Considerations for qualification of Physiologically-Based Biopharmaceutics Models - Beyond the EMA framework

Xavier Pepin (Simulations-Plus, VP R&D PBPK Solutions)

Agenda

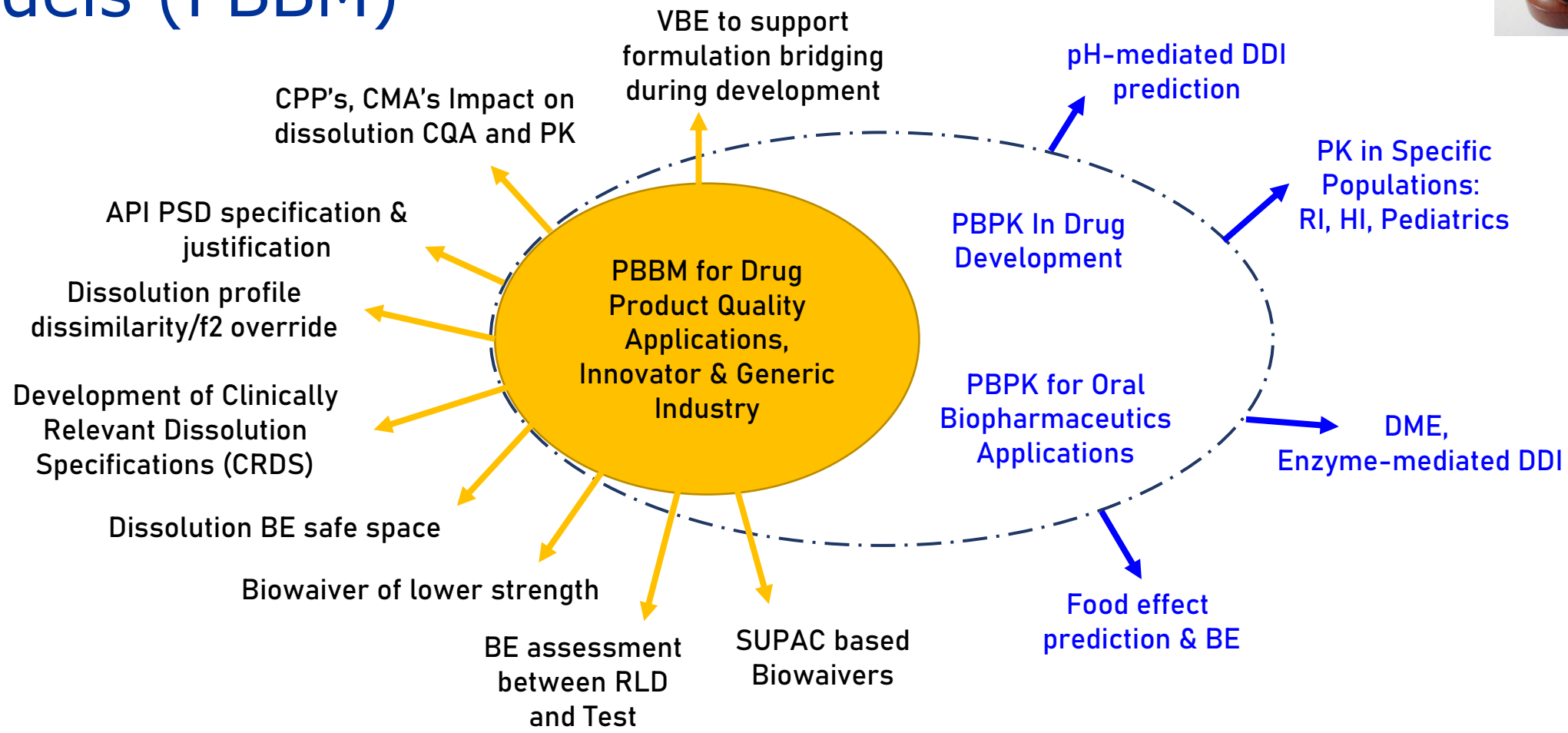
- Definitions around qualification-verification-validation
- PBBM vs PBPK : what do we mean ?
- CMC attributes which can be specified by a PBBM
- Specific requirements for dissolution methods and data
- Specific requirements for food effect and altered GI conditions
- Hurdles for PBBM (re-)qualification
- Ways forward for PBBM (re-)qualification
- Conclusions

Definitions, expectations and responsibilities

Step	Expectations	Who does that?	Deliverable	Who verifies that?
PBPK/PBBM platform verification	Soundness of construction Equations Science behind equations	Software developer	Scientific specifications outlining equations and science	Regulator/User of the software
PBPK model/PBBM verification (FDA) or refinement (EMA)	(justified) updates of the model parameters to increase prediction performance of model	User of the software	PBPK/PBBM report	Regulator
PBPK model/PBBM validation	Demonstration that the model can predict with a certain performance selected clinical PK based on QoI	User of the software	PBPK/PBBM report	Regulator
PBPK/PBBM (re-)qualification	Demonstration that the platform can reliably predict a specific QoI for a significant number of other drugs	Software developer	Qualification procedure (EMA only)	EMA
Modeler's qualification	Modeler's assumptions are sound and correspond to best practices	User of the software	PBPK/PBBM report	Regulator

Out of this presentation scope

Physiologically-Based Biopharmaceutics Models (PBBM)



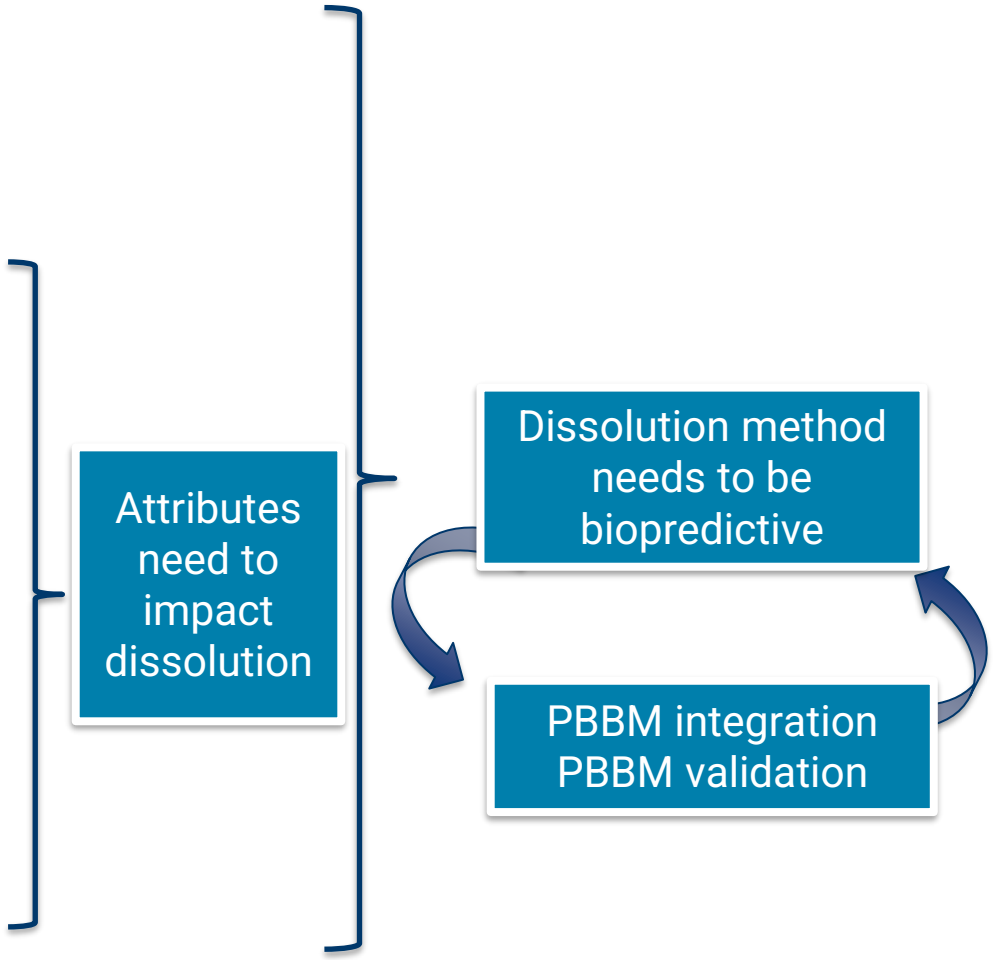
API: Active pharmaceutical ingredient, BE: Bioequivalence, CMA: Critical material attribute, CPP: Critical process parameter, CRDS: Clinically relevant dissolution specifications, DDI: Drug-Drug interactions, DME: Distribution, metabolism and excretion, HI: Hepatic impairment, PBPK: Physiologically-Based Pharmacokinetics, PSD: particle size distribution, RI: Renal impairment, RLD: reference listed drug, SUPAC: Scale-up and post-approval changes, VBE: Virtual bioequivalence

What quality attributes can be specified by a PBBM

Dissolution
- Specifications
- Capsule opening time
- Tablet disintegration time

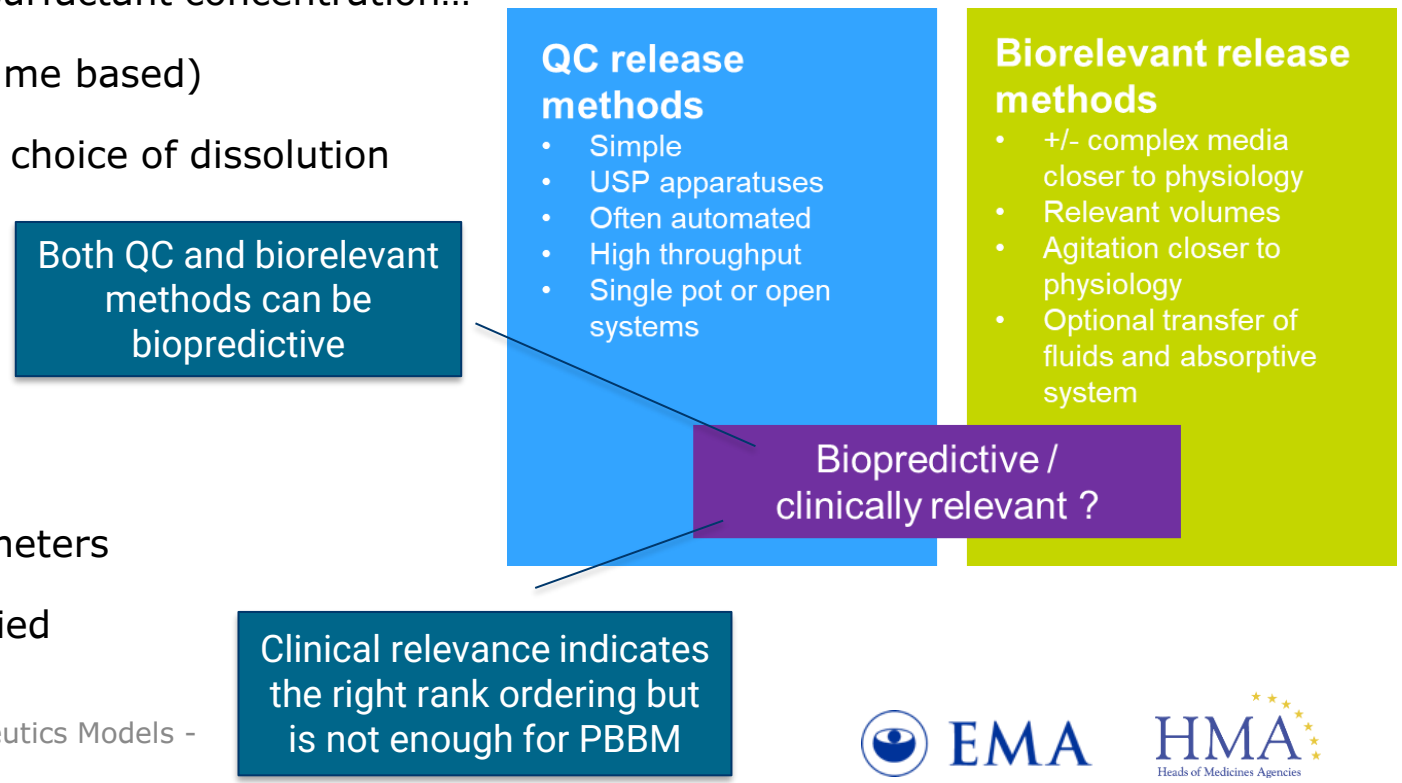
DS attributes which impact dissolution
- Particle size (at manufacture and during stability)
- Polymorphic impurity (at manufacture and during stability)

Any CMA or CPP which impacts dissolution
- Tablet hardness, tablet porosity
- Coating thickness (pellets or tablets)
- Size of a spray dried intermediate
- Amount of excipients
- Excipients grade



Specific Requirements: Dissolution methods and data (bridging, safe space, specification setting)

- Dissolution method biopredictive nature needs to be demonstrated
  - Use of dissolution methods/data for the actual clinical batches
  - Orthogonal dissolution data on representative batches with different methods to validate in vitro the dissolution model choice and performance Model sensitive to pH, volume, dose, agitation, surfactant concentration…
  - Justify integration in the PBBM (mechanistic or time based)
  - Mechanism of release in vitro and in vivo : Drive choice of dissolution method and model and integration strategy
- Discrimination
  - Clinical performance of variant batches
  - Critical material attributes, critical process parameters
  - Variant formulations of the attribute to be specified



Specific Requirements: Questions of Interest

- Food effect prediction
  - Based on sensitivity analysis : Different food types/quantities (bile salt and gastric emptying)
  - Formulations types that are tested in food effect studies (gastric retention)
  - Mechanistic models for dissolution (adapted to changing luminal conditions)
  - Impact of disintegration (in vivo slower than in vitro)
- Altered GI conditions
  - pH-related DDI
  - Transit (pharmacological effect = increase or decrease)
  - Excipients : Osmotic effect, allergic effect (fluid volume and transit)
  - Disease: GI inflammation, diarrhoea (permeability, volume, transit, mucus layer)
  - Lipid dysregulation (bile salts, permeability, transit)

Combined effect of system parameters and formulation

Changes in the system parameters + mechanistic dissolution model

Specific Requirements: All qualification exercises

- Trust the input data and the clinical data for validation and platform qualification
- Highly variable PK data (within- and between-subjects)
  - Drug product
  - Biopharmaceutical properties of the drug
  - Sensitivity of the drug to the system parameters
- How do we judge a model prediction performance (validation and qualification) if the clinical data is not reliable/understood
  - Check correct issues with sampling time
  - Introduce Additional biomarkers
  - Restrict validation to data with minimum number of subjects
  - Prefer cross-over studies for model validation/qualification
  - Define inclusion/exclusion rules for data from clinical trials

Hurdles for the qualification process of PBBMs

- PBBM validation requires amount of precision commensurate with the QoI
  - Bridging between formulation : Prediction error ≤ 20%
  - Clinical food effect or pH-related DDI : 2-fold acceptable ?
- Obtain dissolution data, methods and metadata on the clinical batch of drug product tested in the clinic
  - Not available in the public domain : At best commercial name. Dissolution of batches tested in the clinic not available
  - Composition of products and discrimination of method to quality attributes not disclosed
  - Orthogonal dissolution data not available for dissolution model validation
  - Number of compounds for qualification: 10 independent examples
    - 10 for each QoI?
    - How similar DP and DS be ? : BCS, Mechanism of release, sensitivity to system parameters ?
    - Should we focus on individual processes leading to absorption (mixing, disintegration, segregation, retention, transit, dissolution, precipitation, absorption)

Example : CRS for level of polymorphic impurity

- Can we use PBBM to qualify the clinically relevant specification for an acceptable level of a polymorphic impurity in a drug product ?
  - Yes. How to qualify?

- 10 examples in the literature with polymorphic impurities with right level of characterization
  - 3 batches of DP comprising different levels of polymorphs, fully characterized (dissolution and composition)
  - Data on different dissolution methods to validate dissolution model
  - Reliable solubility on each polymorphs
  - Clinical data in a cross-over (ideally) testing each formulation variants
  - Metadata on the tested population

Data not available to one single company
Data not available to the public
Data available to authorities through submissions ?

Ways forward for PBBM platform qualification 1/2

- 1-Balance quality and quantity of examples
  - Quality : Cross over study, individual PK, additional sampling and biomarkers, mechanistic model for dissolution (in vitro and in vivo), combined effects of formulation and system parameters, sensitivity and validation against clinical data
  - Quantity : 1 or 2 good quality mechanistic models vs 10 average quality ones ?

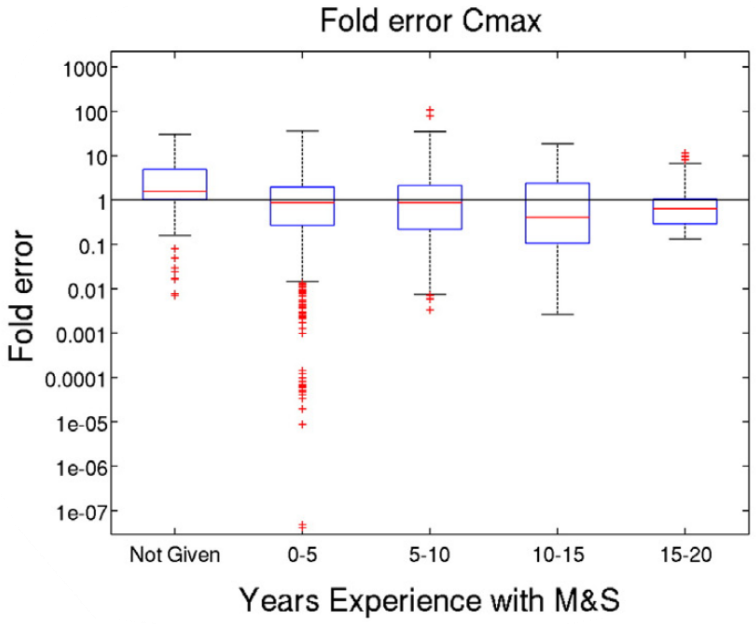
- 2-Commit to creating publicly available data for future PBBM platform qualification
  - Clinical data (PK profiles) should be accompanied with dissolution data in a discriminant method + metadata + brief description of the variants tested :
    - Voluntary basis from sponsor to disclose historical data or incentivized by authorities (e.g. Patent exclusivity extension)
    - Academic, industry, regulatory joint research projects
  - Build database of publicly available information for model validation. Unlock the data for platform qualification
  - Should apply to DDI as well for the dissolution of tested products
  - Disclose food and liquid composition and timing during studies (needed to refine food effect predictions)

Ways forward for PBBM platform qualification 2/2

- 3-Once the database of models is built, run for each model drug/drug products a global sensitivity analysis to easily identify which parameters influence the outcome of the PK
  - With predefined variation range on each parameter, classify models for “no”, “moderately” or “highly” sensitive
  - Use sensitivity analysis to select relevant examples for (re-)qualification of PBBM platforms following a specific change, based on the nature of the change:
    - e.g. A new model for gastric emptying/retention is introduced
      → Use drugs for which in vivo dissolution is limited by gastric transit time for platform (re-)qualification

Reliability of PBBMs beyond qualification

- Develop and ensure best practices
  - Beyond PBBM platform verification and qualification, quality/reliability of a model depends on the quality of the input and model(er's) assumptions
  - Science and best practices → decision trees for modelers and reviewers to guide/assess model quality/risk
  - Ensure modeler's training is documented



Prediction performance during OrBiTo blinded bottom-up exercise

Margolskee, A., A. S. Darwich, X. Pepin, L. Aarons, A. Galetin, A. Rostami-Hodjegan, S. Carlert, M. Hammarberg, C. Hilgendorf, P. Johansson, E. Karlsson, D. Murphy, C. Tannergren, H. Thorn, M. Yasin, F. Mazuir, O. Nicolas, S. Ramusovic, C. Xu, S. M. Pathak, T. Korjamo, J. Laru, J. Malkki, S. Pappinen, J. Tuunainen, J. Dressman, S. Hansmann, E. Kostewicz, H. He, T. Heimbach, F. Wu, C. Hoft, L. Laplanche, Y. Pang, M. B. Bolger, E. Huehn, V. Lukacova, J. M. Mullin, K. X. Szeto, C. Costales, J. Lin, M. McAllister, S. Modi, C. Rotter, M. Varma, M. Wong, A. Mitra, J. Bevernage, J. Biewenga, A. Van Peer, R. Lloyd, C. Shardlow, P. Langguth, I. Mishenzon, M. A. Nguyen, J. Brown, H. Lennernas and B. Abrahamsson (2017). "IMI - Oral biopharmaceutics tools project - Evaluation of bottom-up PBPK prediction success part 2: An introduction to the simulation exercise and overview of results." Eur J Pharm Sci 96: 610-625.

Conclusions

- PBBM holds the promise to reduce unnecessary human evaluation for a variety of QoIs on product quality and interaction of altered physiology and formulations
- Quality/reliability of a model is multifactorial
  - Platform verification (soundness of equations, sciences supporting model construction)
  - Platform qualification on good quality data (balance of amount and quality)
  - Quality input data and clinical data for model validation
  - Good practices: Training/proficiency or “qualification” of the modeler/reviewer
  - Availability of relevant CMC and PK data for PBBM qualification is a bottleneck to cover many QoIs
  - Public databases comprising relevant information could unlock the qualification exercise

Acknowledgments

Susie Zhang
Sandra Suarez-Sharp
Viera Lukacova

Thank you

Xavier.pepin@simulations-plus.com

EMA
EUROPEAN MEDICINES AGENCY

HMA
Heads of Medicines Agencies