Model Credibility Assessment in PBPK: Potential Application of a Risk-Informed Evidentiary Framework

Colleen Kuemmel, PhD

Office of Clinical Pharmacology, US Food & Drug Administration

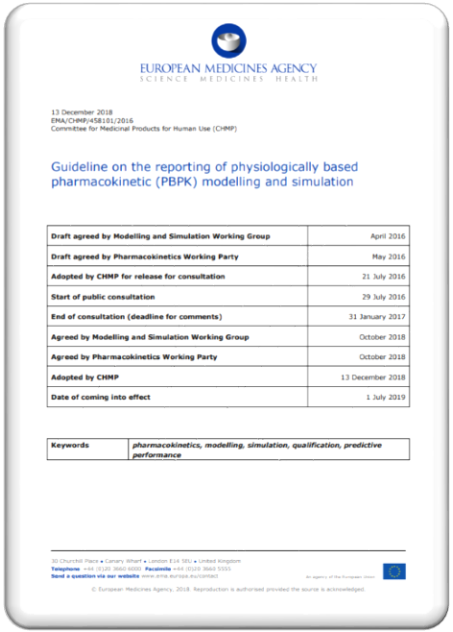
Development of Best Practices in Physiologically Based Pharmacokinetic Modeling to Support Clinical Pharmacology Regulatory Decision-Making FDA Public Workshop

November 18, 2019
Silver Spring, MD

Advancing PBPK through Guidance

What makes a PBPK model credible for regulatory applications?

EMA guideline (2018)



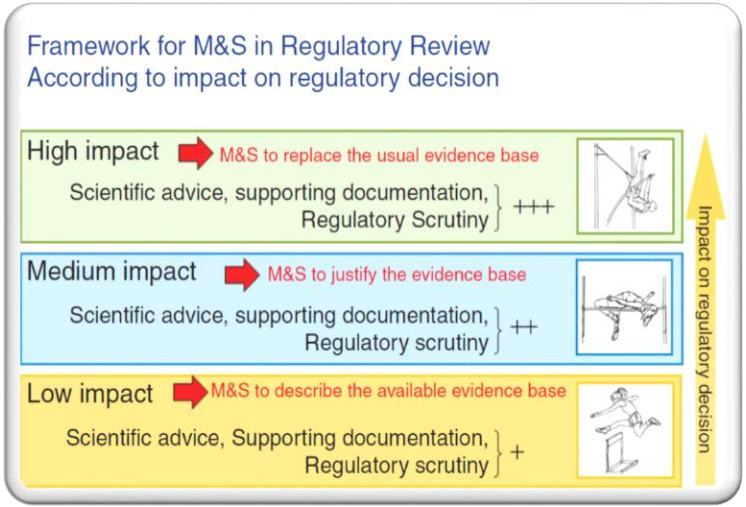
EUROPEAN MEDICINES AGENCY
SCIENCE · MEDICINES · HEALTH

13 December 2018
EMA/CHMP/458181/2016
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*

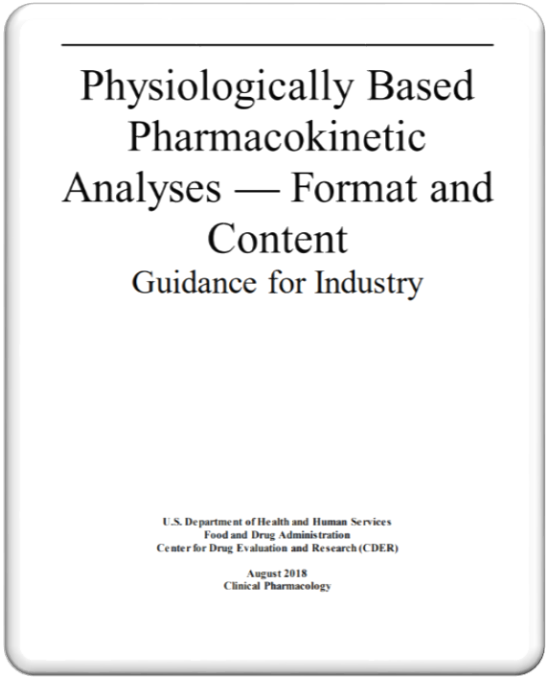


PMID: 23835942
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-reporting-physiologically-based-pharmacokineticpbpk-modelling-simulation_en.pdf

Advancing PBPK through Guidance

What makes a PBPK model credible for regulatory applications?

FDA guidance (2018)



https://www.fda.gov/media/101469/download

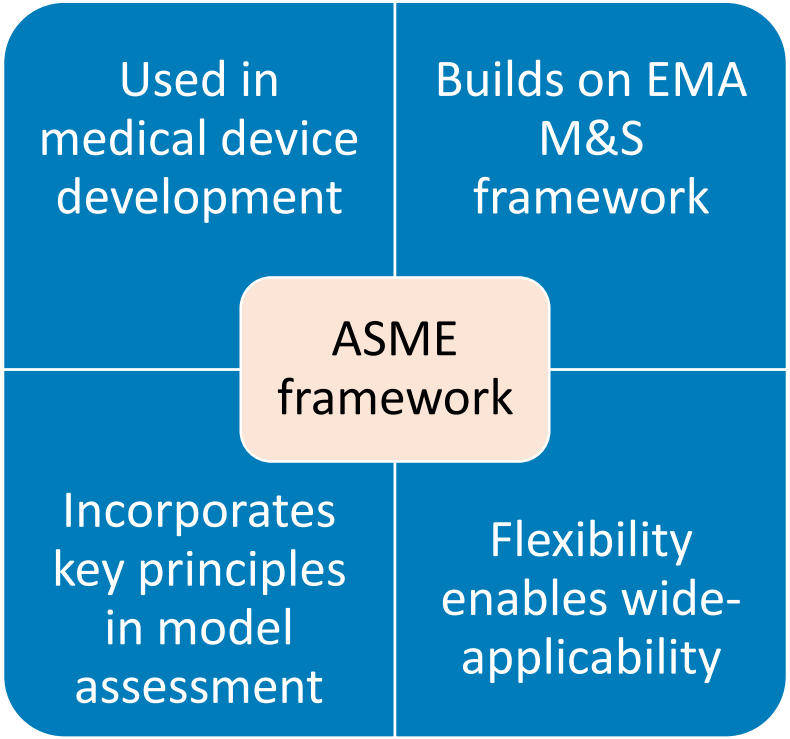
Inflection Point

- Mechanistic knowledge still evolving
- Understanding of high-level model credibility principles
- Inconsistent use of terms and definitions

Consideration for an overarching framework

- Standardize language
- Establish a uniform approach to model evaluation
- Harmonize

Consideration of an Overarching Framework



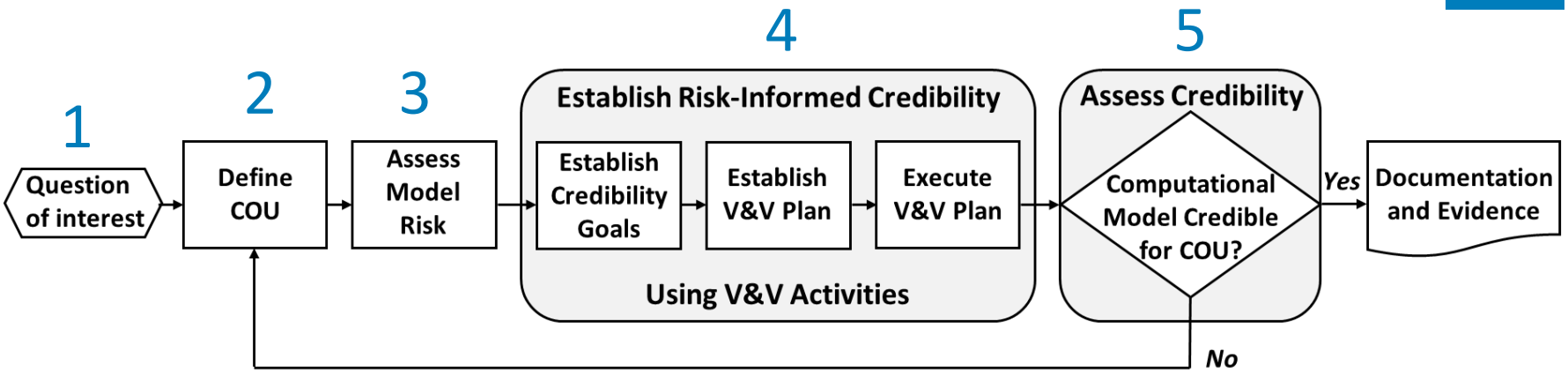
ASME: American Society of Mechanical Engineers

ASME Framework Terminology

Model credibility	: trust in the predictive capability of a model
	// credibility can be established through collection of V&V evidence
Verification	: evaluation of the software
	// Verification demonstrates equations are solved correctly
Validation	: evaluation of the model
	// Validation demonstrates correct equations are being solved

V&V: verification and validation

ASME framework

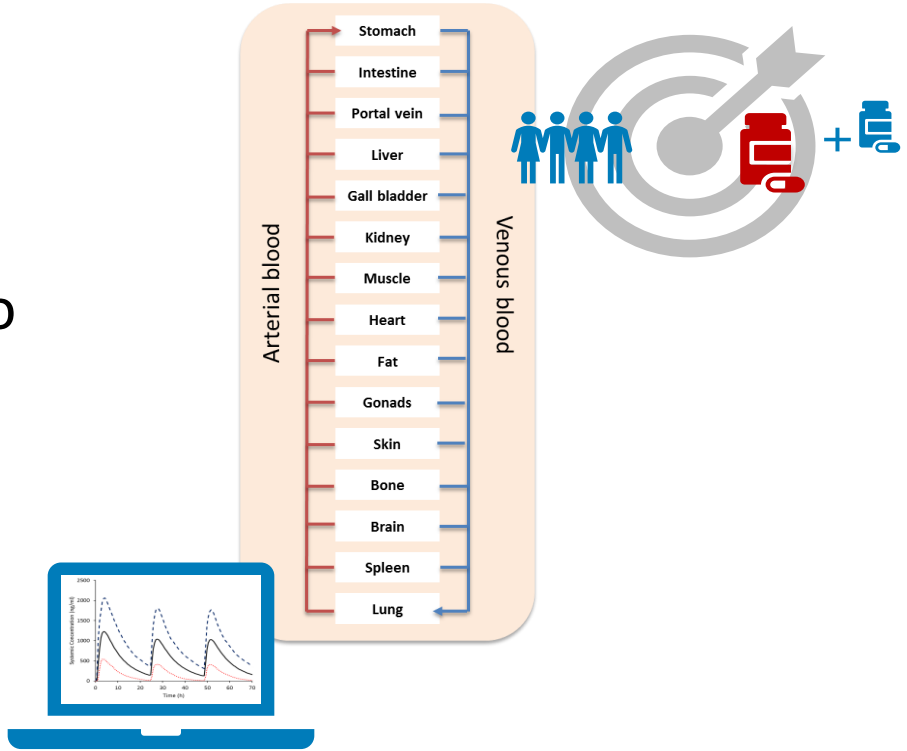


- Five key concepts; not entirely new
- Tailorable steps enable framework to be case-specific
- Requires a team of experts

PMID: 31652029

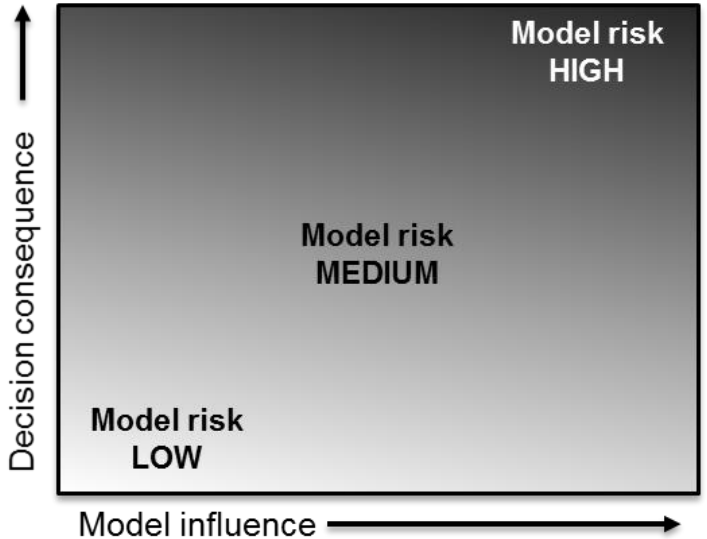
Defining Question of Interest & COU

- Question of interest:
  key question or decision
- Context of use (COU):
  how the model will be used to address the question
- Question of interest maybe broader than COU



Assess Model Risk

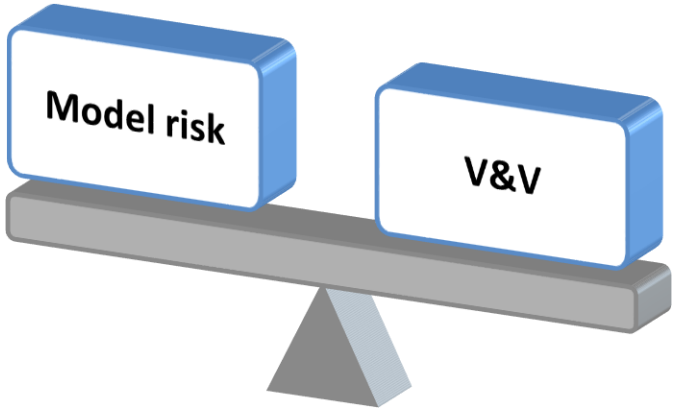
- Model influence: weight of the model in totality of evidence
- Decision consequence: potential consequences of a wrong decision



Modified from ISBN: 9780791872048

Assess Model Risk

- Rigor of V&V evidence commensurate with model risk
- Model risk drives selection of credibility activities (V&V) and goals



Establishing Credibility: Verification

ASME framework

- ☐ Code
- ☐ Calculation

Application to PBPK

Check for errors, ensure reliability & reproducibility

Details of verification based on COU, rigor linked to model risk

Software evaluation not described in FDA guidance but quality checks are routine

Establishing Credibility: Validation

ASME framework

- ☐ Model
- ☐ Comparator
- ☐ Assessment

Application to PBPK

Mathematical model structure and input parameters

Explore uncertainty and sensitivity, including mechanistic assumptions

Establishing Credibility: Validation

ASME framework

- ☐ Model
- ☐ Comparator
- ☐ Assessment

Application to PBPK

New terminology, but familiar concept – observed data serves as 'comparator' for predicted data

Various types of validation evidence maybe considered depending on COU and availability of data

Establishing Credibility: Validation

ASME framework

- ☐ Model
- ☐ Comparator
- ☐ Assessment

Application to PBPK

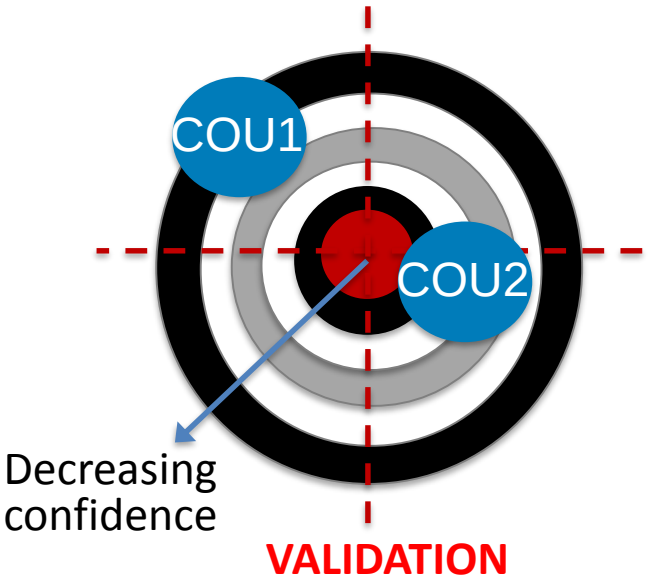
Rigor and agreement of output
E.g., low risk – qualitative vs.
high risk – quantitative assessment

Details of validation based on COU, rigor of evidence to balance model risk

Establishing Credibility: Applicability

ASME framework

☐ Applicability



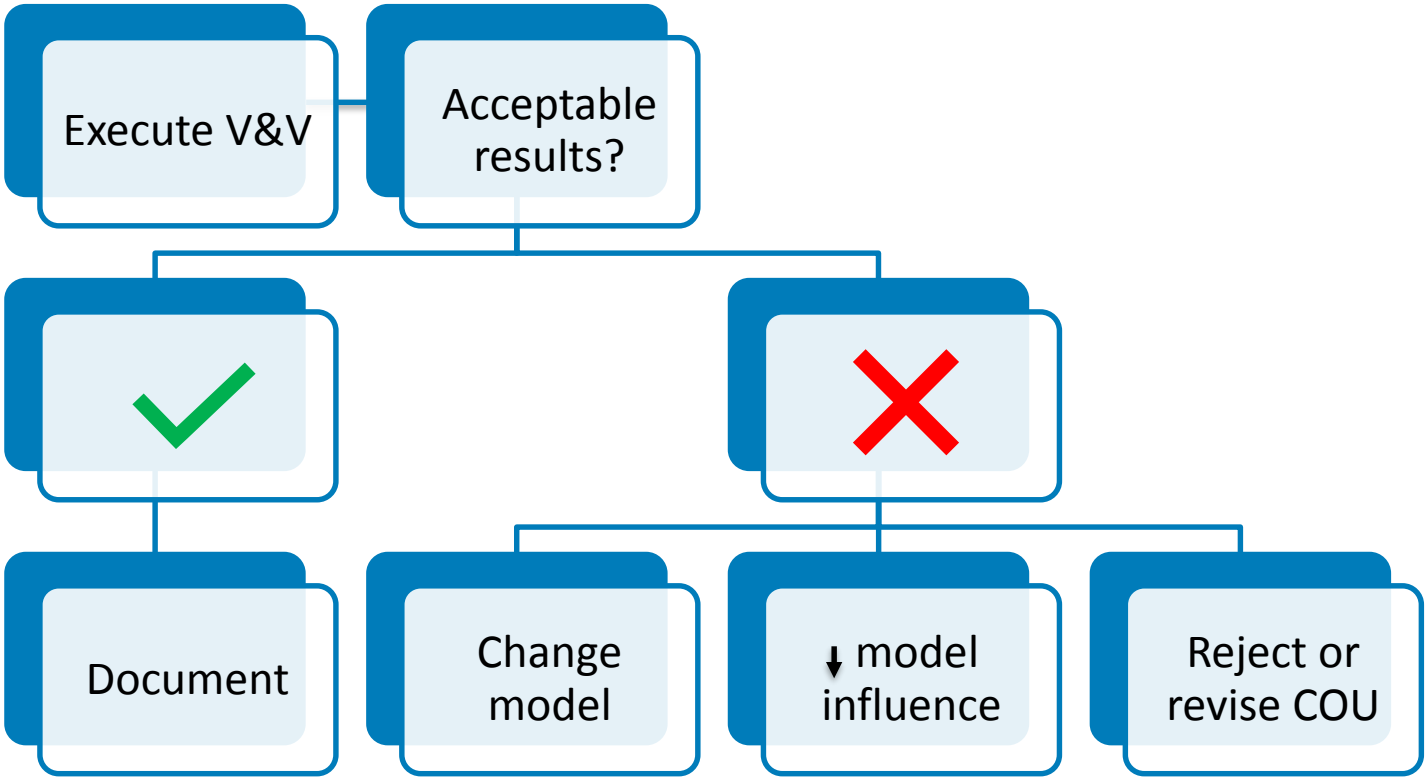
Application to PBPK

Not currently in guidance but intuitive

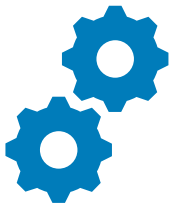
Credibility increases when there overlap between COU and validation

Comparator study conditions will not exactly match simulation but relevance should be considered

Assessing Credibility



Potential Impact



Standardized terminology and approach to assessment

Starting point for discussions in early development

De-risk and advance PBPK and perhaps other MIDD approaches

Provides path towards harmonization

Acknowledgements

- OCP
  - Issam Zineh
  - Yuching Yang
  - Xinyuan Zhang
  - Jeffry Florian
  - Hao Zhu
  - Shiew Mei Huang
  - Yaning Wang
- CDRH
  - Tina Morrison
  - Pras Pathmanathan
- CBER
  - Million Tegenge
- Workshop organizers


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Questions

1. What parts of the framework can be readily applied to drug development and regulatory review for PBPK?

2. What part(s) of the framework may need to be discussed further or modified?

3. What steps should be considered if the goal is harmonization?

ASME Credibility Activities and Factors

Activity	Credibility Factor
Verification	
Code	Software quality assurance Numerical code verification
Calculation	Discretization error Numerical solver error Use error
Validation	
Model	Model form Model inputs (incl. quantification of sensitivities and uncertainties)
Comparator	Test samples (incl. quantity, range of characteristics, uncertainty of measurements) Test conditions " "
Assessment	Equivalency of input parameters Output comparison (incl. quantity, equivalency, rigor, agreement)
Applicability	Relevance of the quantities of interest Relevance of the validation activities to the COU

ISBN: 9780791872048

Summary of FDA PBPK Guidance

Executive Summary	• Objectives (intended uses) • Overview of model development and simulations • Key conclusions
Introduction	• Brief and relevant drug's physicochemical, PK, PD, and E-R properties • PBPK related regulatory history including cross-referencing to PBPK study reports for different intended uses
Materials and Methods	• Details about model development, verification/modification (justification), and application • Details and sources of input parameters and key assumptions • Simulation design • Software (version)
Results	• Results from model verification/validation, and sensitivity analysis • Results from model application
Discussion	• Discuss the adequacy of PBPK analyses to support intended uses • Discuss any recommendation based on PBPK analyses and additional relevant evidence • Discuss model limitation
Appendices	• List of tables, figures, acronyms and abbreviations, references

https://www.fda.gov/media/101469/download

Summary of EMA PBPK Guideline

Background information	• Objectives and intended regulatory purpose • Information about the drug including physicochemical properties, ADME, solubility, permeability, E/R, PK, DDI, pharmacogenetics • Summary of clinical studies (data relevant to intended use) • Quantitative mass-balance diagram
Platform qualification	• Evaluation of 8-10 compounds with similar ADME to intended use • Verification of correct mathematical model structure; error-free
Model parameters	• Data to support assumptions and their rationale • Justification of system-dependent parameters • Description of drug model structure and drug-dependent parameters
Model development	• Overview of model building process
Simulation with intended scenario	• Description of study design to be simulated and virtual population
Platform and drug model evaluation and results	• System and drug model evaluation; predictive performance of drug model assessed by comparison of predicted and observed data • Sensitivity analyses
Discussion of regulatory application	• Contribution of PBPK M&S to regulatory decision-making and use • Confidence/Uncertainty

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