Biopharmaceutics and Bioequivalence A Day in the Life

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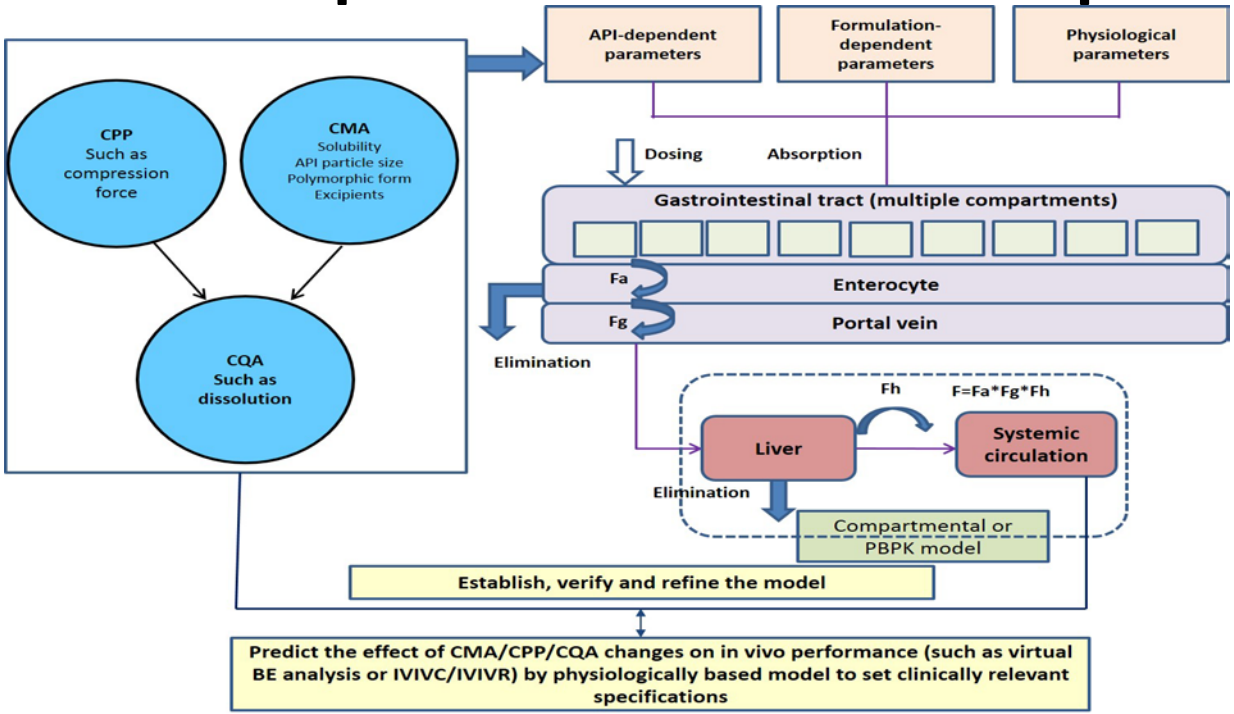
Physiologically Based Pharmacokinetic (PBPK) Absorption Model used in Biopharmaceutics



CPP: Critical Process Parameters; CMA: Critical Material Attributes; CQA: Critical Quality Attributes; API, Active Pharmaceutical Ingredient; IVIVC/R: in vitro in vivo correlation/Relationship

What is a In Silico Virtual BE Study?

- Use of model to compare test and reference formulations
- The model must have a formulation variable that can be adjusted to represent the difference between T and R
- The model generates a population for BE study, compares T and R in that population
  - Simulate an appropriate number of studies to estimate probability of success or failure

Courtesy of Dr. Liang Zhao

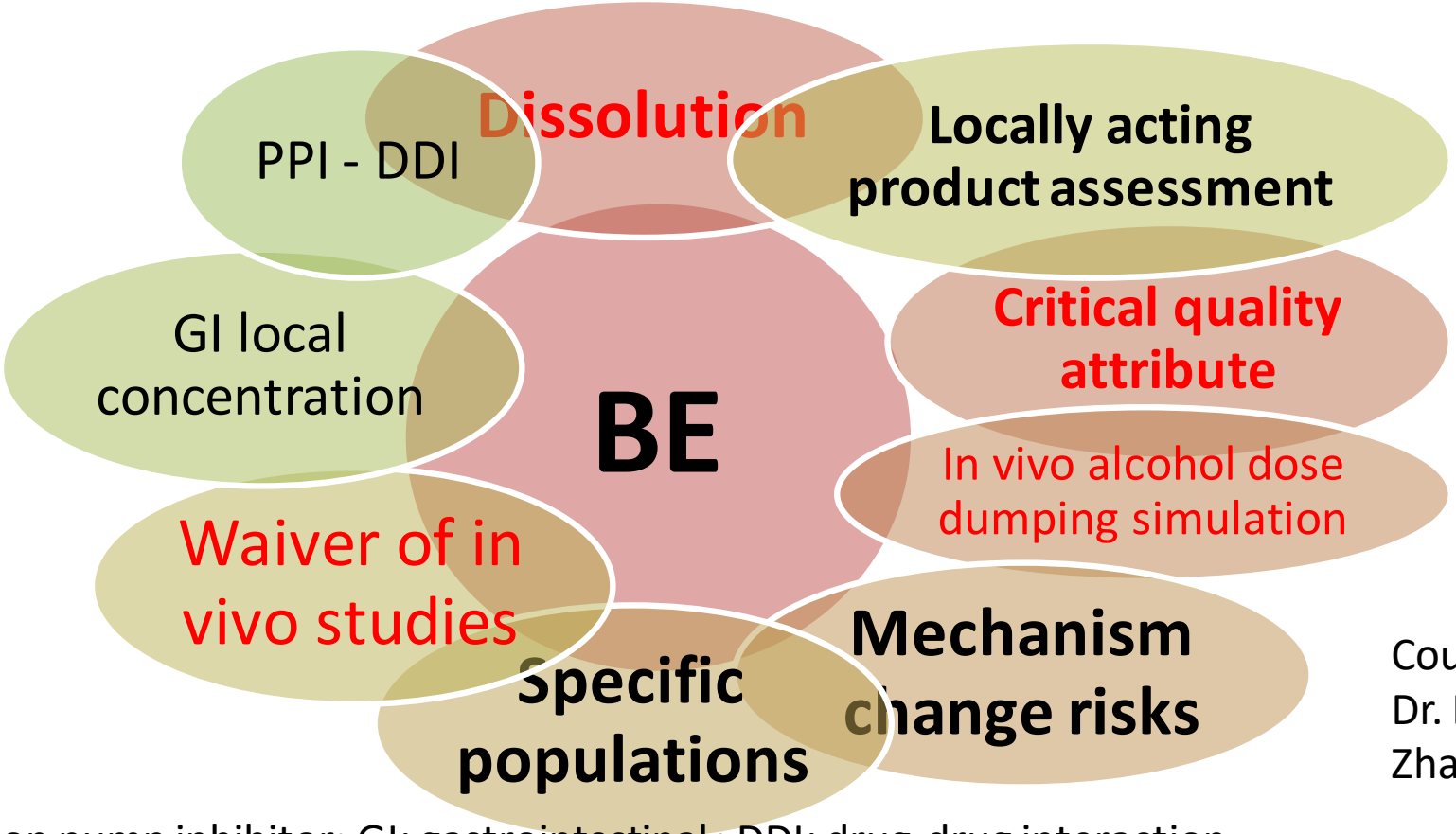
BE: bioequivalence; T: test product; R: reference product

NDA vs. ANDA Review Process

New Drug NDA Requirements	Generic Drug ANDA Requirements
1. Drug Substance	1. Drug Substance
2. Manufacturing	2. Manufacturing
3. Drug Product	3. Drug Product
4. Microbiology	4. Microbiology
5. Biopharmaceutics	5. Biopharmaceutics
6. Preclinical Studies	
7. Clin. Pharm.	6. Bioequivalence(BE)
8. Clinical Studies	

ANDA: abbreviated new drug application; NDA: new drug application

Types of Questions Our Models (PBPK for Generic Drugs) Inform



Courtesy of Dr. Liang Zhao

PPI : proton pump inhibitor; GI: gastrointestinal ; DDI: drug-drug interaction

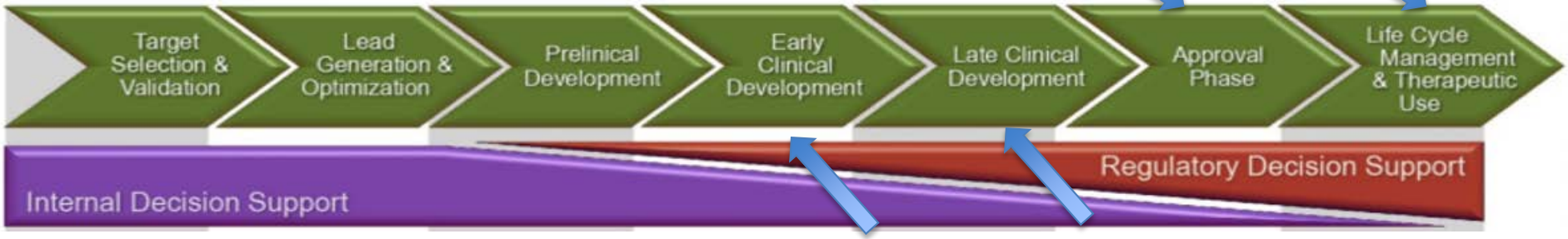
The Applications and Current Approaches of PBPK Absorption Modeling and Simulation for Biopharmaceutics Assessment

	Main Application	Current Approach
Dissolution Method and Acceptance Criteria	Justify discriminatory capability of dissolution method	• Use a verified PBPK/absorption model combined with bioequivalence (BE) clinical study and dissolution profiles to show that the proposed dissolution method can reject a non-BE batch
	Set clinically relevant dissolution specification	• Used to support a wider dissolution acceptance criteria
Set clinically relevant specifications of CMAs and CPPs	CMAs (e.g., particle size, polymorphic form)	• Used to predict the effect of upper limit of drug substance particle size distribution on the *in vivo* performance of drug product • Used to predict the effect of drug substance polymorphic form on *in vivo* performance of drug product
	CPPs (e.g., milling method, compression force/hardness)	• Used to evaluate the impact of the proposed change of milling method on *in vivo* performance of drug product as milling method is linked to particle size. • Used to justify specification range of compression force based on the predicted *in vivo* performance of drug product
Risk assessment and bio-waiver	Waive required BE study based on physiologically based IVIVC/IVIVR or based on the risk of failure of BE between post-change and pre-change of drug product (target) due to pre-approval changes or SUPAC changes	• Used in combination with dissolution similarity test to perform risk assessment on the Chemistry Manufacturing and Controls (CMC) changes based on parameter sensitivity analysis and virtual BE prediction • Mechanistic IVIVC based on PBPK absorption model to increase the success rate of IVIVC prediction for supporting bio-waivers

Role of Biopharmaceutics and Bioequivalence to Support Regulatory Decision

Biopharmaceutics evaluation (e.g., dissolution and PBPK absorption modeling to set clinically relevant specification)

Bioequivalence evaluation during SUPAC change and generic drug development



Biopharmaceutics evaluation (e.g., dissolution and PBPK absorption modeling to support formulation development)

Biopharmaceutics evaluation (e.g., dissolution and PBPK absorption modeling to support formulation bridging)

Types of Models We Use

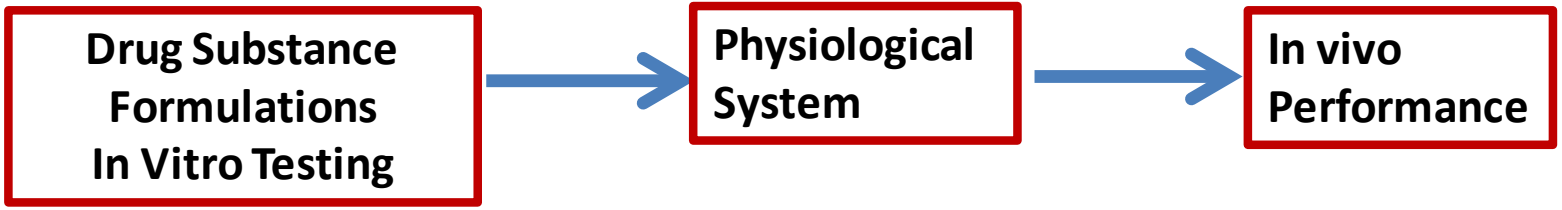
- NCA for BE analysis
- PBPK: Physiologically Based Pharmacokinetic Modeling
- IVIVC/IVIVR : In vitro in vivo correlation/Relationship
- PD: direct, indirect response (e.g., Emax model)

NCA: noncompartmental analysis; PD: pharmacodynamic; PBPK: physiologically based pharmacokinetic modeling

Software/Programs We Use

- Commercially available software (e.g., GastroPlus, SimCYP and PK-sim) for PBPK
- NONMEM, PsN for PK/PD modeling
- Phoenix to support BE analysis, IVIVC/R
- R, SAS (NLME and other packages specifically made for BE analysis, pharmacometrics, or to support statistical, graphical analysis)

Data Sources We Use



- In vitro data: physicochemical properties of drug substance and product information (e.g., dissolution)
- ADME properties of drug substance
- In vivo data: dosing regimen, demographics, PK concentrations, biomarkers, PD endpoints
- From NDA/ANDA/BLA submission and literature data

How We Validate/Qualify/Evaluate Our Models

- IVIVC/R: Internal and external validation, report PE%
- PBPK: Internal and external verification, visual predictive check (VPC), predicted vs observed PK parameters and profiles, report CV%, PE%
- PK/PD: diagnostic plots, objective functions, VPC, residual plots, CV%

Challenges and Opportunities (e.g. When Using PBPK Absorption Model)

Current status

- GI physiology could be incorporated in PBPK model and more understanding is on the upper part of GI tract
- Population predictions are generally used in PBPK model
- Drug substance and product attributes such as solubility, permeability, dissolution profiles and particle size are used as model inputs

Further Improvement

- Need further understanding of physiology in the lower small part of GI tract, such as colon for the drug which will be absorbed in colon
- Subject variabilities should be considered when needed
- Consistent and adequate approach of generating (biorelevant) solubility, dissolution profiles, permeability and particle size changes during the possible precipitation process is needed

Challenges and Opportunities (e.g., When Using PBPK Absorption Model)

Current status

- Some drug/formulation dependent or system dependent parameters are used as model inputs with assumptions
- Validation/verification of PBPK model is conducted before the application of the model

Further Improvement

- Uncertain drug/formulation dependent or system dependent parameters need adequate justification
- Sufficient purpose-dependent model validation/verification is needed

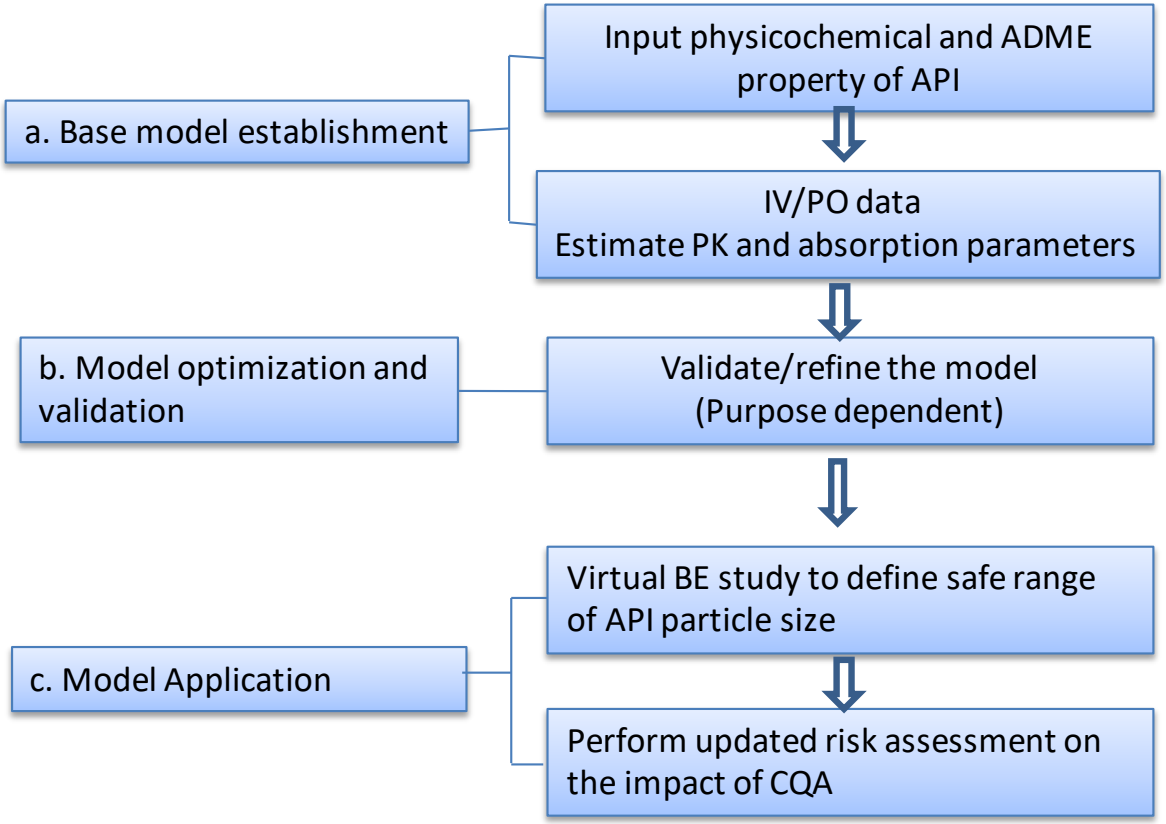
Example: Highlights of PBPK Impacts in OGD

Category	Example Drug	Impact on regulatory decision making
Dissolution	Oxybutynin	Risk assessment for not conducting in vivo studies for lower strength generic products when bioequivalence has been established at higher strengths
Product quality	Prasugrel	Conclusion that less than 20% free base in prasugrel HCl product ensures in vivo BE of the generic product including subjects on PPI
Mechanism change risks	Venlafaxine	Model predicted that a delayed onset of venlafaxine release up to 4 h predicted to demonstrate BE for the openable matrix release mechanism against the osmotic pump based release mechanism
PPI effect	Several ER products	Risk assessment of changing drug release to a PH dependent mechanism
PK metrics determination	Mesalamine Suppositories	Determination of PK metrics for BE evaluation
Alcohol dose dumping	Metformin Hydrochloride ER Tablet	Assessment of alcohol dose dumping potential
Virtual simulation	Methylphenidate	Assessment of using PBPK model in combination with a two way crossover study to meet the guidance recommendation of a four way crossover study for BE assessment

Courtesy of Dr. Liang Zhao

PPI: proton pump inhibitor; ER : extended release

Using PBPK for Risk Assessment on the Impact of CMAs



ADME: Absorption, Distribution, Metabolism and Elimination
IV: Intravenous
PO: Oral

Case Example
Establishment, Validation of PBPK Absorption Model

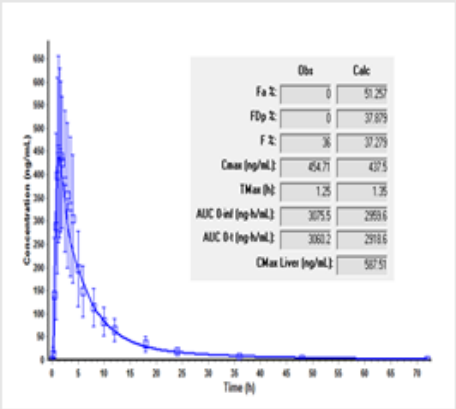


Fig 1. Observed (dots) and simulated (line) plasma concentration-time profile using refined PBPK model with updated clinical relevant solubility for reference listed drug product (RLD) following single dosing of IR tablet , PE%<20%

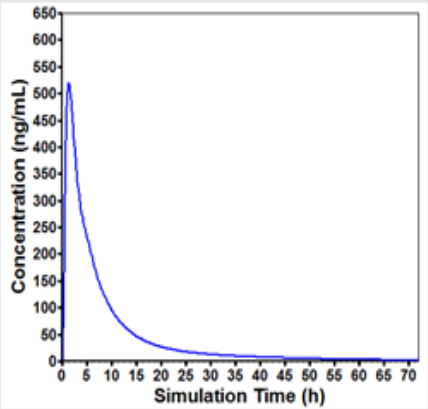


Fig 2. Validation: simulated plasma concentration-time profile using refined PBPK model for generic drug product following single dosing of IR tablet. When compared with observed pharmacokinetic parameters (AUC, Cmax), model prediction Error (PE%)<20% (data not shown)

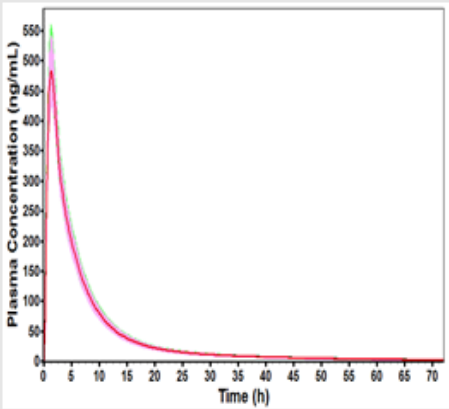


Fig 3. Further Validation: virtual BE study indicated bioequivalence for Drug X IR tablet between generic drug product (Test) and RLD (Reference). Measured mean particle size and SD for both Test and Reference are used in PBPK model

Using PBPK Modeling as a Supportive Tool for Risk Assessment on the Critical Quality Attribute of a Generic Drug Product and set Clinically Relevant Specifications

Application of PBPK Absorption Model

Table 1. Simulated bioequivalence analysis between the biobatch (Reference) and a virtual batch with particle size at the upper limit of the proposed Particle Size Distribution (PSD) specification (Test)

Pharmacokinetic Parameters	Geometric Mean Ratio (% T/R)	90% Confidence Interval of the Ratio (%)
C_{max}	95.52	(85.32-106.93)
$AUC_{0\text{-}inf}$	95.72	(84.80-108.03)
$AUC_{0\text{-}t}$	9.72	(84.88-107.93)

• BE was demonstrated between the bio-batch with the particle size at R=3.672 µm, SD= 2.118 and the same formulation with PSD within proposed specification (D(0.1): ≤ 5 µm, D(0.5): ≤ 12 µm, D(0.9): ≤ 20 µm). There is a low risk on having a significant effect on in vivo performance if using API within the PSD specification.

Case Summary

- The current study proposed and implemented an approach using PBPK absorption modeling and simulation as a risk assessment tool
- The approach provided more confidence for decision making to accept the proposed particle size distribution specification and mitigate the risk
- In order for this approach to provide more quantitative contributions, categorization of the risk (low, medium and high risk) of the changes of critical quality attributes to the patient using the virtual BE results may need to be studied

Conclusion

- Currently, modeling and simulation tools e.g., PBPK absorption modeling and simulation (M&S) has been increasingly used in new and generic drug applications.
- With continuous improvement along with more submissions, PBPK absorption M&S would aid in setting clinically relevant specification, support (alternative) bioequivalence approach design, support high impact applications such as alternative bioequivalence approach as well as safe and effective use of drug products.
- Submit modeling and simulation data and communicate with Agency at early stage, e.g., in pre-ANDA meeting package is encouraged.

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