Medicines & Healthcare products Regulatory Agency

# Application of PBBM in regulatory submissions

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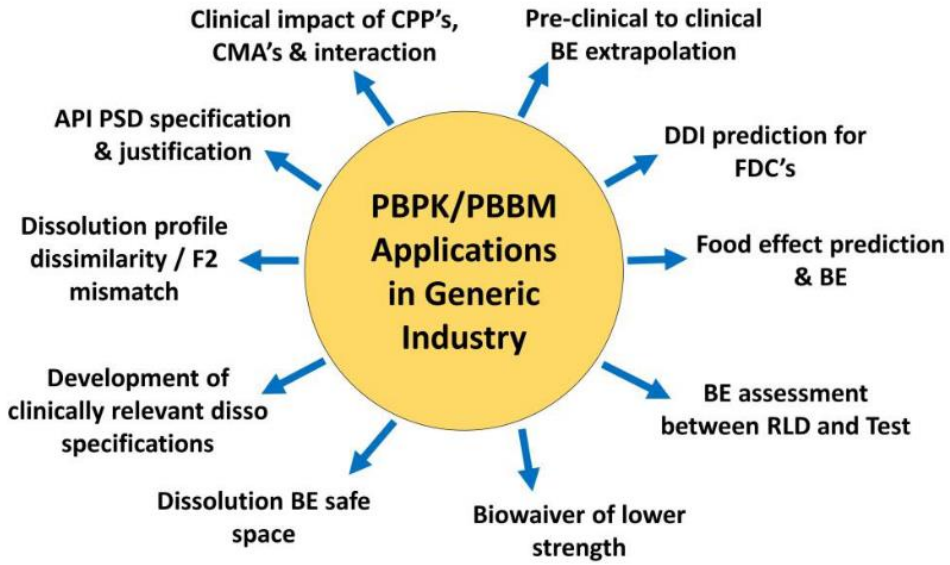
# Disclaimer

Any opinions expressed in the presentation are my own, are not necessarily shared by other assessors at the MHRA, and cannot be considered UK policy

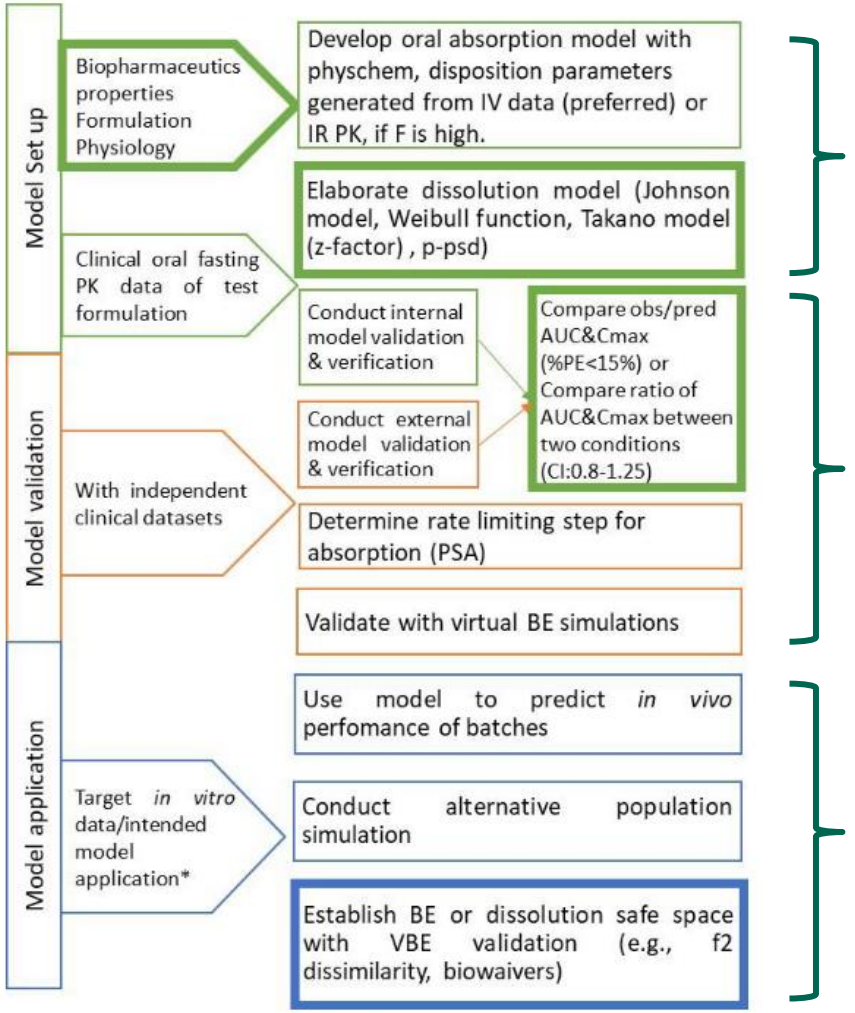
# Physiologically-based biopharmaceutics modelling

- PBBM is a useful tool that combines properties of the drug substance, formulation and PK with physiology to enable prediction of in vivo exposures (i.e., plasma concentration vs time profiles)
- PBBM can be used in product development of both innovative and generic drug products




Applications of PBBM

# PBBM model development




- **Experimental data, literature data, ADMET predicted data**
- **Adequate justification for all input parameters**
- **PSA for predicted parameters**

- **Internal validation: validation with data used to build the model**
- **External validation: validation with independent datasets**
- **Population should be representative of clinical study incorporating variability**

- **Apply model for intended application, conduct virtual BE simulations**

# Take-home messages

- Model objective(s) should be clearly stated
- High quality experimental data (e.g., solubility, permeability, precipitation) should be available while preparing models for regulatory submission
- Predicted parameters can be used when justified, but they should be followed by a parameter sensitivity analysis
- Assumptions made upon drug disintegration, dissolution, precipitation etc should be clearly defined in the model
- It is recommended to use intravenous data or oral solution data during initial model development to appropriately derive the disposition parameters
- Use of biorelevant dissolution methods is recommended
- Justification should be provided on the method selected for dissolution data input (e.g., z-factor, P-PSD etc.)
- The limitations of the method selected for dissolution data input should be discussed

# Take-home messages

- It is advised that the model needs to be validated by the in vivo data from a batch exhibiting unacceptable bioavailability to demonstrate the model's ability to predict the in vivo performance of non-bioequivalent batches
- Pre-specified acceptance criteria for judging predicted vs observed data during validation should be provided
- A discussion should be provided on how variability is incorporated in the model and how it can affect the results of the virtual BE studies
- A safe space should be demarcated wherever possible
- Use of the of the checklist for PBBM regulatory submissions is highly recommended