Federal agency for medicines and health products

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Introduction

Introduction

- Modelling and Simulation (M&S) approaches are increasingly included in regulatory submissions.
- Pharmacometric models are now part of most of regulatory submissions.
- The use of the models often exceed *descriptor* roles and this *change* in their context of use come with *some costs in establishing their credibility.*
- The risk informed credibility framework is a tool that can aid in addressing some of the current challenges.
- We suggest the framework is suitable both for mechanistic and empirical models.

- Their role is also evolving from low to higher impact application
- The EMA PBPK guideline is currently the reference document for regulatory assessment of mechanistic models in the EU network
- The risk informed credibility framework is a tool that can aid in addressing some of the current challenges.
  - We suggest the framework is suitable both for mechanistic and empirical models.

Introduction

Some barriers to a larger acceptability of model informed approaches for High regulatory impact applications

- Lack of standards/consensus/Best Practices for:

- Model planning
- Model development (implementation)
- Model evaluation
- **Data sources and data quality**
- Reporting of modelling and simulation results

- Poor communication between stakeholders

- Terminology issues
- Different perspectives
- Too much/too little technical details on the modeling exercice

Regulatory assessment of M&S: EMA Regulatory procedures

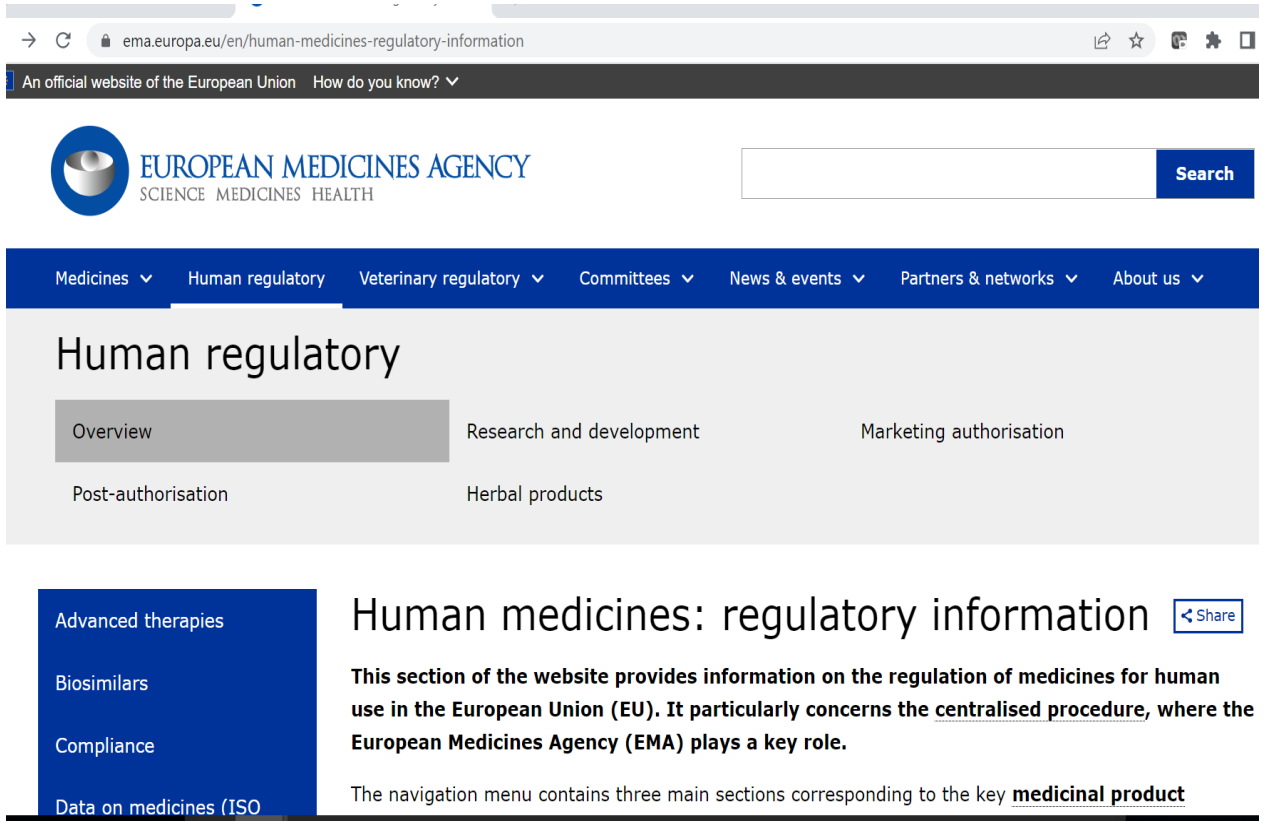
Applications of modelling and simulation in regulatory submissions

- Trial design optimization
- Dose finding/selection for early phase and peadiatric studies
- Description of PK data and quantitative characterization of their determinants (e.g. age, bodyweight, organ (liver, kidney) impairment, co-medications, co-morbidities)
- Characterization of Pharmacokinetic (PK) Drug-drug interactions (waiver of dedicated studies)
- Waiver of efficacy/safety study (extrapolation)
- Characterization of the impact of change in formulation or regimen on drug efficacy or safety (e.g. modified release, biosimilars, etc.)
- Etc.

EMA Regulatory procedures where M&S assessment is needed

models and related applications are included in the following regulatory procedures:

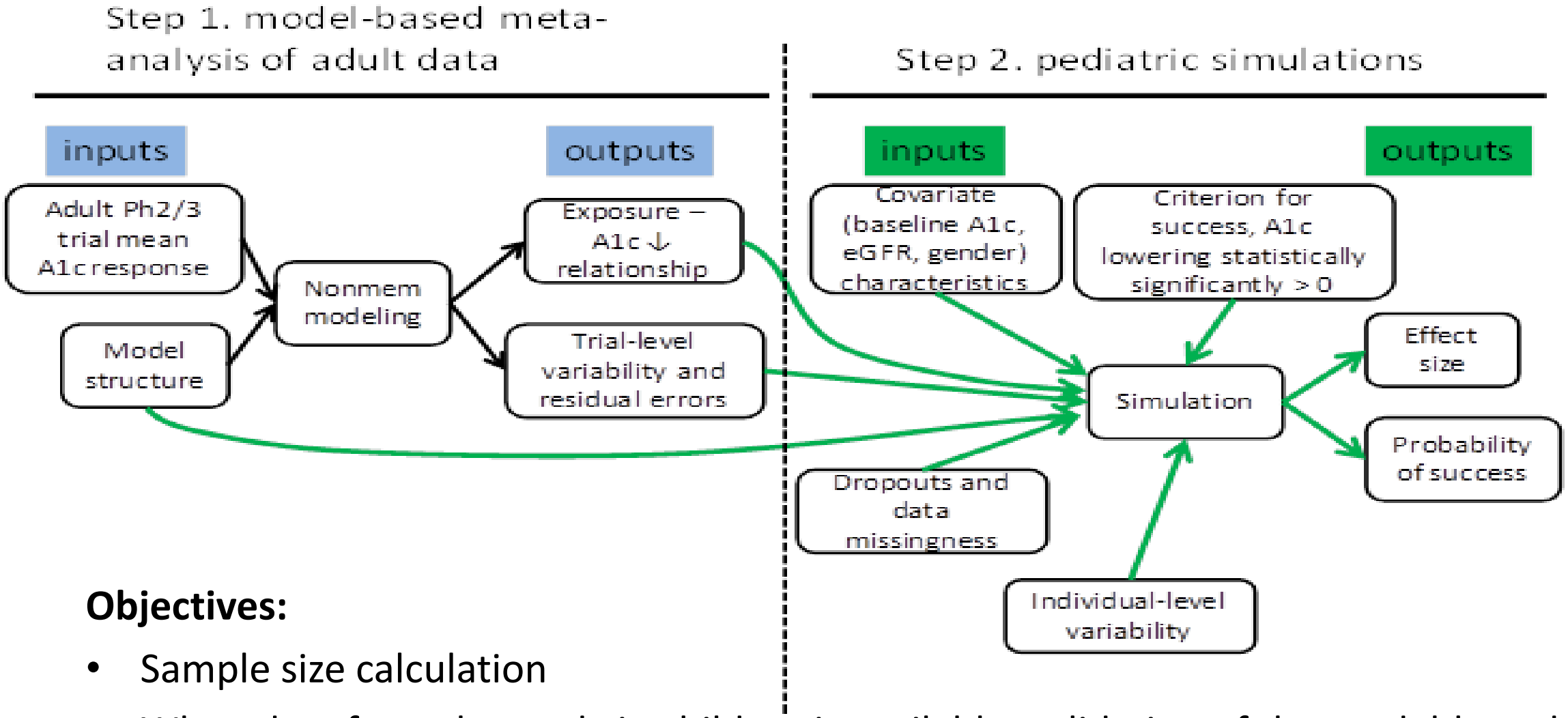
- ***Innovation Task Force (ITF) briefing meetings***
- *Scientific advices*
- *Protocol assistance*
- *Pediatric investigation plans (PIP)*
- ***Qualification advice***
- ***Qualification opinion***
- *Marketing authorization applications*
- *Post-marketing Signals*
- *Referrals*
- *Etc.*



Example:

Request for *Scientific advices to support a modification of the Pediatric investigation plan(PIP) for an Sodium-glucose Cotransporter-2 (SGLT2) inhibitor*

- **Advice on the Paediatric development programme**
- The agreed PIP included two studies: **PK/PD study and Safety/Efficacy (SE) study**
- High likelihood that agreed paediatric programme will not meet its scientific or regulatory goals due to **poor recruitment Sponsor Proposal:** Changes to the T2DM paediatric programme utilising an **extrapolation framework**

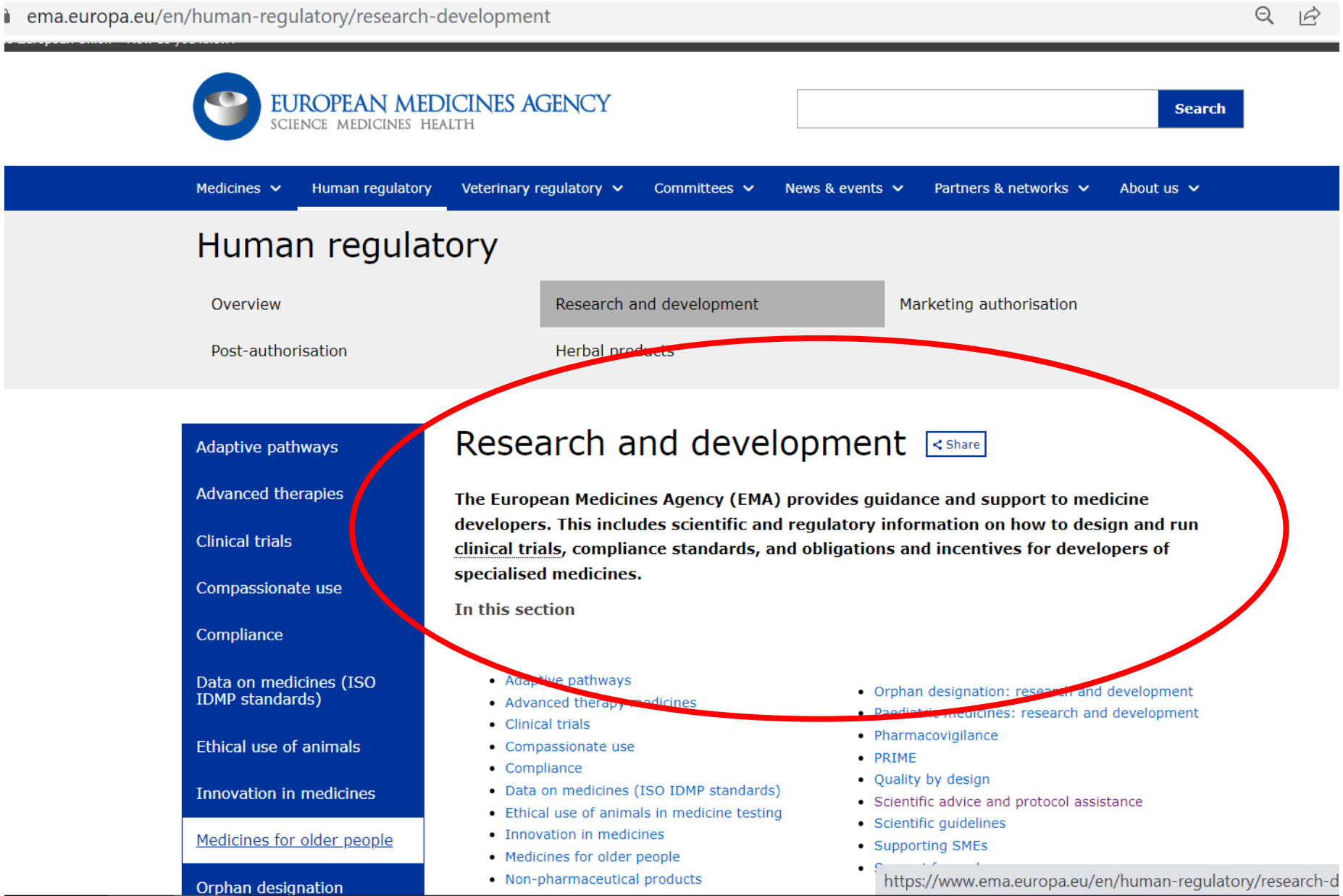


Objectives:

- Sample size calculation
- When data from the study in children is available, validation of the model-based extrapolation of efficacy from adults to children

Regulatory assessment of M&S: EMA Regulatory Guidance documents

EMA guidance documents



EMA guideline on reporting of PBPK

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-reporting-physiologically-based-pharmacokinetic-pbpk-modelling-simulation_en.pdf

EUROPEAN MEDICINES AGENCY
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

EMA guideline on reporting of PBPK

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-reporting-physiologically-based-pharmacokinetic-pbpk-modelling-simulation_en.pdf

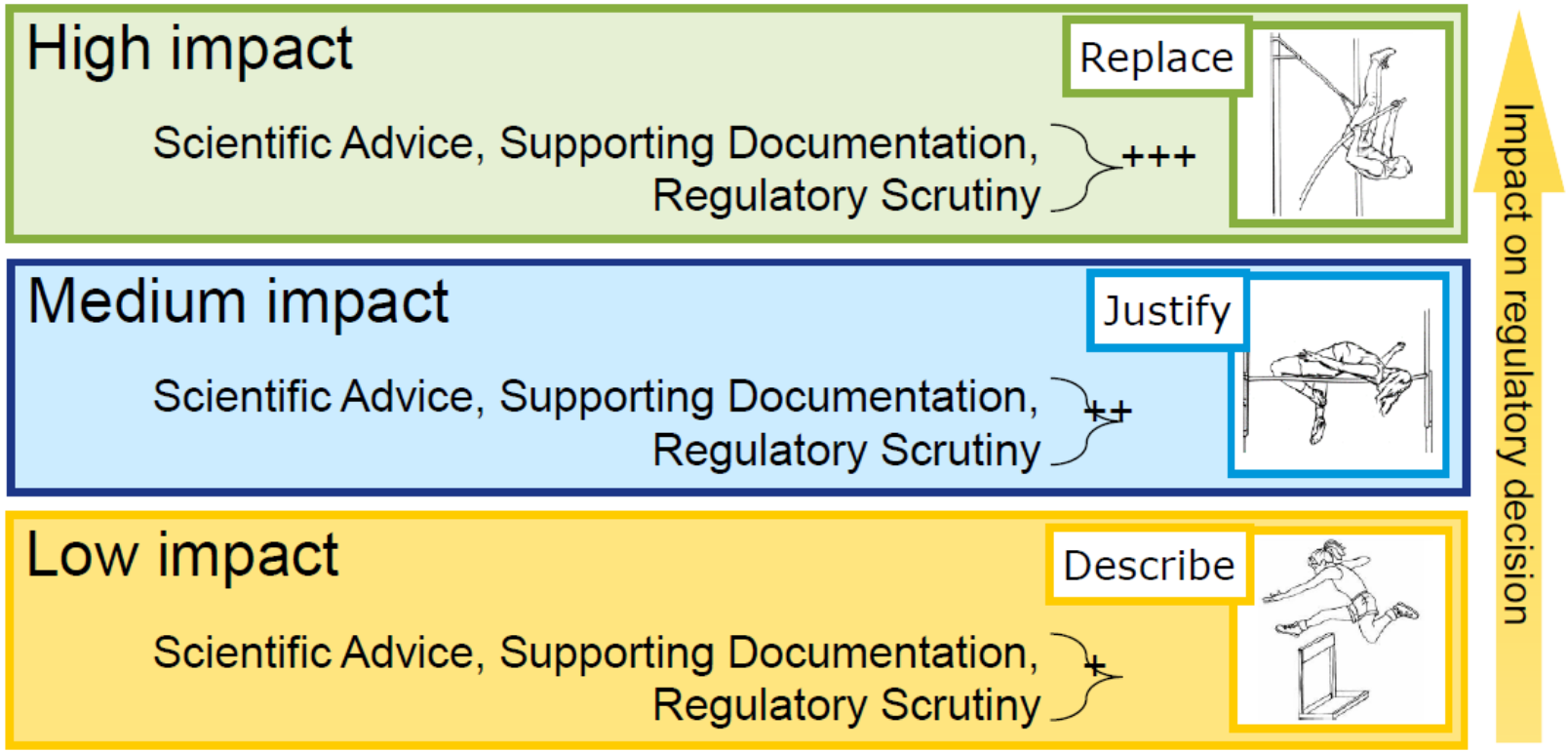
Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

Table of Contents

Regulatory assessment of M&S: Regulatory impact

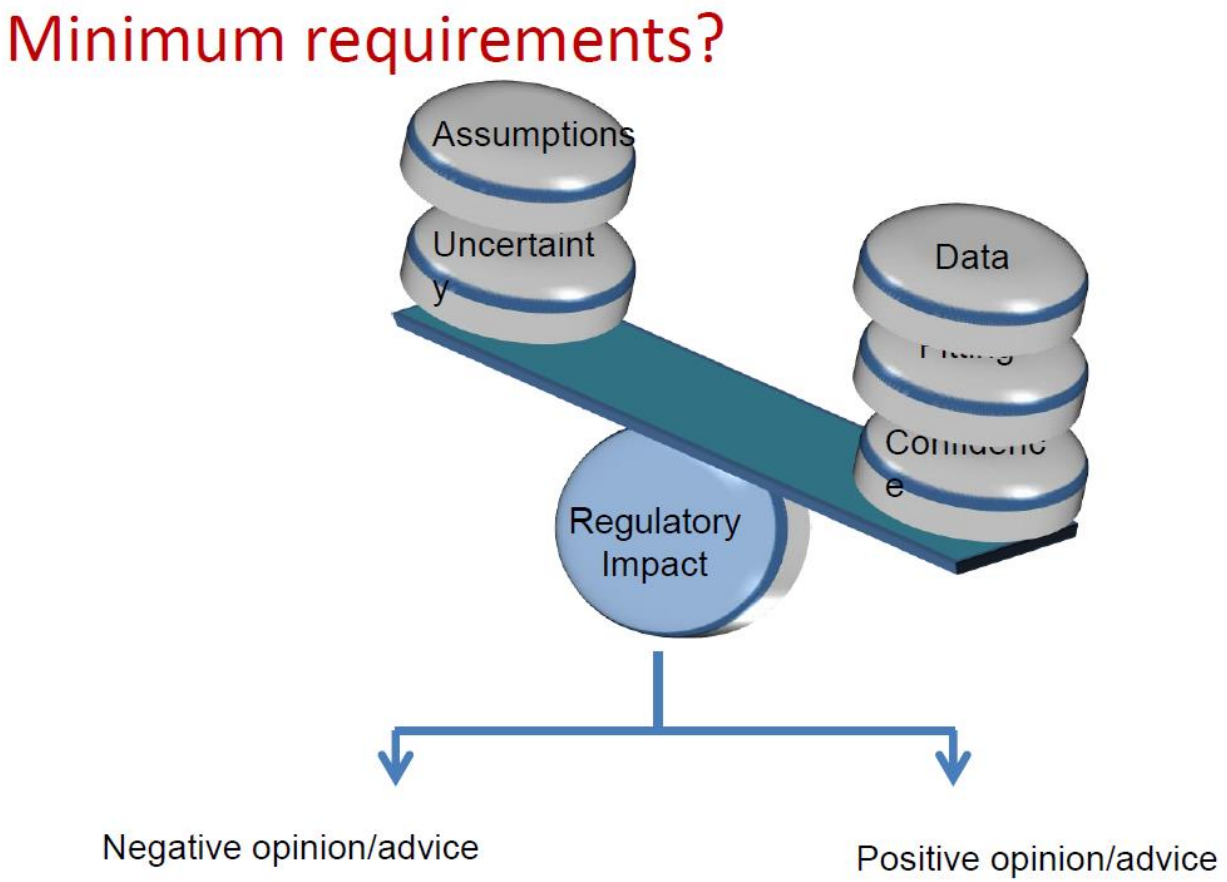
Regulatory impact

Framework for M&S in Regulatory Review
According to impact on regulatory decision



From EMA-EFPIA Modelling and Simulation Workshop, December 2011

Regulatory impact



Regulatory assessment of M&S: Risk-based credibility assessment framwork

MIDD vs credibility assessment

- Model as backbone of knowledge
  - consolidate knowledge
  - inform next step
  - …iterate…
  - open sponsor/regulator dialogue on potential applications

  -> model informed drug development (MIDD)

- Model as a **method** to answer **a question**
  - specific applications
  - model assessment

  -> credibility framework

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Assessing Credibility of Computational Modeling Through Verification and Validation: Application to Medical Devices

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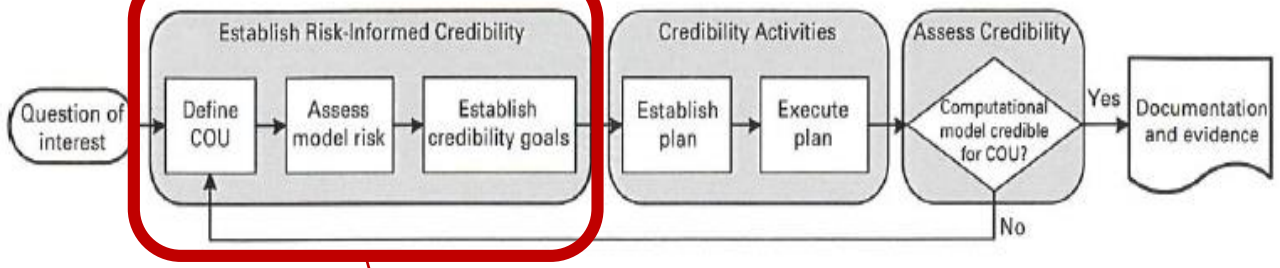
Figure 2.4-1 Process Diagram of the Risk-Informed Credibility Assessment Framework



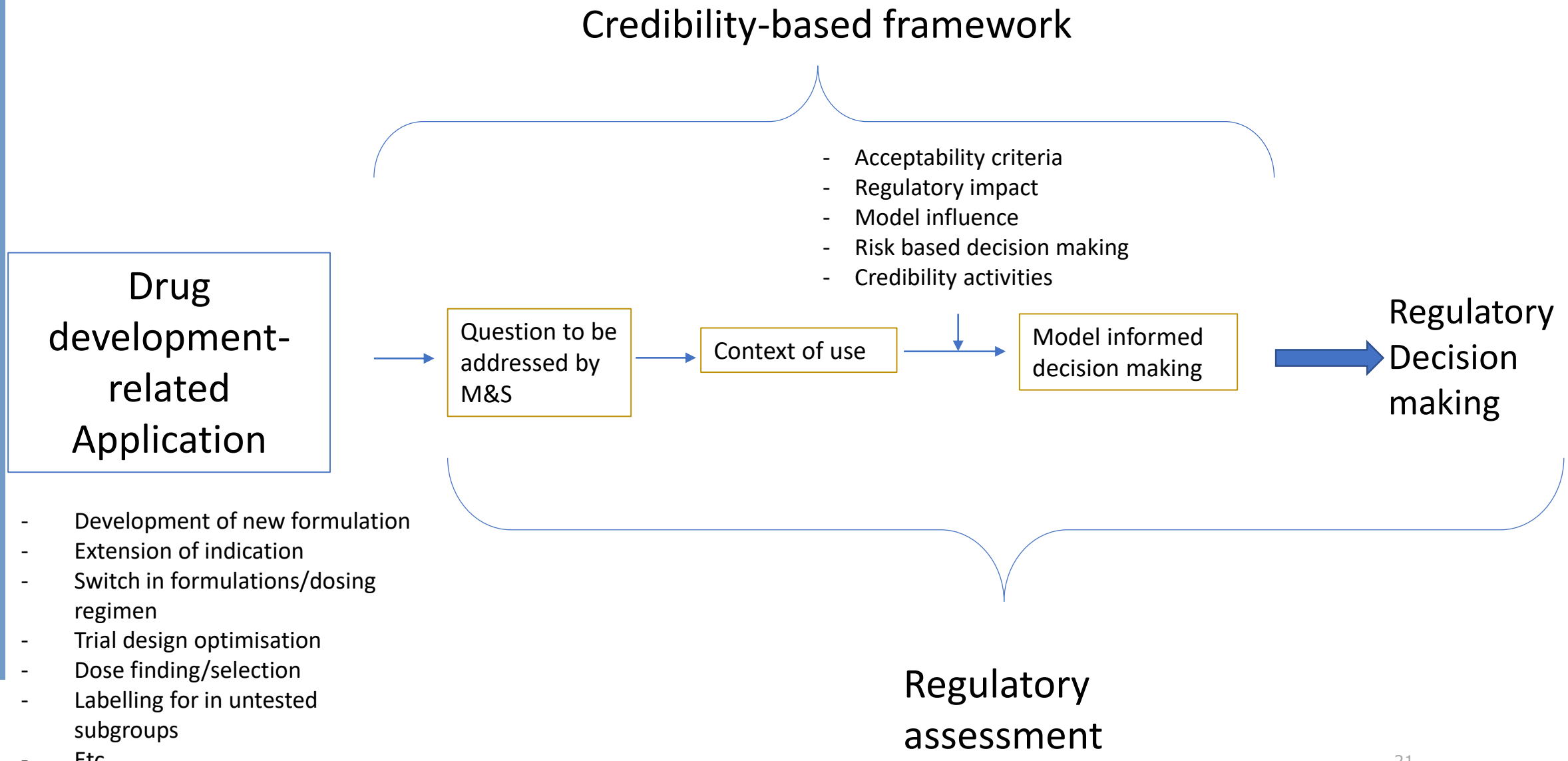
Standard may also be used by regulatory bodies to evaluate the appropriateness and adequacy of credibility activities and the overall model credibility.

2.2 Purpose

Interface between

- what we want to know
- the method (proposed) used to answer

Risk-based credibility assessment as a supporting tool for model evaluation



- Development of new formulation
- Extension of indication
- Switch in formulations/dosing regimen
- Trial design optimisation
- Dose finding/selection
- Labelling for in untested subgroups
- Etc,

Risk-based assessment of medical products

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Methods 185 (2021) 120–127

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journal homepage: www.elsevier.com/locate/ymeth

In silico trials: Verification, validation and uncertainty quantification of predictive models used in the regulatory evaluation of biomedical products

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Citation: CPT Pharmacometrics Syst. Pharmacol. (2020) 9, 21–28; doi:10.1002/psp4.12479

WHITE PAPER

Consideration of a Credibility Assessment Framework in Model-Informed Drug Development: Potential Application to Physiologically-Based Pharmacokinetic Modeling and Simulation

Colleen Kuemmel[1]*, Yuching Yang[1], Xinyuan Zhang[1], Jeffry Florian[1], Hao Zhu[1], Million Tegenge[2], Shiew-Mei Huang[1], Yaning Wang[1], Tina Morrison[3] and Issam Zineh[1]

Submission to "CPT: Pharmacometrics & Systems Pharmacology" 3/2/2021

Scientific and regulatory evaluation of mechanistic *in silico* drug and disease models in drug development: building model credibility

Flora T. Musuamba[1,2,3,], Ine Skottheim Rusten[1,4], Raphaëlle Lesage[5,6], Giulia Russo[7], Roberta Bursi[8], Luca Emili[8], Gaby Wangorsch[1,9], Efthymios Manolis[1,10], Kristin E. Karlsson[1,11], Alexander Kulesza[12], Eulalie Courcelles[12], Jean-Pierre Boissel[12], Cécile F. Rousseau[13], Emmanuelle Voisin[13], Rossana Alessandrello[14], Nuno Curado[15], Enrico Dall'ara[16], Blanca Rodriguez[17], Francesco Pappalardo[7], Liesbet Geris[5,6 18]*

WHITE PAPER

Scientific and Regulatory Evaluation of Empirical Pharmacometric models:

An application of the risk informed credibility assessment framework.

Ine Skottheim Rusten[1, 2], Flora Musuamba Tshinanu[2, 3]

Risk-based assessment of medical products

Credibility matrix	Entry
Investigational product	
Type of model	
Scientific question(s) of interest	
Context of use	
Acceptability criteria	
Regulatory impact	
Risk based analysis of decision consequence	
Credibility activity results	
Model informed decision	

Refs: Skottheim Rusten and Musuamba Tshinanu. White paper. Scientific and regulatory evaluation of empirical pharmacometric models: An application of the risk informed credibility assessment framework. Submitted.
Musuamba Tshinanu et al. White paper. Scientific and regulatory evaluation of mechanistic in silico drug and disease models in drug development: building model credibility. CPT. Pharmacometrics & Systems Pharmacology

Risk-based assessment of M&S

Data quality is Key!!!

- Data sources
- Data relevance

EMA guideline on reporting of PBPK

4.4. Model parameters

4.4.1. Assumptions

An explicit and systematic discussion of the assumptions made in the submitted system and drug model and in the associated analysis should be provided. Data to support the assumptions and their biological and/or pharmacological rationale should be presented and discussed, as well as the impact the assumptions have on the model and the outcome. A better contextual understanding of what might be expected if important assumptions are incorrect may be obtained through testing alternative values, with modified models or via a sensitivity analysis of the relevant parameters (see Section 4.7.1). The approaches used to test the assumptions and the outcomes should be presented.

4.4.2. System-dependent parameters

The system-dependent parameters, including physiological parameters for the population(s) for which qualification is claimed, should be presented and justified. Any modification of default values of system-dependent parameters of the dataset should be highlighted. Literature references should be provided as full articles and the rationale for the chosen system-dependent parameter values should be given. The data should be presented in an appendix to the report in a structured way to allow assessment

Any modification of the default values of system-dependent parameters of the dataset should be summarised and justified e.g., changing the values of the degradation constant (k_{deg}) of metabolising enzymes (Guideline on investigation of drug interactions, CPMP/EWP/560/95/Rev. 1). For paediatric modelling the effect of ontogeny and allometry on system values e.g. renal function or albumin concentrations, could be justified using a worst case approach supported by peer reviewed references.

4.4.3. Drug parameters and the drug model

The PBPK report should include a thorough description of the drug model structure and drug-dependent parameters.

A summary of the drug-specific parameter names and values (mean with known or predicted variability: SD or range [min-max]), and the sources of the values should be included in a tabular format. The value of the drug-specific parameter should particularly be justified in the text.

The parameters described should include physicochemical properties and ADME data that were used to parameterise the model. If there is more than one source of a parameter with notably different values, the value chosen should be justified and the consequences discussed.

V&V - Credibility activities

Activity	Credibility factor	Rigor			Credibility	Comment
		Selected	Range	Current/ Obtained		
Verification						
Code	Software quality asssurance		(a-c)			
	Numerical code verification		(a-d)			
Caclulation	Discretization error		(a-c)			
	Numerical solver error		(a-c)			
	Use error		(a-d)			
Validation						
Computational model	Model form		(a-c)			
	Model inputs					
	Quantification of sensitivities		(a-c)			
	Quantification of uncertainties		(a-c)			

Activity	Credibility factor	Rigor			Credibility
		Selected	Range	Current/ Obtained	
Comparator	Test samples. Measurement uncertainty				
	Quantity		(a-c)		
	Range of characteristics		(a-d)		
	Measurements		(a-c)		
	Uncertainty		(a-d)		
	Intrinsic and extrinsic factors****				
	Quantity		-		
	Range		(a-d)		
	Measurements		(a-c)		
	Uncertainty of test condition measurements		(a-d)		
Assessment	Equivalency of input parameters		(a-c)		
	Output comparison				
	Quantity		(a-b)		
	Equivalence		(a-c)		
	Rigour		(a-d)		
	****Agreement		(a-c)		
Applicability					
	Relevance of quantities of interest		(a-c)		
	Relevance of the validation activities to the COU		(a-d)		

Refs: Skottheim Rusten and Musuamba Tshinanu. White paper. Scientific and regulatory evaluation of empirical pharmacometric models: An application of the risk informed credibility assessment framework. Submitted.
The American Society of Mechanical Engineers. Assessing Credibility of Computational Modeling through Verification and Validation: Application to Medical Devices (American Society of Mechanical Engineers, New York, 2018).

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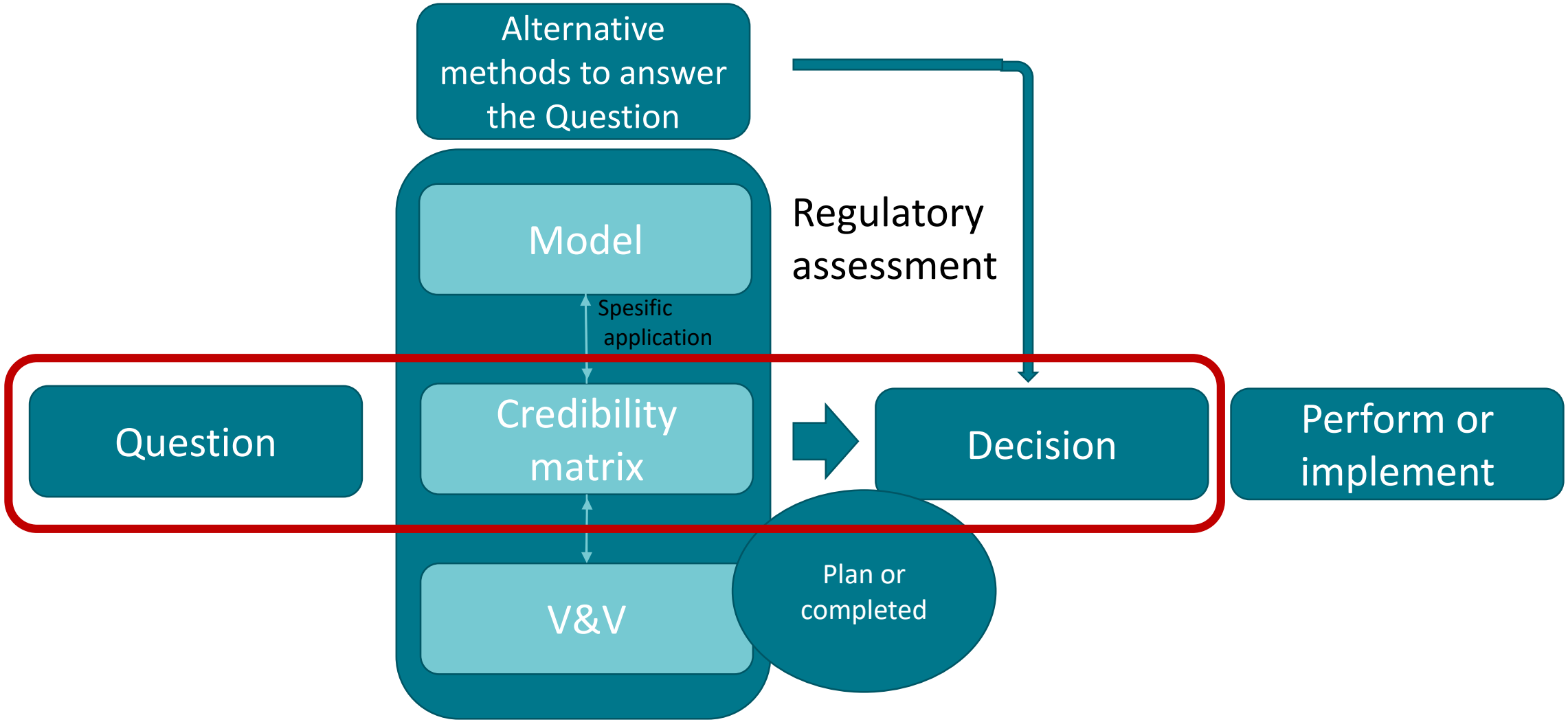

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Conclusion

Conclusion

- **Regulatory assessment is maturing with the increasing experience.**
- **In the context of drug assessment, M&S is a method to answer a question.**
- **The risk informed credibility framework is an interesting tool for submission of modelling and simulation results for regulatory assessment**
- **The regulatory impact, the data quality and the credibility assessment are important considerations for regulatory qualification of PBPK models**

Thank you!

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