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Considerations for Model Validation, Model Acceptance/Verification Criteria in Physiologically based Biopharmaceutics Modeling (PBBM) in View of Available Clinical Data and Model Risks (Impact and Consequences)

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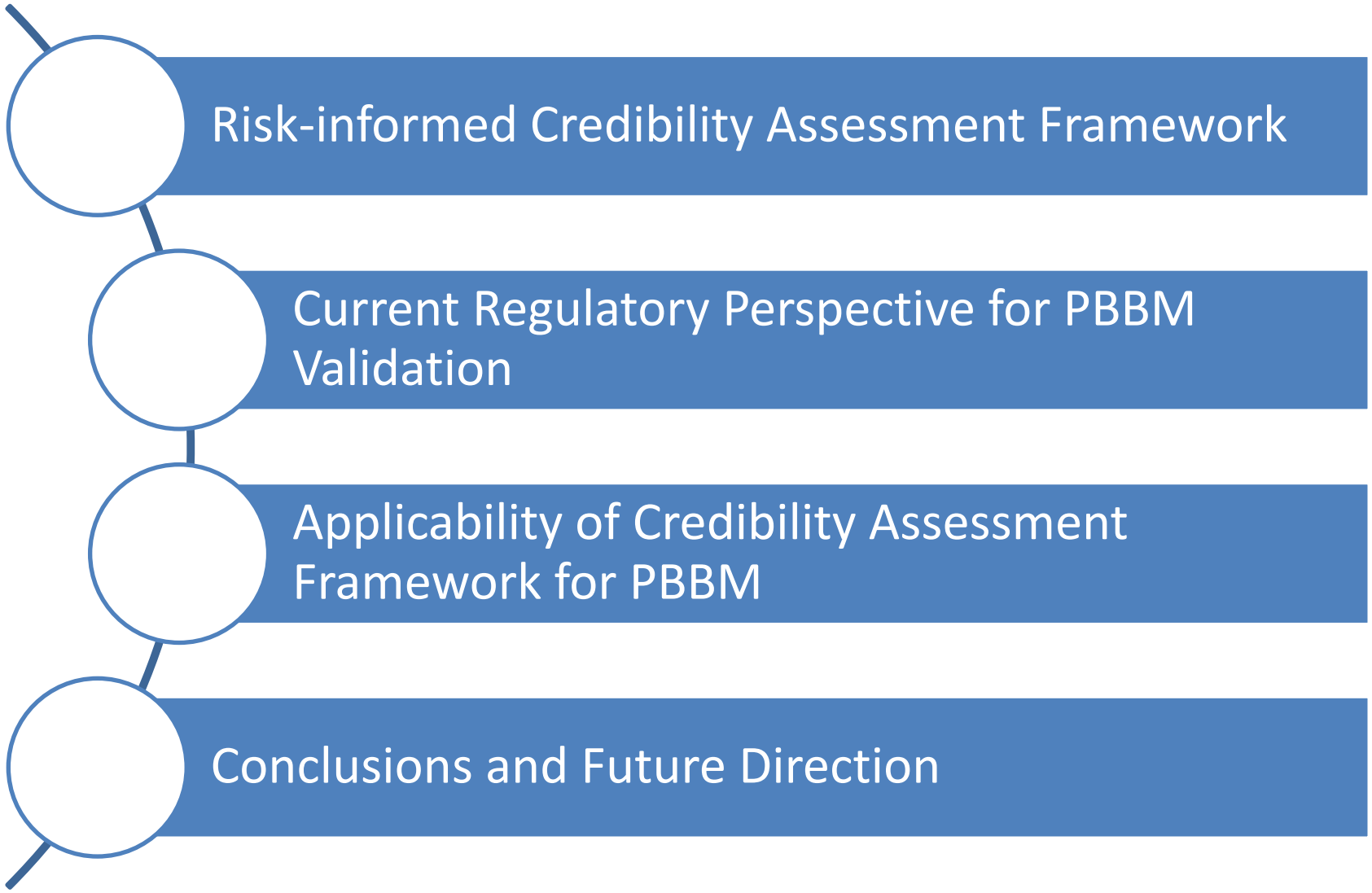
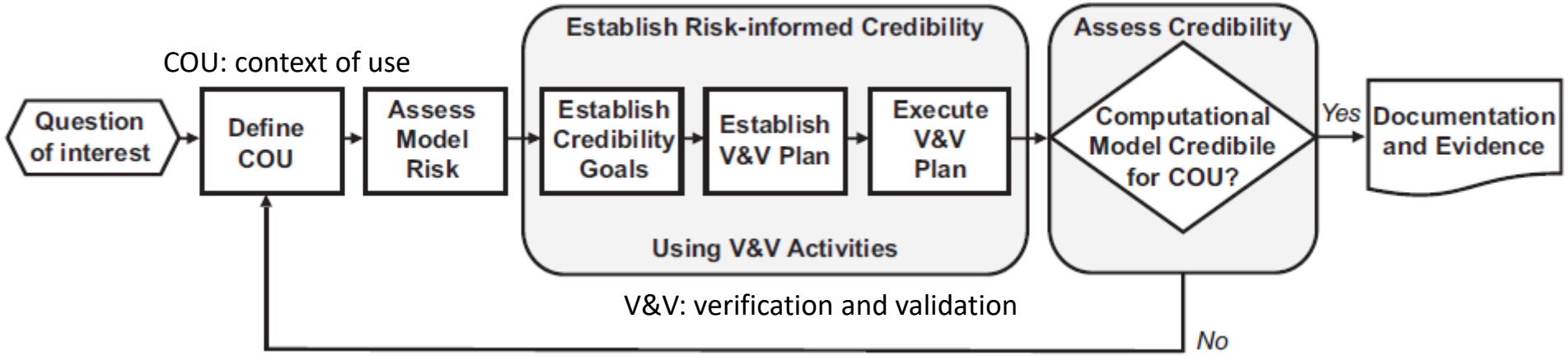
Overview


Risk-informed Credibility Assessment Framework
Current Regulatory Perspective for PBBM Validation
Applicability of Credibility Assessment Framework for PBBM
Conclusions and Future Direction

Risk-informed Credibility Assessment Framework



- **Model Credibility:** Trust, established through the collection of evidence, in the predictive capability of a computational model for a context of use.
- **Model Risk:** Possibility that the computational model and the simulation results may lead to an incorrect decision and adverse outcome
  - Model Influence: Contribution of the computational model relative to other contributing evidence in making a decision
  - Decision Consequence: Significance of an adverse outcome resulting from an incorrect decision
- **Model Verification:** Process of determining a model or simulation represents the underlying mathematical model and its solution from the perspective of the intended uses of modeling and simulation
- **Model Validation:** Process of determining the degree to which a model or simulation is an accurate representation of the real world

Kuemmel C, et al. CPT Pharmacometrics Syst Pharmacol. 2020;9(1):21–8.

Defining Model Risk

Model influence: weight of the model in totality of evidence (similar to model impact)

Model influence	Description
Low	Model provides minor evidence; substantial ~~nonclinical and clinical~~ In vitro and in vivo data are available to inform the decision
Medium	Model provides supportive evidence; some clinical trial data are available to inform the decision
High	Model provides substantial evidence; no clinical trial data relevant to the context of use or limited clinical trial data from similar scenarios are available to inform the decision

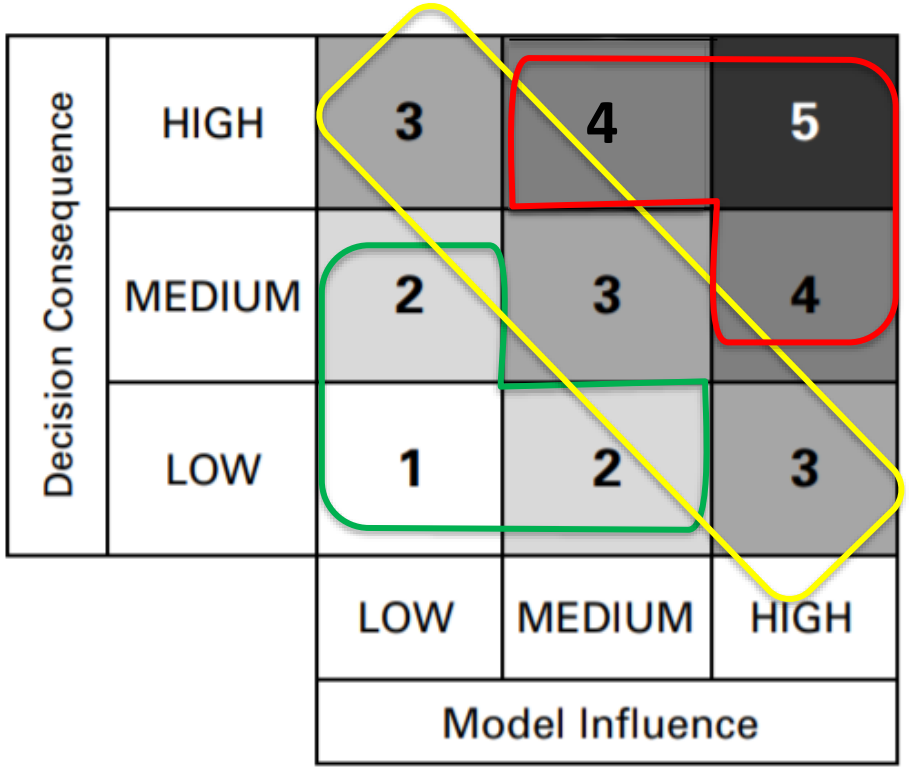
Decision consequence: potential consequences of a wrong decision

Decision consequence	Description
Low	Incorrect decision would not result in adverse outcomes in patient safety or efficacy
Medium	Incorrect decision could result in minor to moderate adverse outcomes in patient safety or efficacy
High	Incorrect decision could result in severe adverse outcomes in patient safety or efficacy

Kuemmel C, et al. CPT Pharmacometrics Syst Pharmacol. 2020;9(1):21–8.

Assessment of Model Risk

- Before **model risk** can be assessed, the **question of interest** and **context of use** must be understood
- **Model influence** and **decision consequence** can then be independently mapped to a risk matrix
- An increase in either factor leads to an increase in **overall model risk**



Slide courtesy of Dr. Yuching Yang

Model Validation

To determine the accuracy of the model to predict observed data and assess the correctness of model assumptions

- ***Evaluating the underlying assumptions in the model structure, including mechanistic equations, and their relevance to the COU***
- Assessing model input (sensitivity analysis and uncertainty assessment)
- Comparing prediction with observed data

Kuemmel C, et al. CPT Pharmacometrics Syst Pharmacol. 2020;9(1):21–8.

The Uniqueness of PBBM

- PBBM is defined as “PBPK absorption models including ACAT (Advanced Compartmental Absorption Transit) and ADAM (Advanced Dissolution, Absorption, and Metabolism) as well as other mechanistic models, which mimic physiological conditions and incorporate dissolution information while accounting for relevant physicochemical and physiological factors leading to a prediction of systemic exposure versus time”
  - Mechanistic absorption modeling
  - In vivo dissolution prediction

Heimbach T, et al. AAPS J. 2019;21(2):29.

Current Regulatory Perspective on PBBM Validation

FDA Draft Guidance: The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls (Sep, 2020)

- *"Depending on the clinical risk and the intended purpose, the amount and type of data needed for model validation may vary."*

Risk based and fit for purpose

- *"we strongly recommend that sponsors demonstrate the model's predictive performance based on PK data from batches exhibiting unacceptable BA"*

Model assumption validation

- Mostly used acceptance criteria for validation:
  - Prediction error for PK parameters within 10-20%
  - Ratio of predicted/observed PK parameters within 80–125% range

Challenges in Validation of PBBM Assumptions

- The lack of complete understanding on the interaction of drug product and GI tract
- The lack of excipients' effect on in vivo dissolution
- Knowledge gap between in vitro and in vivo dissolution
- The currently used dissolution models (or theories) have not yet been evaluated comprehensively for in vivo dissolution prediction (with multiple drug products)
- The validation of mechanistic absorption model is often confounded with incomplete understanding on drug disposition

Applicability of Risk-informed Credibility Assessment Framework

Using a BCS class 2 IR product (not NTI) as a hypothetical example focusing on validation activity on mechanistic absorption part of PBBM

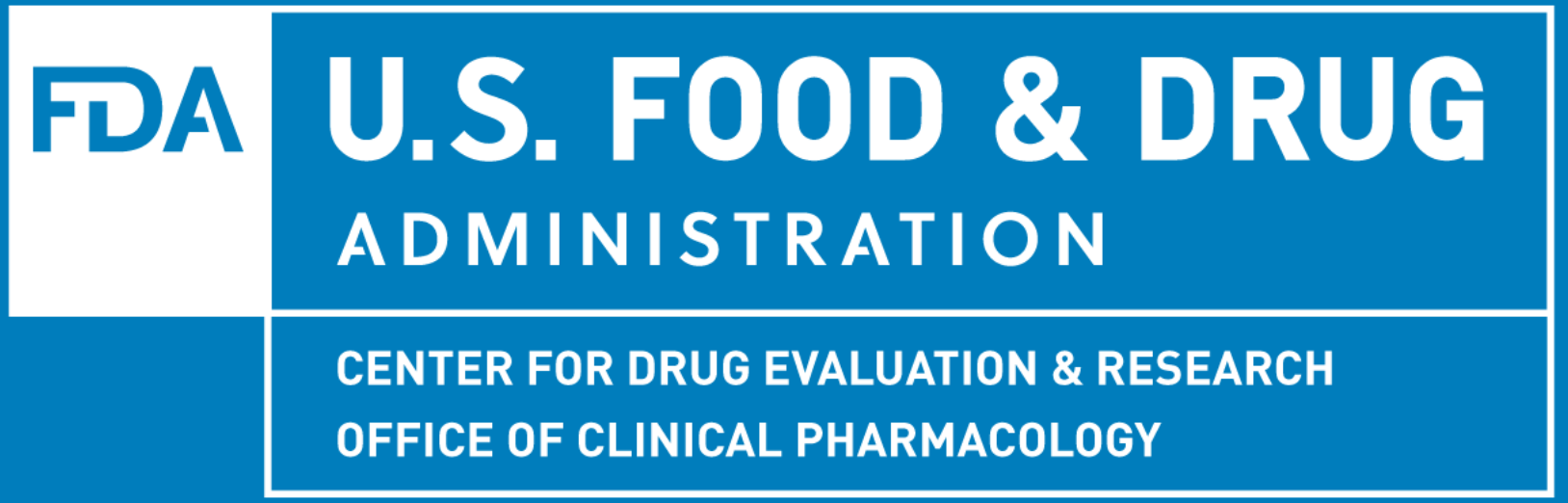
COU	Decision Consequence	Model Influence	Model Risk	Data needed for validation	Comments
To support biopredictive dissolution method	Low (if there are clinical data to support dissolution specifications)	Low to medium (if clinical PK data is available)	Low	PK data for different dissolution rates	Further validation may be needed when biopredictive dissolution test is used for other applications
To support clinically relevant dissolution specification	Medium to high (as a wrong decision may release drug product with adverse efficacy for IR formulations)	Low to medium (if clinical PK data available)	Medium to high	PK data for different dissolution rates and with different BA	If formulation is changed, it needs to further assure the validity of the assumption for mechanistic models.
To support biowaiver for a major formulation change	High (as a wrong decision may release drug product with adverse safety/efficacy)	High (as no clinical data to support)	High	Data to assure no change on drug permeability, precipitation, drug release mechanism; PK data for different dissolution rates and with different BA	Risk assessment might consider CMC understanding and general understanding on the similar change on similar formulations.

CMC: Chemistry, Manufacturing and Controls

Conclusions and Future Directions

- Risk-informed model credibility assessment can help standardize risk understanding and risk communication
- PBBM validation is risk based and purpose driven
- Validation activities emphasize assumptions on mechanistic absorption/dissolution models
- Model risk assessment might also consider the understanding on CMC and exposure-response relationship
- Future research is needed to increase the understanding of drug dissolution in the GI tract
- Platform validation for certain types of formulation will increase the confidence in PBBM

Thank you!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