in 2020

Optimise capabilities in modelling, simulation and extrapolation	▸ Enhance modelling and simulation and extrapolation use across the product lifecycle and leverage the outcome of EU projects; ▸ Develop guidance and standards on the use of AI in modelling and simulation for regulatory submissions; ▸ Deploy advances in RWD, modelling, simulation and extrapolation to benefit special populations particularly neglected patient populations; ▸ Promote development and international harmonisation of methods and standards via a multi-stakeholder platform; ▸ Increase capability and redesign the operations of relevant working parties to ensure wider knowledge exchange: » Invest in Centres of Excellence in regulatory science at an EU level, to work with regulatory agencies to provide training and research on modelling & simulation tools; » Enhance collaboration with external partners/consortia with expertise in modelling and simulation, and EU funded or co-founded projects e.g. IMI, Horizon 2020; ▸ Investigate possibilities for conducting modelling and simulation analyses to address key regulatory questions as part of product specific assessment or development of guidelines and policies; ▸ Consider working with stakeholders to foster data sharing through developing data standards and platforms for data exchange.

Regulatory value of MIDD

- **Early:** Enable early informed discussion with sponsors regarding study designs, endpoints, dose regimens, data needed to support benefit risk decisions
- **At Market Authorization Application:** Support benefit risk decisions by quantifying uncertainties and their clinical consequences based on prior knowledge at disease, mechanism and compound level
- Propose Risk mitigation activities
  - Update posology section in SmPC particularly for special populations
  - Inform contents of the RMP
- **Post Marketing:** Support signal detection and assessment, and Lifecycle management

Main challenges to wider acceptance of model informed approaches for high impact applications

- Poor communication between sponsors and regulators
- Poor communication and understanding within regulatory experts

Interacting with regulators in EU

- EMA Innovation Task Force (ITF)
  - Provide a forum for early dialogue with applicants, to proactively identify scientific, legal and regulatory issues of emerging therapies and technologies
- ITF briefing meetings
  - Facilitate informal exchange of information and guidance in the development process, complementing and reinforcing existing procedures such as advanced-therapy-medicinal-product (ATMP) classification and certification, designation of orphan medicinal products and scientific advice
  - Intended to take place much earlier than when one would normally seek scientific advice

Interacting with regulators in EU

- Scientific advice and protocol assistance
  - Clinical aspects (appropriateness of studies in patients or healthy volunteers, selection of endpoints, i.e. how best to measure effects in a study, post-authorisation activities including risk management plans);
  - Methodological issues (statistical tests to use, data analysis, modelling and simulation)

- Prepared by Scientific Advice Working Party, with support from other experts such as Modelling and Simulation Working Party

Interacting with regulators in EU

- Qualification of novel methodologies for medicine development
  - Support the qualification of innovative development methods for a specific intended use in the context of research and development into pharmaceuticals.
  - Outcomes: **Opinion** on the **acceptability of a specific use of a method** or a **letter of support** when the novel methodology under evaluation cannot yet be qualified but is shown to be promising based on preliminary data

- Examples:
  - Qualification Opinion of MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty (europa.eu)
  - Letter of support for “Islet autoantibodies as enrichment biomarkers for type 1 diabetes prevention studies, through a quantitative disease progression model” (europa.eu)
  - Letter of support for Model-based CT enrichment tool for CTs in aMCI (europa.eu)

Interacting with regulators in EU

- National competent authorities within EU
  - Scientific advice
  - Pre-submission meetings

Interacting with regulators in EU

- Paediatric committee
  - The PDCO's main role is to assess the content of paediatric investigation plans (PIPs), which determine the studies that companies must carry out in children when developing a medicine. This includes assessing applications for a full or partial waiver and for deferrals.
  - The assessment of Modelling and Simulation Studies, and Extrapolation Studies are supported by Modelling and Simulation Working Party

Current use of modelling and simulation in regulatory submissions

- ✓ Description of PK and PD data and quantitative characterization of their determinants (e.g. age, bodyweight, organ impairment, co-medications, co-morbidities)
- ✓ Characterization of the impact of change in formulation on drug efficacy or safety (e.g. modified release, biosimilars, etc.)
- ✓ Characterization of the impact of change in dosing regimen on drug efficacy or safety (e.g. change in dosing frequency for more convenience or better compliance)
- ✓ Clinical trial design optimization
- ✓ Dose finding/selection
- ✓ Waive a dose finding study for a new indication
- ✓ Waive a clinical drug-drug interaction study
- ✓ Waive a PK, PKPD or efficacy and safety trial or parts of such trials in unstudied or limitedly studied (sub)populations (e.g. children, aged patients, rare disease.)
- ✓ Paediatric investigation plans

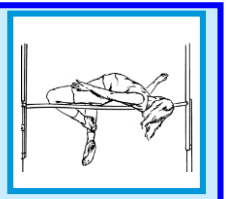
Regulatory scrutiny of MIDD approaches

HIGH IMPACT ← M&S to replace

Scientific Advice, Supporting Documentation, Regulatory Scrutiny +++

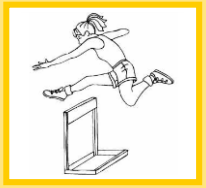
MEDIUM IMPACT ← M&S to justify

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)

What a regulatory assessor looks for in a MIDD report

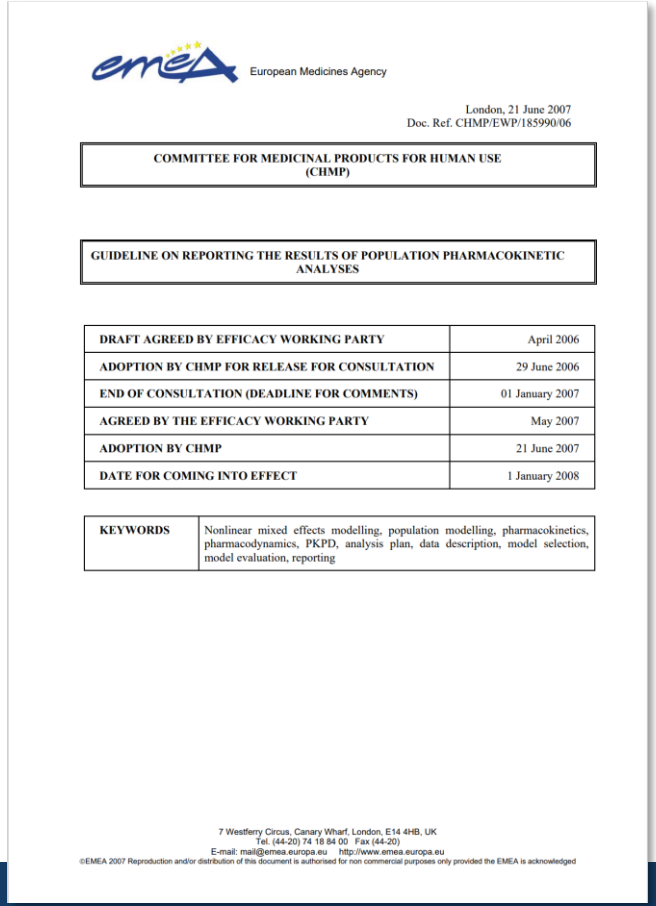
- Scientific question of interest
- Regulatory impact
- Type of model(s)
- Context of use of the model(s)
- Credibility assessment
- Risk based analysis of decision consequence
- Model informed decision

PopPK guideline

Published June 2007

Aim:

This guideline provides guidance on how to present the results of a population pharmacokinetic analysis, in order to provide a level of details that will enable a secondary evaluation (i.e. assessment by regulatory authorities of the conducted analysis and conclusions drawn). Guidance on the content of the analysis plan for the population PK analysis is presented and recommendations for information to be included in key sections of the report are provided.



European Medicines Agency

London, 21 June 2007
Doc. Ref. CHMP/EWP/185990/06

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)

GUIDELINE ON REPORTING THE RESULTS OF POPULATION PHARMACOKINETIC ANALYSES

DRAFT AGREED BY EFFICACY WORKING PARTY	April 2006
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	29 June 2006
END OF CONSULTATION (DEADLINE FOR COMMENTS)	01 January 2007
AGREED BY THE EFFICACY WORKING PARTY	May 2007
ADOPTION BY CHMP	21 June 2007
DATE FOR COMING INTO EFFECT	1 January 2008

KEYWORDS	Nonlinear mixed effects modelling, population modelling, pharmacokinetics, pharmacodynamics, PKPD, analysis plan, data description, model selection, model evaluation, reporting

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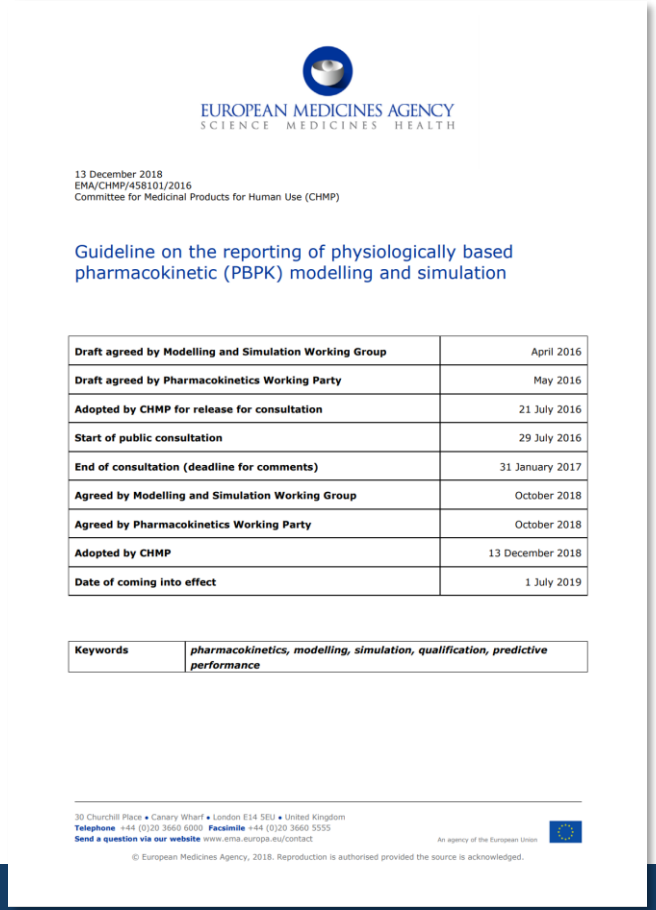
PBPK guideline
Published December 2018

Aim:

To describe the expected content of PBPK modelling and simulation reports included in regulatory submissions, such as applications for authorisation of medicinal products, paediatric investigation plans and clinical trial applications. This includes the documentation needed to support the qualification of PBPK platform for the intended use and the evaluation of the drug model. The guideline applies to commercially available platforms and to in-house built platforms.



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SCIENCE MEDICINES HEALTH

13 December 2018
EMA/CHMP/458101/2016
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

Draft agreed by Modelling and Simulation Working Group	April 2016
Draft agreed by Pharmacokinetics Working Party	May 2016
Adopted by CHMP for release for consultation	21 July 2016
Start of public consultation	29 July 2016
End of consultation (deadline for comments)	31 January 2017
Agreed by Modelling and Simulation Working Group	October 2018
Agreed by Pharmacokinetics Working Party	October 2018
Adopted by CHMP	13 December 2018
Date of coming into effect	1 July 2019

Keywords	***pharmacokinetics, modelling, simulation, qualification, predictive performance***

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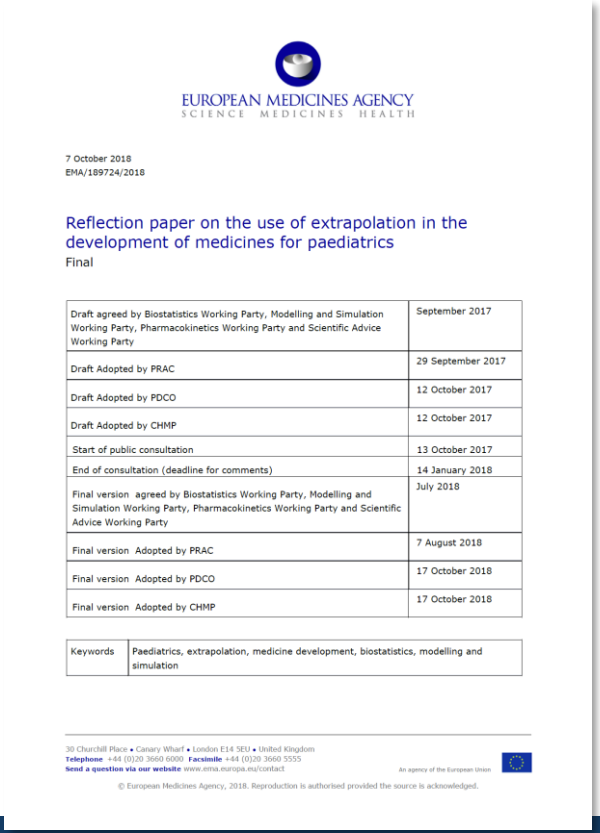
Extrapolation Reflection Paper

Published October 2018

Aim:

The main focus of this document is to provide a framework for extrapolation as an approach to generate evidence on one or more specific research questions to support regulatory assessment of marketing authorisation application in a target population. Specifically, the document promotes the use of quantitative methods to help assess the relevance of existing information in one or more source populations to one or more target population(s) in respect of the disease, the drug pharmacology and clinical response to treatment.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

7 October 2018
EMA/189724/2018

Reflection paper on the use of extrapolation in the development of medicines for paediatrics
Final

Draft agreed by Biostatistics Working Party, Modelling and Simulation Working Party, Pharmacokinetics Working Party and Scientific Advice Working Party	September 2017
Draft Adopted by PRAC	29 September 2017
Draft Adopted by PDCO	12 October 2017
Draft Adopted by CHMP	12 October 2017
Start of public consultation	13 October 2017
End of consultation (deadline for comments)	14 January 2018
Final version agreed by Biostatistics Working Party, Modelling and Simulation Working Party, Pharmacokinetics Working Party and Scientific Advice Working Party	July 2018
Final version Adopted by PRAC	7 August 2018
Final version Adopted by PDCO	17 October 2018
Final version Adopted by CHMP	17 October 2018

Keywords	Paediatrics, extrapolation, medicine development, biostatistics, modelling and simulation

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Guidance documents in the pipeline

- ICH E11A Paediatric Extrapolation
- ICH M12 Drug Interaction Studies
- ICH MIDD Discussion Group – One year remit (2021)
- EMA Role of pharmacokinetics in the development of medicinal products in the paediatric population - revision

Concluding remarks

- It is highly encouraged to discuss MIDD plans with EU regulators
  - Make sure to write the request such that it is clear that M&S experts are desirable in the meetings
- When reporting/communicating models
  - Provide a description of the MIDD approach in the context of the drug development program, not only technical reporting of the model development
  - Clearly state what the purpose of the modelling is and specifically if that is different from previous use of the model(s)
  - Clearly state how the model has been developed and the setup for simulations
  - At any level of communication, make sure to provide sufficient documentation for secondary review of the modelling quality and credibility of the results

- **MIDD is a multidisciplinary effort!**

Useful links

- Innovation in medicines | European Medicines Agency (europa.eu)
- Scientific advice and protocol assistance | European Medicines Agency (europa.eu)
- Qualification of novel methodologies for medicine development | European Medicines Agency (europa.eu)

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- Colleagues at Swedish MPA
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