Case Studies on Application of PBBM for Generics

FDA/M-CERSI Physiologically-Based Biopharmaceutics Modeling Workshop

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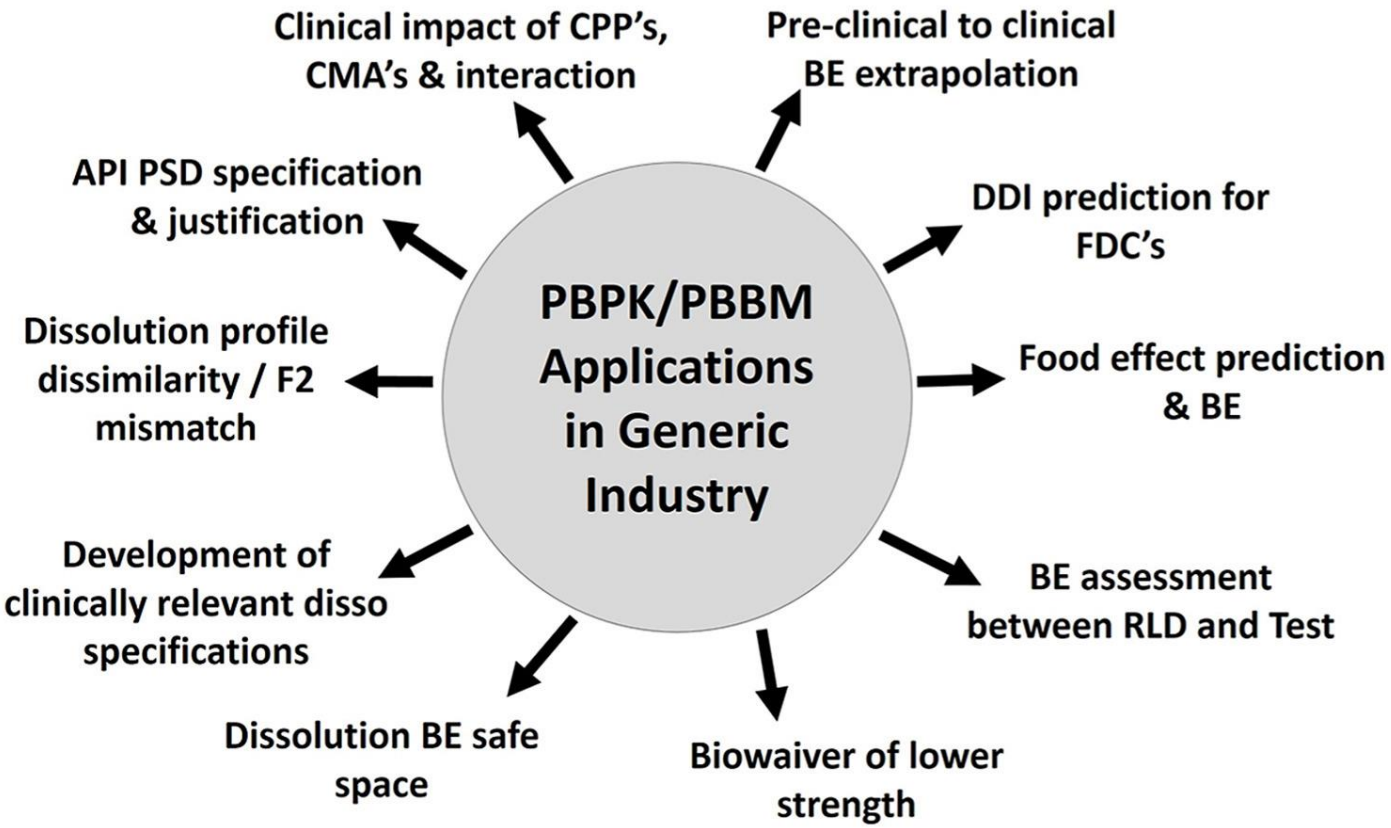
Disclaimer

- This presentation reflects the view of the presenter and should not be construed to represent FDA's views or policies


Everyone deserves
confidence in their *next* dose
of medicine.
Pharmaceutical quality
assures the
availability,
safety,
and efficacy
of *every* dose.



Yuvaneshwari K, Kollipara S, Ahmed T, Chachad S. Applications of PBPK/PBBM modeling in generic product development: An industry perspective. J Drug Deliv Sci Tec. 2022;69. doi: ARTN 103152 10.1016/j.jddst.2022.103152. PubMed PMID: WOS:000788094300004.

General Workflow of PBPK Model Assessment

- Model Objectives
  - How the specified question(s) related to drug substance, formulation or physiology affect the PK performance
  - Modeling and simulation rationale
  - Level of confidence in the modeling outcome
- Model Development
  - Model structure
    - Considering the objectives
    - Compartmental PK model or minimal PBPK model vs full PBPK model
    - Factors affecting dissolution/absorption
  - Model assumptions
    - Scientifically justified
    - Effect on model parameters/performance
  - Model parameters
- Selection, estimation, value and incorporation
- Model Validation and Refinement
    - Validation for the intended purpose
    - Uncertainty analyses and justification of model refinement
    - Model sensitivity and robustness
- Model Application
    - Considering variability, sample size, number of trials for virtual BE simulations

CASE I: LEVERAGING THE RLD MODEL TO JUSTIFY DISSOLUTION SPECIFICATION FOR IR PRODUCTS

Case I: RLD Model for IR Product Dissolution Specification

- Background
  - Objective
    - Utilizing a PBBM in GastroPlus to justify a new dissolution specification of a BCS Class I IR drug product.

Case I: RLD Model for IR Product Dissolution Specification

- Model Development
  - Source of model parameters
    - Physiochemical parameters were from literature.
    - PK parameters were fitted with a 2-compartment model in PKPlus
    - Absorption model was optimized by fitting fast pivotal data of the RLD formulation
    - Dissolution profiles were included using z-factor model
- Model Validation
  - Source of validation dataset
    - External validation was performed based on Test formulation from fast pivotal data

Case I: RLD Model for IR Product Dissolution Specification

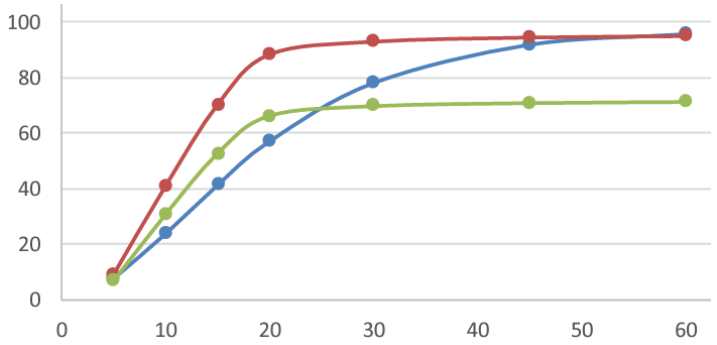
- Model Application
  - Applying a virtual batch with 25% slower release rate than pivotal test formulation.

Formulation	Predicted T/R Ratio
25% Slower vs Test	
>Cmax	0.98
>AUCt	0.98

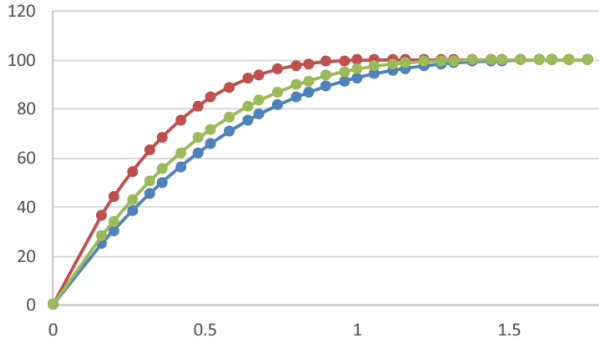
Case I: RLD Model for IR Product Dissolution Specification

- Reviewer's response
  - The virtual batch has slower drug release than RLD and could not achieve a complete release.
  - The Reviewer reproduced the z-factor dissolution model and found that it predicted that the virtual batch has consistently higher release than the RLD throughout the dissolution time and could achieve a complete release.

Case I: RLD Model for IR Product Dissolution Specification



In vitro dissolution profiles



Simulated dissolution profiles based on z-factors

- Red – Test
- Green – Virtual Batch
- Blue - RLD

Case I: Justifying Dissolution Specification for IR Products

- Recommendations
  - The applicant should use additional in vitro and in vivo data to show that the model is still robust to predict PK parameters when the dissolution profile is slow as that of the virtual batch.

CASE II: LEVERAGING RLD MODEL TO JUSTIFY DISSOLUTION SPECIFICATIONS FOR ER PRODUCTS

Case II: RLD Model for ER Product Dissolution Specification

- Background
  - Objective
    - Utilizing PBBM in GastroPlus to justify dissolution specification for an ER product with a BCS class I drug.

Case II: RLD Model for ER Product Dissolution Specification

- Model Development
  - Source of model parameters
    - Physiochemical and formulation properties were from FDA dissolution database recommended media
    - PK parameters were from simultaneously fitting PK data of IV and IR formulation
    - Gut physiology was optimized based on IR PK data
    - Dissolution profiles were fitted to Weibull functions
- Model Validation
  - Source of validation dataset
    - Single VBE were performed, and T/R ratios were calculated from in-house BE in fasting and fed from a single release rate of the test product

Case II: RLD Model for ER Product Dissolution Specification

- Model Application
  - VBE for proposed dissolution specification in fasting/fed condition

	Cmax Ratio	AUCi Ratio	AUCt Ratio
Fasted			
Lower Spec	0.91	0.88	0.87
Upper Spec	1.07	1.08	1.09
Fed			
Lower Spec	0.97	0.96	0.96
Upper Spec	1.05	1.02	1.03

Case II: RLD Model for ER Product Dissolution Specification

- Reviewer's response
  - The Test product and RLD product used to build the PBBM have different formulations including different release-controlling agents.
- Recommendations
  - Model developed based on a single release rate has very limited regulatory utility. Two or more formulation variants of the test product with different release rates are recommended.

CASE III: EXPLORING METHODS TO ESTABLISH PSD SPECIFICATIONS

Case III: Exploring Methods to Establish PSD Specifications

- Background
  - Objective
    - To evaluate the absorption model that links particle size distribution (PSD) with in vivo PK and justify the PSD specification

Case III: Exploring Methods to Establish PSD Specifications

- Model Development
  - Source of model parameters
    - Johnson model was used to incorporate 3-tier PSD profiles
- Model Validation
  - Source of validation dataset
    - Verified by multiple formulations PK data with a range of PSD profiles.

Case III: Exploring Methods to Establish PSD Specifications

- Model Application
  - Method 1: Conducted single subject simulations by proportionally increasing D10, D50, and D90 until the resulting PSD failed to achieve BE
  - Method 2: Conducted single subject simulations by using fixed D50 and increasing standard deviations until the PSD failed to achieve BE.
  - Method 3: Starting with Method 1 as initial values, the optimization module was utilized to simultaneously fit both the smallest and largest particle sizes using VBE.

Case III: Exploring Methods to Establish PSD Specifications

- Reviewer's response
  - Method 1 is a commonly used method and it generally considered acceptable
  - Method 2 is acceptable in this case because the impact of D10 and D90 on in vivo PK is small
  - Method 3 is acceptable because the particle size range determined from VBE is narrower than the particle size range from Method 1

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