Challenges in Model Qualification: When One Size Does Not Fit All

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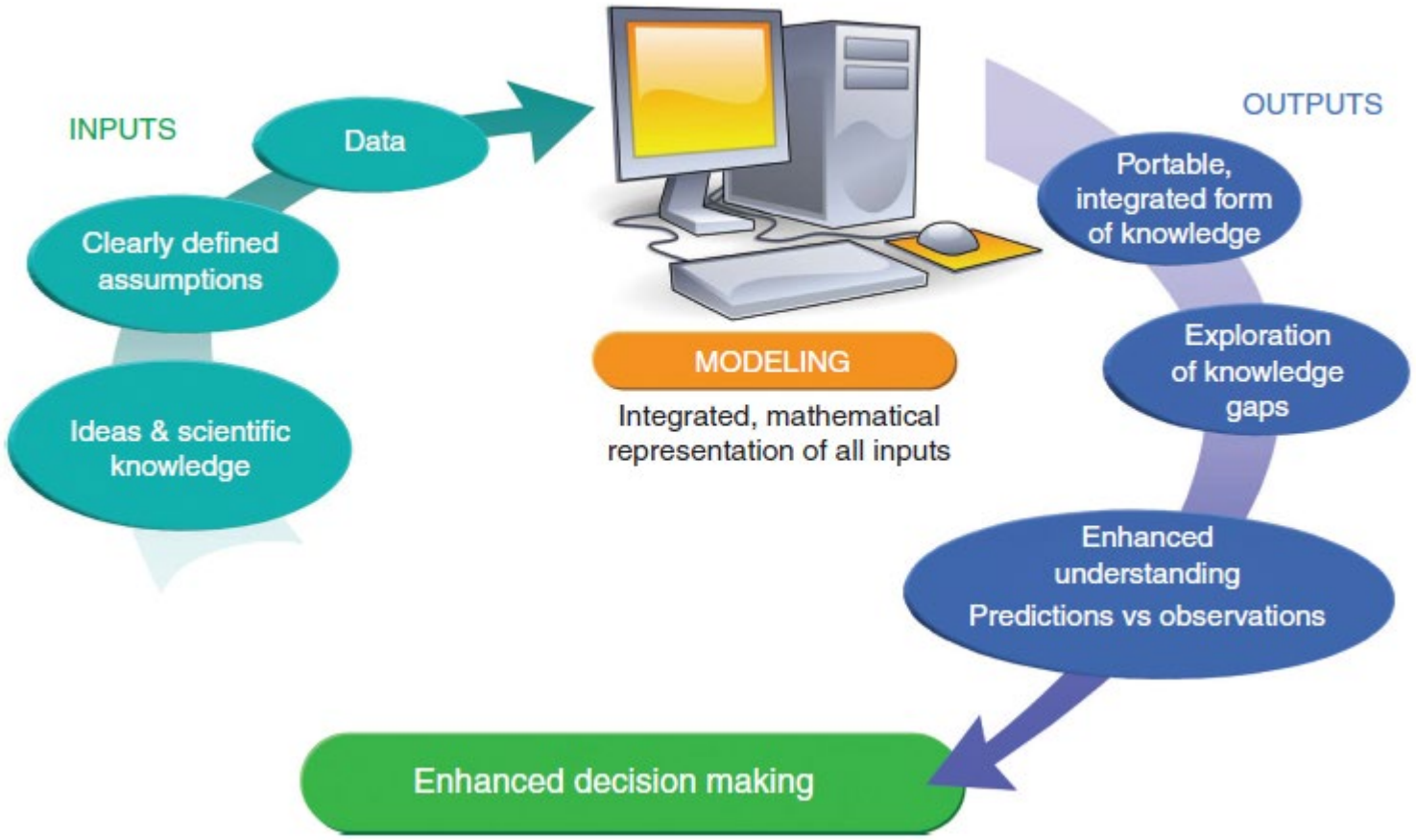
Disclaimer

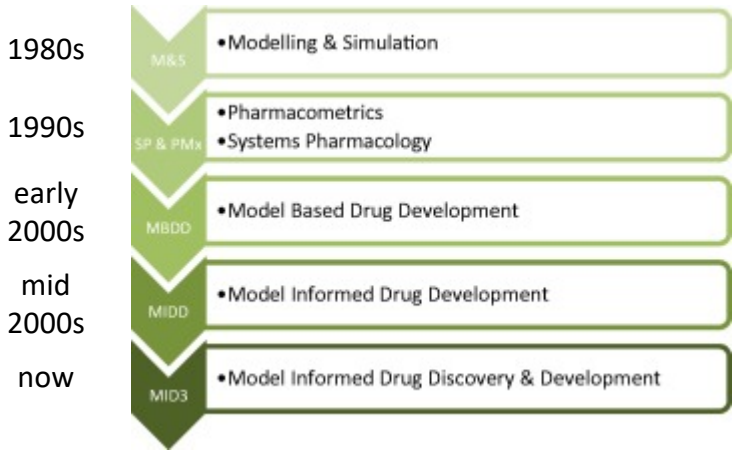
- I am a consultant to pharmaceutical industry
- I like applied & interdisciplinary research

The Idea Behind Using Models



Visser et al. (2014) CPT Pharmaco Sys Pharmacol

A Reflection on Where We "…" :



… "Were":

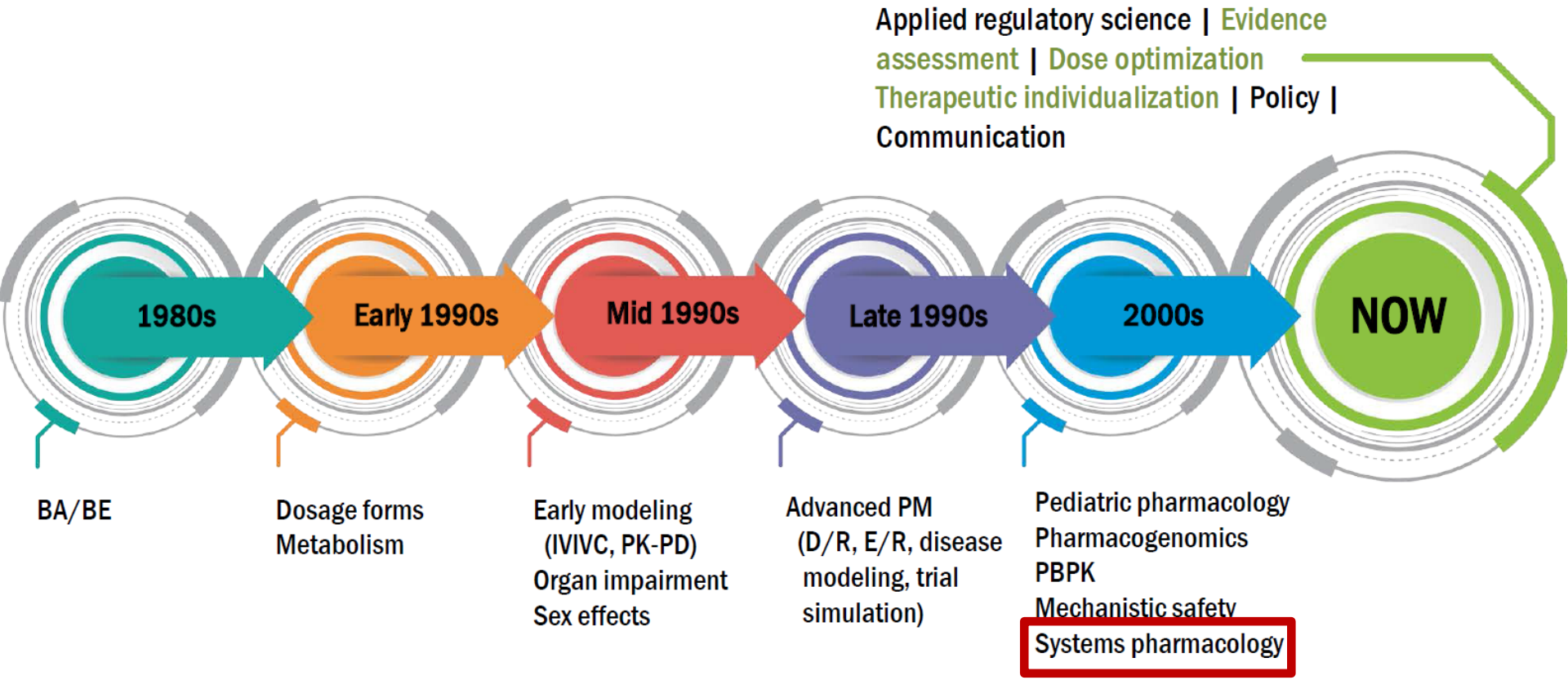
The **learn & confirm** paradigm as the basis for modern M&S:

1) What do we want to know?
2) How confident do we want to be?
3) What are we willing to assume?

… "Are":

MID3: "A quantitative framework for prediction and extrapolation, centered on knowledge and inference generated from integrated models of compound, mechanism and disease level data and aimed at improving the quality, efficiency and cost effectiveness of decision making"

Regulatory Buy-In Along the Way

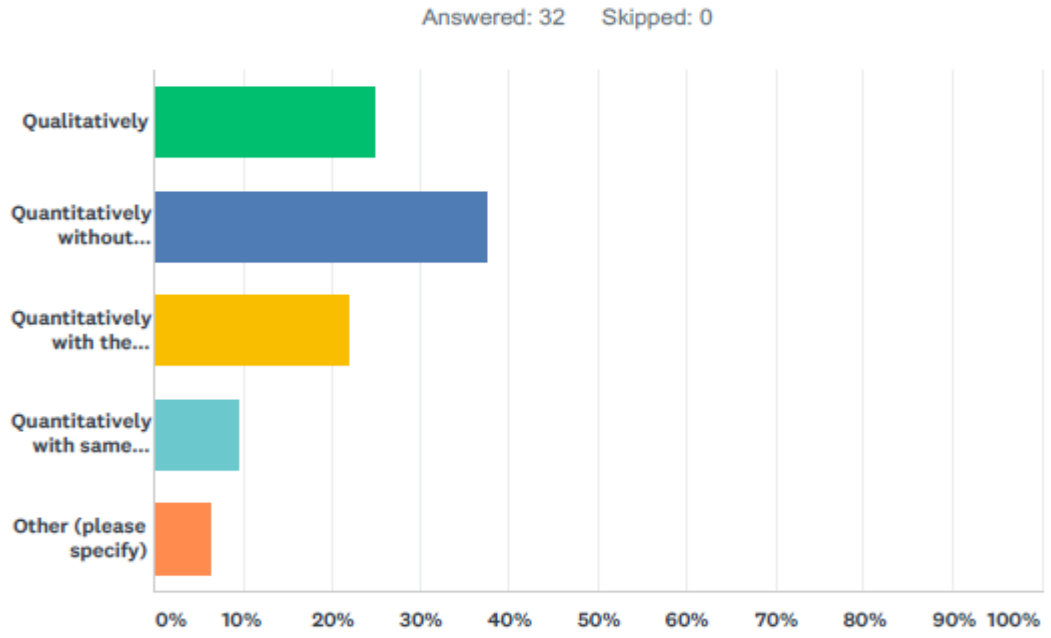


Courtesy of Joe Grillo, FDA

Latest tool in the tool box

This Calls for Challenges to Be Overcome

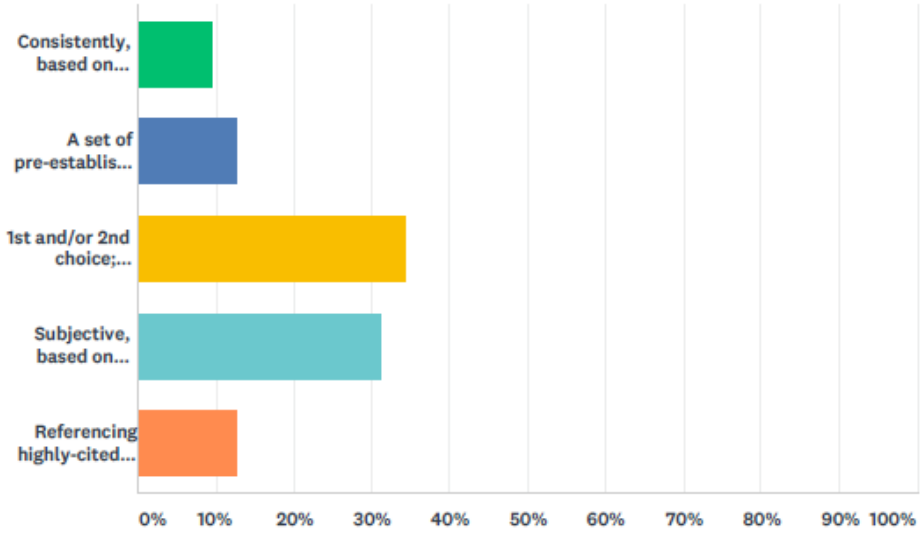
How does your company assess predictions of PD biomarkers and clinical endpoints when calibrating or validating the model?



ANSWER CHOICES	RESPONSES	
Qualitatively	25.00%	8
Quantitatively without consistent criteria	37.50%	12
Quantitatively with the criteria for PD biomarkers different from that for clinical endpoints	21.88%	7
Quantitatively with same criteria for PD biomarkers and clinical endpoints	9.38%	3
Other (please specify)	6.25%	2
TOTAL		32

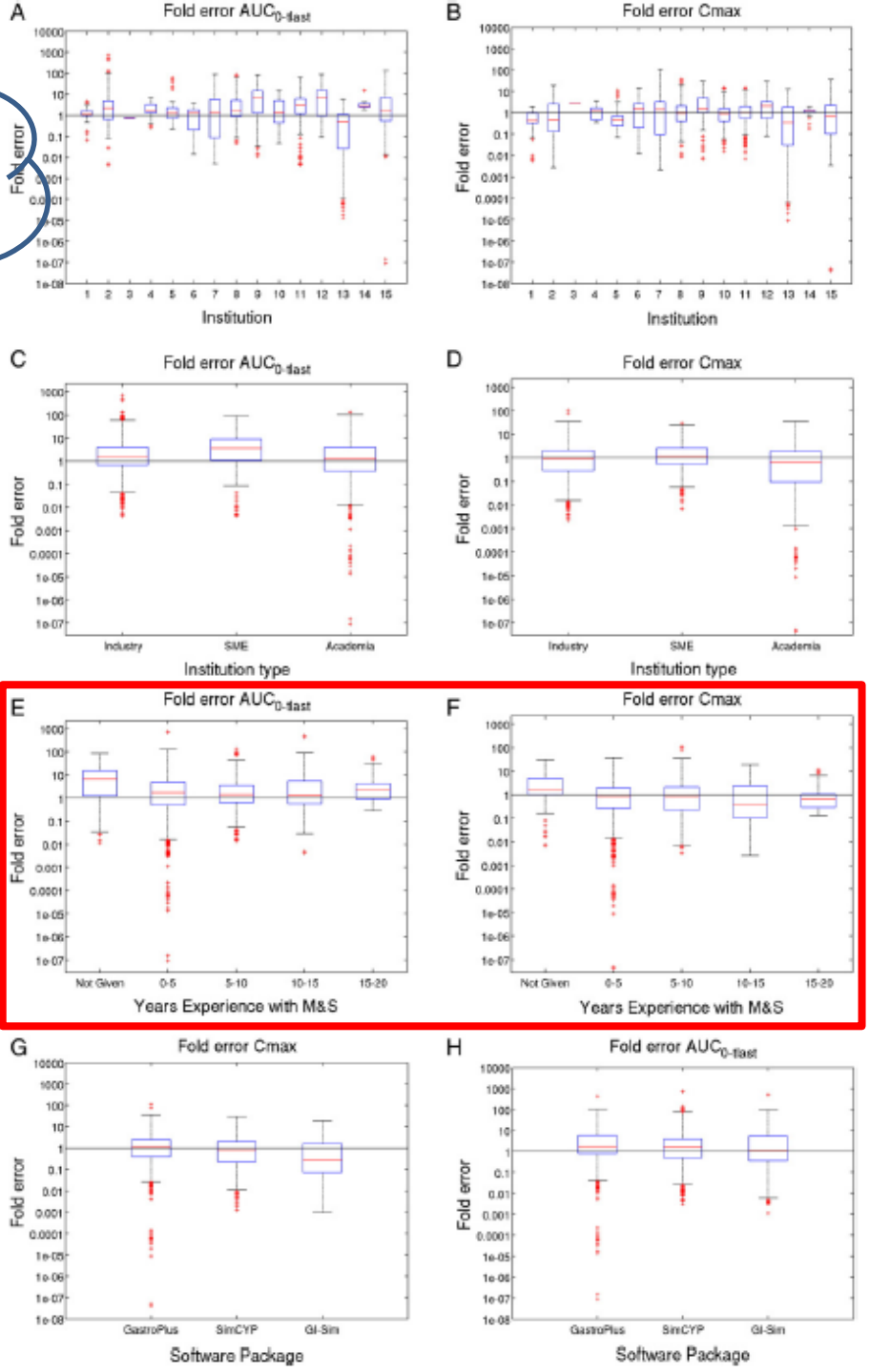
Challenges To Be Overcome Con't

How does your company assess the quality of QSP models in the process of model building in order to establish the confidence in QSP model predictions?



ANSWER CHOICES	RESPONSES	
Consistently, based on pre-established internal criteria regardless of the stage of drug discovery and development	9.38%	3
A set of pre-established internal criteria that vary depending on the stage of drug development	12.50%	4
1st and/or 2nd choice; however, this can vary from scientist to scientist or from group to group within the organization	34.38%	11
Subjective, based on modeler's experience	31.25%	10
Referencing highly-cited models in literature	12.50%	4
TOTAL		32

Needless to say, nobody was happy!



To Make Matters Worse

Citation: CPT Pharmacometrics Syst. Pharmacol. (2019) XX, 1–6; doi:10.1002/psp4.12390

REVIEW

Reproducibility of Quantitative Systems Pharmacology Models: Current Challenges and Future Opportunities

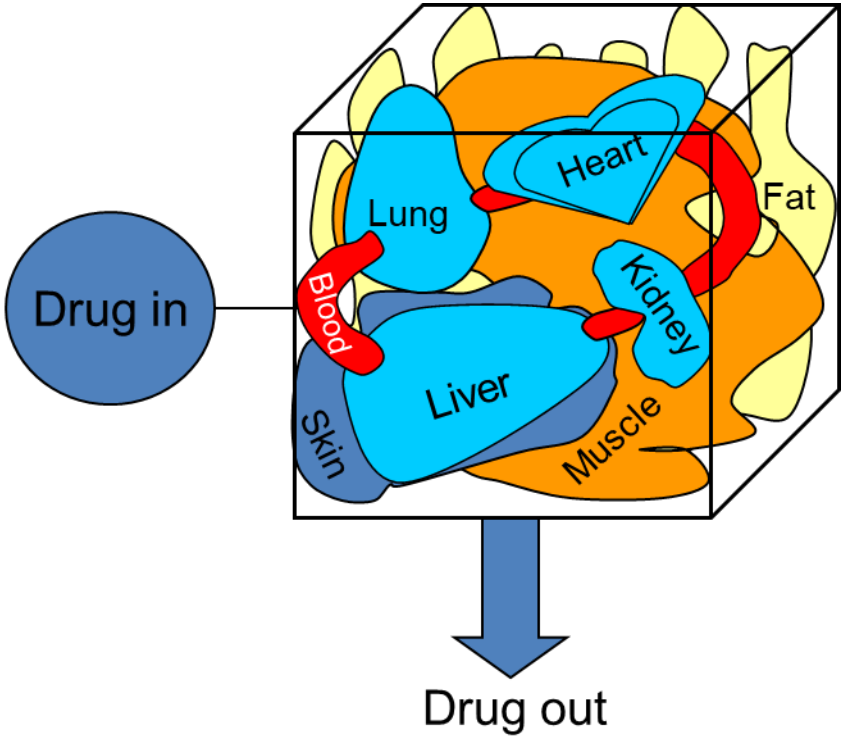
Daniel C. Kirouac[1,3,*], Brian Cicali[2,3] and Stephan Schmidt[2,3]

The provision of model code is required for publication in *CPT: Pharmacometrics & Systems Pharmacology*, enabling quantitative systems pharmacology (QSP) model availability. A searchable repository of published QSP models would enhance model accessibility. We assess the feasibility of establishing such a resource based on 18 QSP models published in this journal. However, because of the diversity of software platforms (nine), file formats, and functionality, such a resource is premature. We evaluated 12 of the models (those coded in R, PK-Sim/MoBi, and MATLAB) for functionality. Of the 12, only 4 were executable in that figures from the associated manuscript could be generated via a "run" script. Many researchers are aware of the challenges involved in repurposing published models. We offer some ideas to enable model sharing going forward, including annotation guidelines, standardized formats, and the inclusion of "run" scripts. If practitioners can agree to some minimum standards for the provision of model code, model reuse and extension would be accelerated.

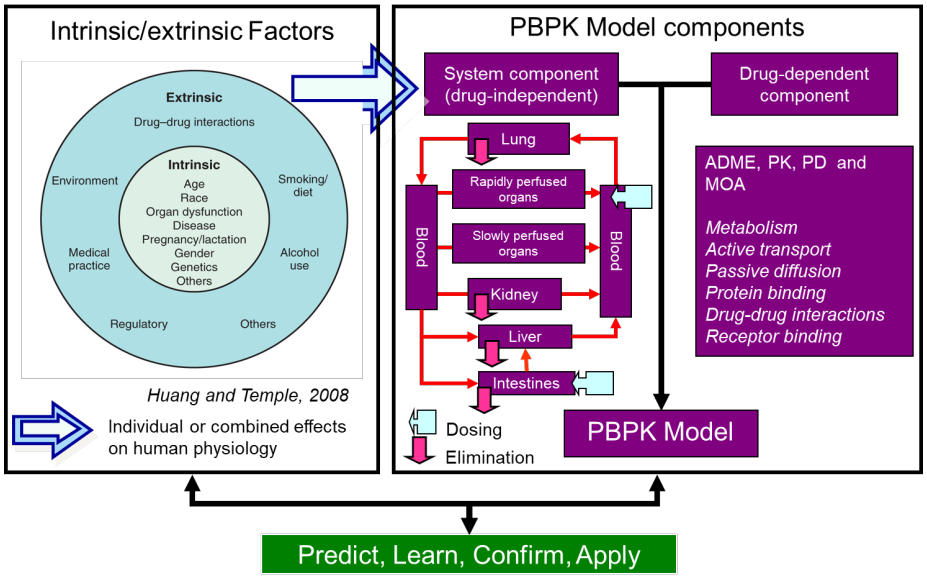
There is a clear need for standardization!

Maybe There Is a Lesson to Be Learned From Population Models & PBPK Models?

Population Model



PBPK Model



Barrett, ASCPT, 2014

Zhao et al. (2011) Clin Pharmacol Ther ***89****: 259-67*

Commonalities & Differences

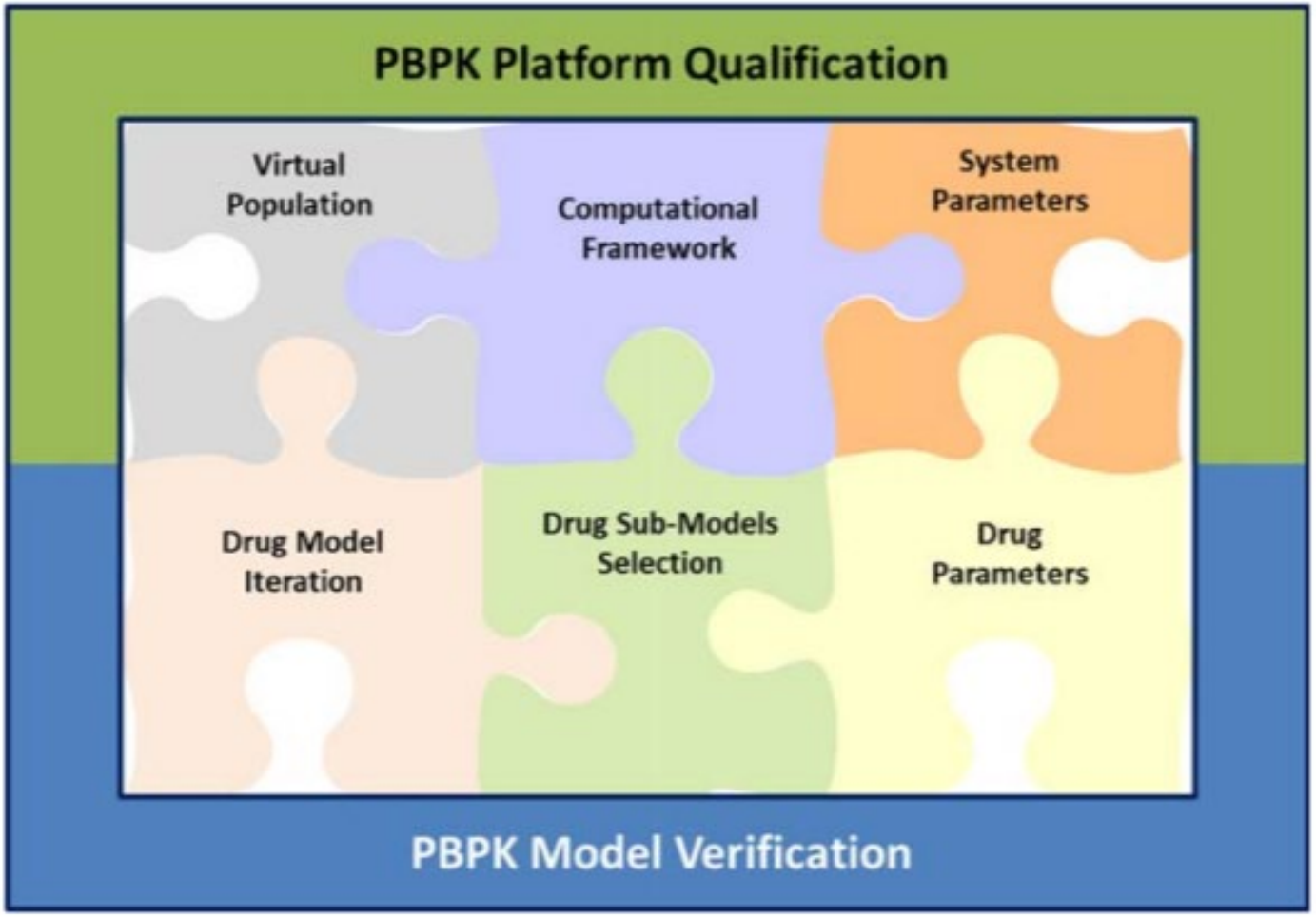
Commonalities:

1) A set of equations (structural model) that adequately describe the (patho)physiological processes of interest.
2) A set of parameters that adequately capture “the data”.

Differences:

Population Models	PBPK Models
Data-driven model structure	Anatomically-driven model structure
Empirical body compartments	Physiological organs, blood flow
Drug-dependent rate processes	Drug-independent system properties
Physiologically empirical parameters	Physiologically mechanistic parameters
Parameter-based sensitivity analysis	Physiology-based sensitivity analysis
Statistically-robust model selection criteria	**Process & product verification**
Well-established modeling tool	Rapidly evolving modeling tool

PBPK platform qualification



Shebley et al, 2018.

PBPK platform qualification

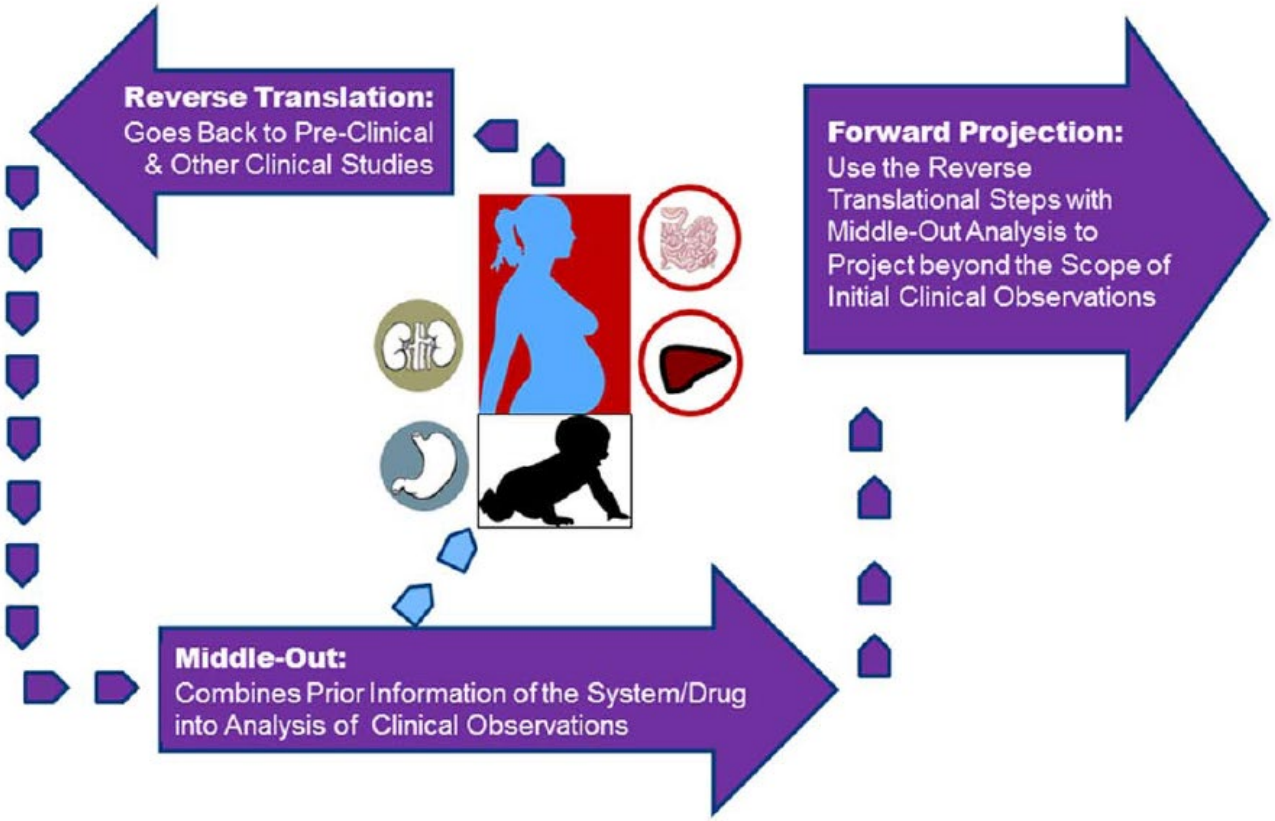
- Platform qualification
  - Design qualification (DQ)
  - Installation qualification (IQ)

- Qualification of virtual population
  - Development of the system-dependent parameters
  - Integrative middle-out approaches may suffer from structural identifiability issues
  - Require a matrix of evidence from various datasets, e.g. different drugs

Shebley et al, 2018 and Rostami-Hodjegan, 2018.

PBPK Model Verification - Reverse Translation

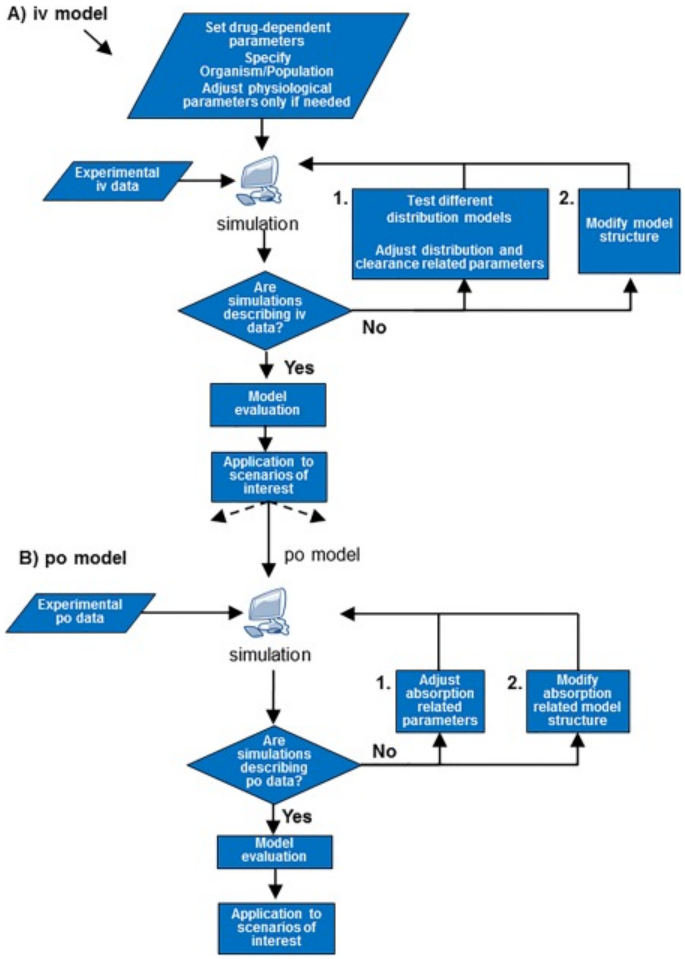
- PBPK model development is an iterative process that may involve multiple cycles of "predict, learn, confirm."
  - Going backwards in order to go forward with confidence



Rostami-Hodjegan, 2018.

I think We Are on the Right Track

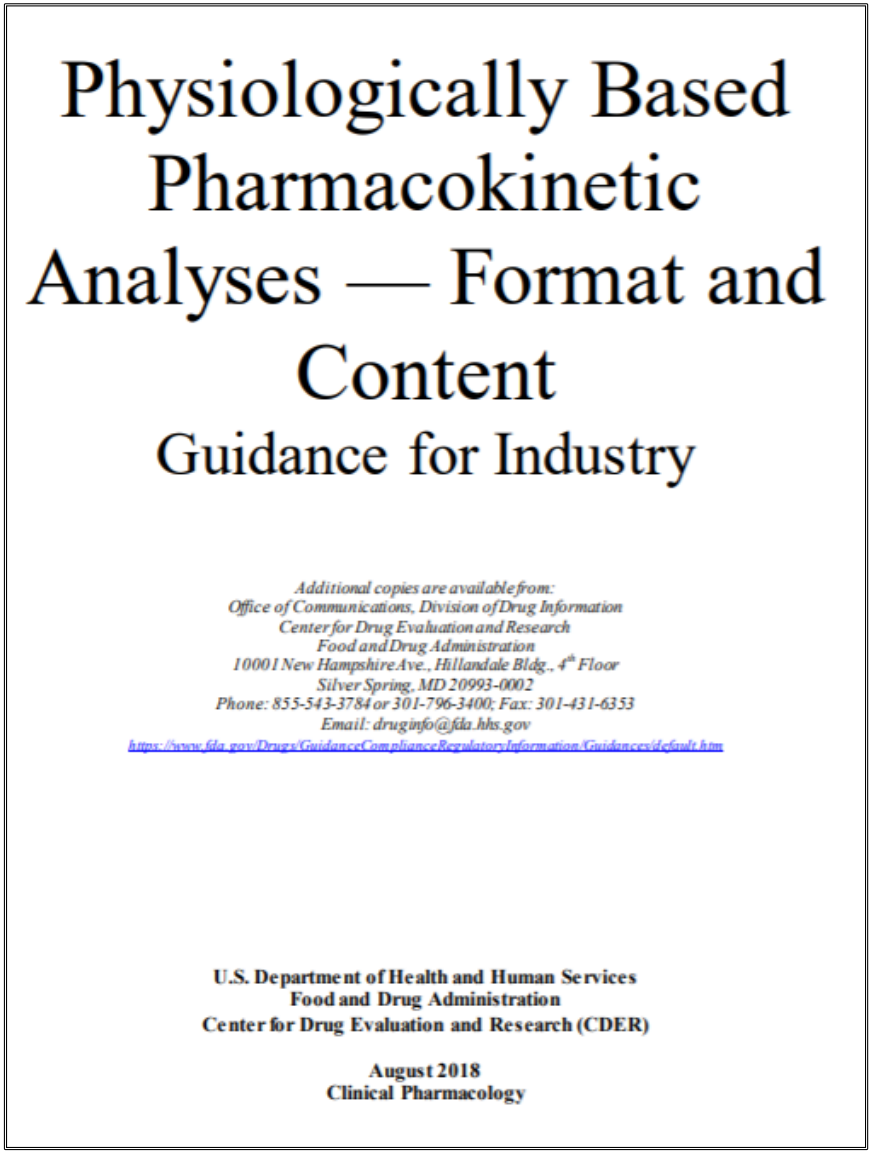
PBPK



QSP

Regulatory Documents

FDA draft guidance focuses on the format and content of reporting PBPK analyses for regulatory submissions.



Physiologically Based Pharmacokinetic Analyses — Format and Content

Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

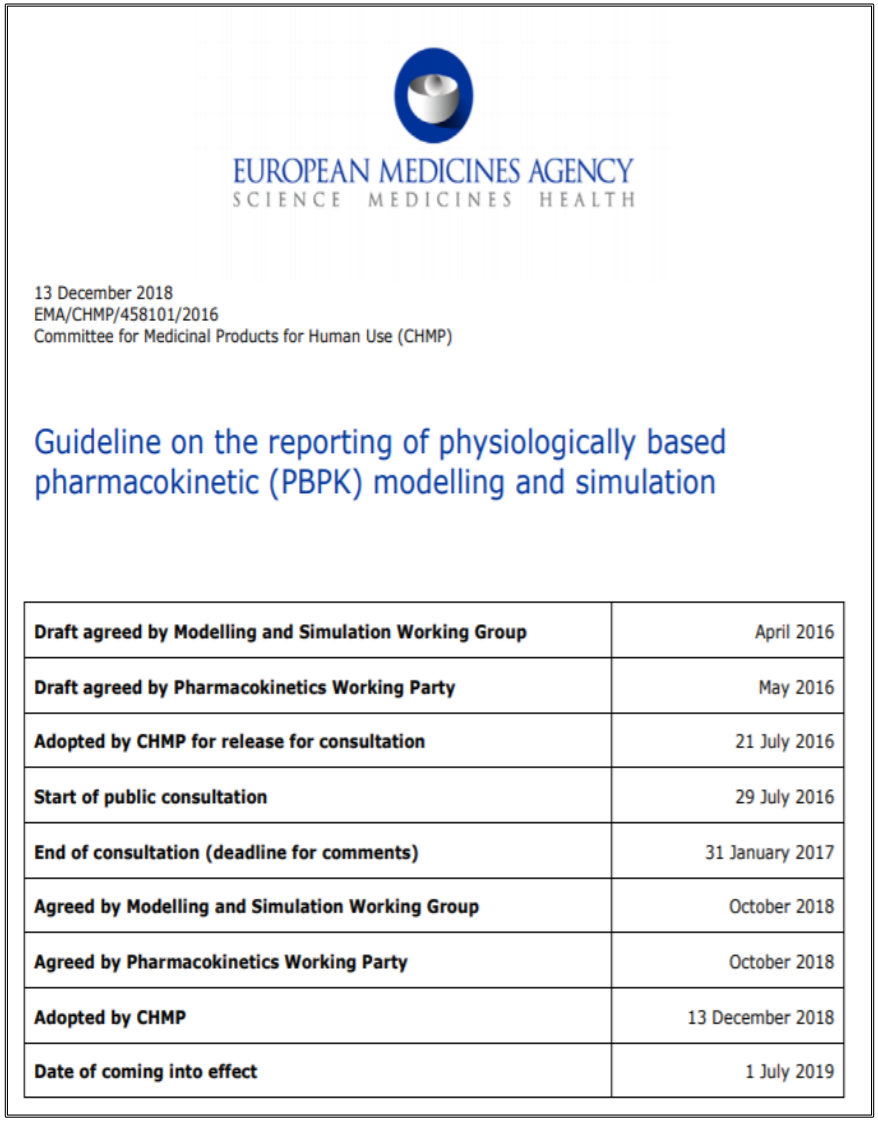
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

August 2018
Clinical Pharmacology

Shebley et al, 2018.

Regulatory Documents

Verification requirements at different levels of regulatory impact – "*Verification-for-intended-purpose*"



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

Shebley et al, 2018.

Food For Thought – Impact of Data Source on Inference Making