Sandoz Development Center
Clinical development

PBPK Modeling to Support Risk Assessment for Oral Drug Products, Including Waiver of Fed BE Studies

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Best Practices for Utilizing Modeling Approaches to Support Generic Product Development (Virtual Public Workshop)
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Agenda

- PBPK Modeling to Support Risk Assessment for Oral Drug Products
- Case study 1
- PBPK Modeling of Food Effect
- Waiver of Fed BE Study
- Case study 2

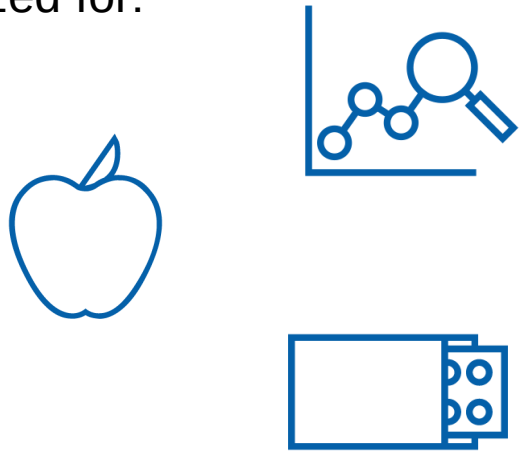
PBPK Modeling to Support Risk Assessement for Oral Drug Products

HA guidance

- US FDA: **Physiologically Based Pharmacokinetic Analyses — Format and Content Guidance for Industry** (Sep 2018, final)
- US FDA: **The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls** (Sep 2020, draft)
- EMA: **Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation** (Dec 2018)
- Japan MHLW: **Guidelines for Analysis Reports Involving Physiologically based Pharmacokinetic Models** (Dec 2020)

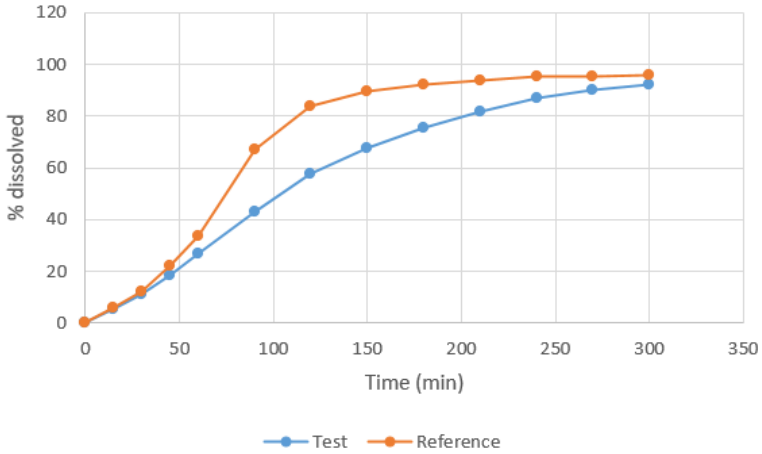
PBPK Modeling to Support Risk Assessement for Oral Drug Products

- **Physiologically based biopharmaceutics modeling (PBBM)** can be a helpful tool to assess potential BE risks and predict the outcome of BE studies
- PBBM in generic drug development has been utilized for:
  - API/formulation property selection
  - Assessment of effect of dissolution changes
  - Setting of clinically relevant specifications
  - *In vitro in vivo* correlations
  - Food effect prediction
  - Assessment of DDI' effect of acid reducing agents



Case study 1

- The dissolution profiles of T and R products were not similar in dissolution medium SGF without enzyme, pH 1.2 (f2=41), but despite this, both products were bioequivalent. We evaluated the effect of *in vitro* dissolution at pH 1.2 on *in vivo* tablet performance (c_p profiles and PK parameters)
- PBPK model in GastroPlus™ v. 9.6
- Literature data, experimental data, and in house BE study
- BCS III class drug (high solubility, low permeability)

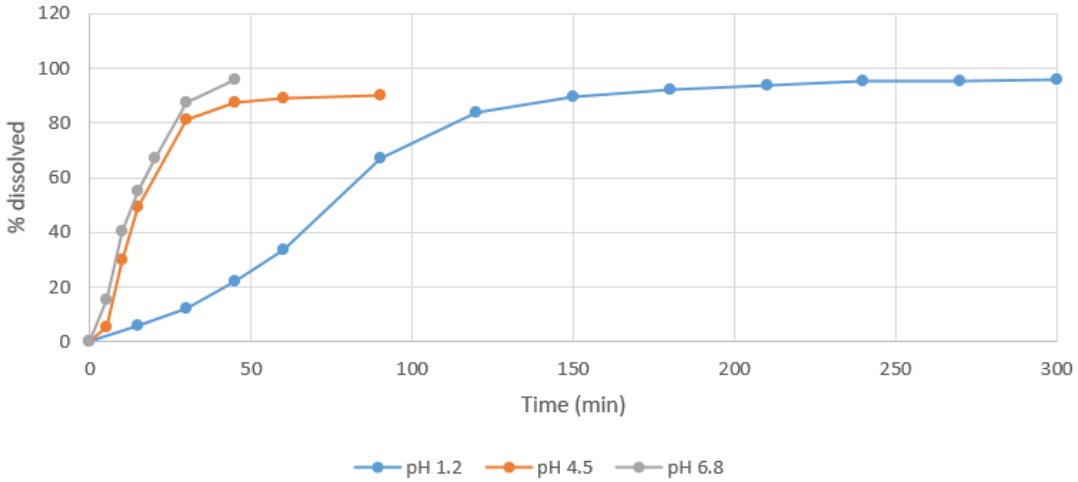


Case study 1

- **Model development and validation**
  - PK parameters from IV profile (two doses)
  - Optimizations – volume of fluid in SI and C lowered according to literature
  - Tablet – *in vitro* dissolution for T and R tablets from BE study
  - PSA – API particle size, solubility, permeability, FPE, clearance, Vd, GIT transit time, volume of fluid in GIT, pH in GIT
  - Population simulation and VBE
- **Model application**
  - Simulations using different stomach transit times

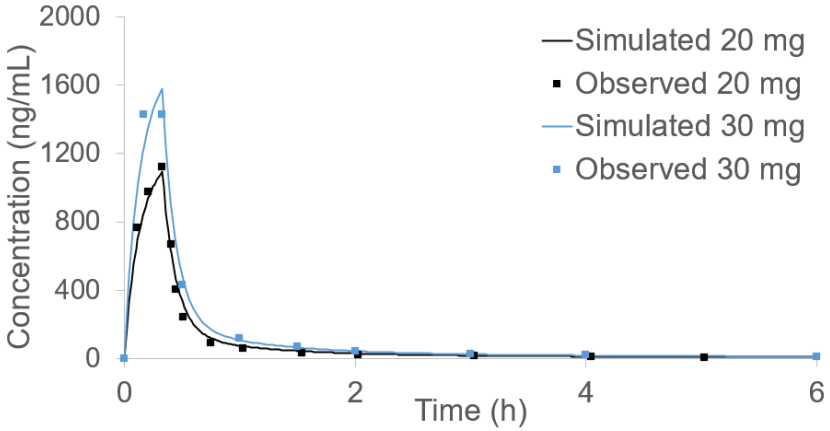
Case study 1

- Z-factor fitted to dissolution profiles at pH 1.2, 4.5, and 6.8
- Z-factor vs pH table used for simulations



Case study 1

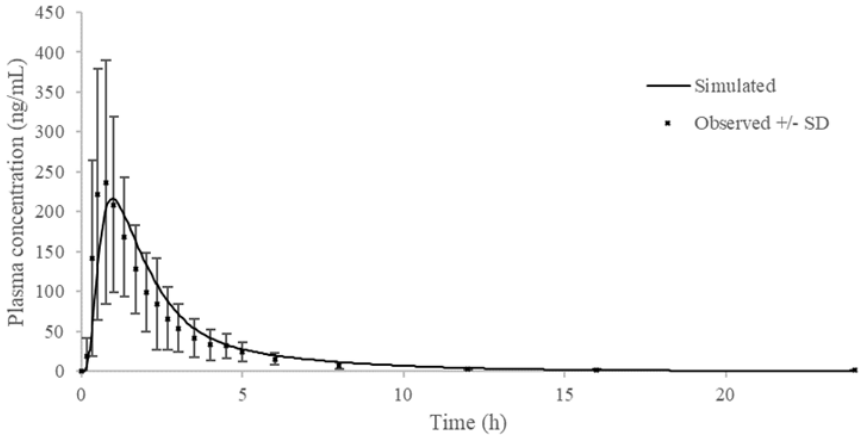
- IV model validation
  - Low %PE

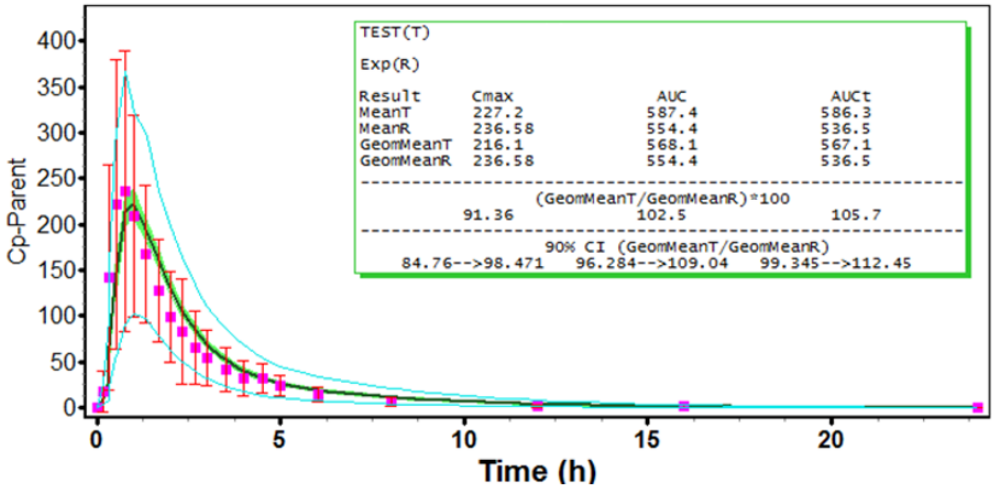


	IV 20 mg			IV 30 mg			
	Observed	Simulated	% PE	Observed	Simulated	% PE	Average % PE
C_{max} (ng/mL)	1122.80	1094.70	2.50	1429.00	1582.00	-10.71	6.6
AUC_t (ng*h/mL)	502.72	528.18	-5.06	846.92	796.26	5.98	5.5
AUC_{inf} (ng*h/mL)	507.30	557.65	-9.93	860.03	807.06	6.16	8.0
T_{max} (h)	0.33	0.33		0.33	0.33		

Case study 1

- Tablet simulations
  - Low %PE

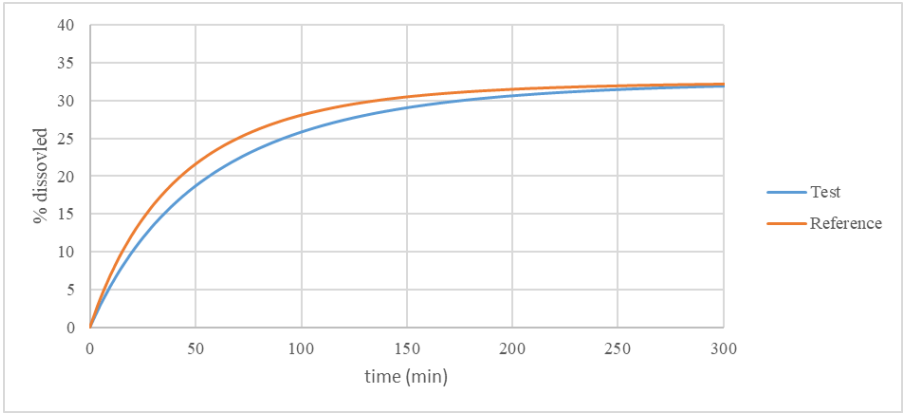


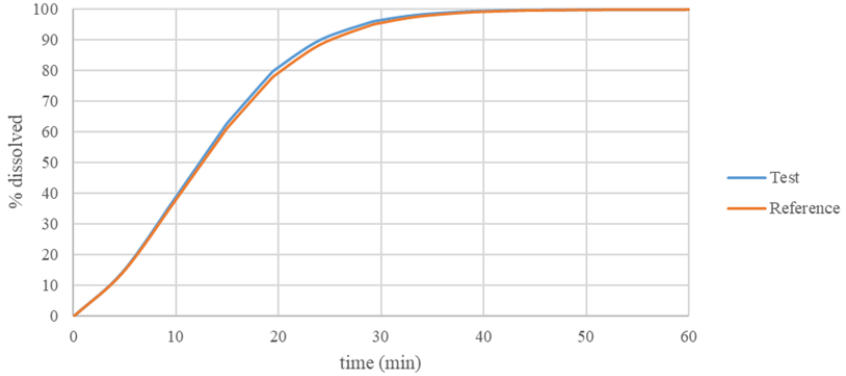


Case study 1

- Hypothetical *in vivo* dissolution (tablet stays in the stomach for infinite time)
  - Difference between T and R
  - Not in line with BE study results
  - pH 1.2 not biorelevant

- Simulated *in vivo* dissolution
  - Tablet transits through GIT
  - Similar dissolution profiles
  - In line with BE study results





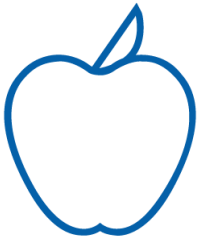
PBPK Modeling of Food Effect

- EMA BE guidance: BE study should be conducted under fasting conditions (the most sensitive condition to detect a potential difference between formulations).
  - For products that are recommended to be taken with food, the BE study should be conducted only under fed conditions.
- US FDA BE guidance: fasting and fed studies might be needed for IR products.
  - Exceptions can be made when the product is recommended to be taken only on an empty stomach. If the product is to be taken only with food, **fasting and fed studies are recommended**, except when there is safety concern with fasting administration.
- **Can PBPK modeling be used to waive fed BE study?**

PBPK Modeling of Food Effect

Effect of food

- Changes in GIT environment - GIT times, fluid volume, pH, bile salt concentration, increased hepatic blood flow
- In addition – possible binding to food components, chelation, increased viscosity, degradation, impact on influx and efflux transporters, enzymes
- Impact on drug dissolution and absorption – positive, negative or no impact on C_{max}, AUC, and T_{max}
  - BCS 1 – impact of gastric emptying time on C_{max}
  - BCS 2/4 – increased solubility (positive food effect)



PBPK Modeling of Food Effect

PBPK models more or less capable of predicting food effect

- Kesisoglou. Can PBPK Modeling Streamline Food Effect Assessments? 2020
  - Proposed workflow to streamline food effect assessment for different BCS classes
  - *In vitro* method relevant to specific food effect?
  - Model optimization – precipitation time, permeability – not unusual
- Cheng and Wong. Food Effects on Oral Drug Absorption: Application of PBPK Modeling as a Predictive Tool. 2020.
  - To predict fed state, account for physiological changes as well as drug properties (biorelevant solubility in fed state)
  - Inability of models to capture lymphatic uptake
  - Inability of models to capture negative food effect – unknown mechanism
    - Viscosity, interactions, degradation, inhibition of transporters

PBPK Modeling of Food Effect

- Emami Riedmaier et al. Use of PBPK Modeling for Predicting Drug-Food Interactions: An Industry Perpective. 2020.
  - Assessment of 30 compounds
  - High food effect prediction confidence – effect of bile acids, transit times
  - Moderate food effect prediction confidence – effect of blood flow, lymphatic uptake, precipitation
  - Low food effect prediction confidence – microenvironment pH, viscosity, solubilization
- Pepin et al. Understanding Mechanism of Food Effect and Developing Reliable PBPK Models Using a Middle-out Approach. 2021.
  - Combination of bottom-up *in vitro* approach and top-down fitting to clinical data
  - Adjustment of volume of fluid (accounting for mucus), P_{eff} based on fasted data, biorelevant solubility

PBPK Modeling of Food Effect

- Wagner et al. Use of PBPK Modeling for Predicting Drug-Food Interactions: Recommendations for Improving Predictive Performance of Low Confidence Food Effect Models. 2021.
  - Fasted and fed state biorelevant solubility
  - Changes in pH in time (pH-dependent solubility)
  - Simulation of salt formation and common ion effects
  - Changes in permeability and hydrodynamics
  - Supersaturation and precipitation

PBPK Modeling of Food Effect

- Emami Riedmaier. Predicting Food Effects: Are We There Yet? 2022.
  - Following validation with fasted data, models can be successfully applied to predict the fed state in lieu of a dedicated clinical food effect study, especially for BCS 1 and 3 compounds.
  - Gaps: transporters, enzymes, biopredictive *in vitro* method for negative food effect
  - A middle-out approach can be applied with high confidence, where the **fed model is verified with a clinical anchor study and subsequently extrapolated to additional food effect questions**, e.g., following formulation or dosage changes, thereby **avoiding additional clinical studies**.

→ **option for generics?**

PBPK Modeling of Food Effect

Generics

- In general, a lot of clinical data to develop and validate PBPK model
- **Middle-out approach** as food effect study already performed by originator
- Most important:

How to incorporate **difference between T and R** in the model?

Waiver of fed BE study

Jereb et al. Prediction of fasted and fed bioequivalence for immediate release drug products using PBBM. 2020.

- 6 case studies (four BCS 2, one BCS 1, one BCS 3)

BE in fed state predicted based on model developed on data from fasting BE study and known food effect

- **Difference between T and R**
  - Dissolution method (500 mL FaSSIF, App2, 75 rpm; 500 mL SGF, App 2, 50 rpm; 900 mL 0.01M HCl, App 2, 75 rpm)
  - API particle size
  - Solubility

Waiver of fed BE study

Disposition parameters – determined from IV, oral suspension

Optimization – reduced volume of fluid in GIT, increased gastric pH (1.2->2.0), change in precipitation time, stomach transit time, ASF (BCS 3)

P_{eff} from Caco-2 cells, MDCK

Virtual trials

- No. of subjects – as in *in vivo* study
- No. of studies simulated – 10 per condition
- Inter- and intra-subject variability in physiological and/or PK parameters

Waiver of fed BE study

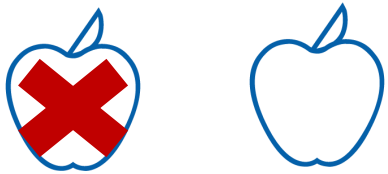
Model validation

- Scientific justifications for parameter values selection/optimization
  - PSA
- Include all available data
  - Larger %PE

Identified prerequisites

- BCS 1 or 2 with known food effect
- Linear PK
- Moderate to high BA
- Reliable PK parameters (IV, single oral dose, popPK)
- Available BE study data in the fasting conditions
- Reliable estimates of PK parameters variability

Case study 2



- BCS 2 class drug
- Data to **develop and validate model**
  - Literature data
  - Published clinical data (IV, capsule, tablet, different doses)
  - **Pilot studies in fasting and fed conditions** with 2 T batches and R
  - **Pivotal study in fasting conditions** with T and R

- Different **dissolution methods** for fasting and fed simulations
  - Fasting: SGF pH 1.2 – acidic conditions in fasting stomach
  - Fed: 0.25% SLS in Na-phosphate buffer pH 4.5 – to account for pH in fed stomach and effect of bile salts

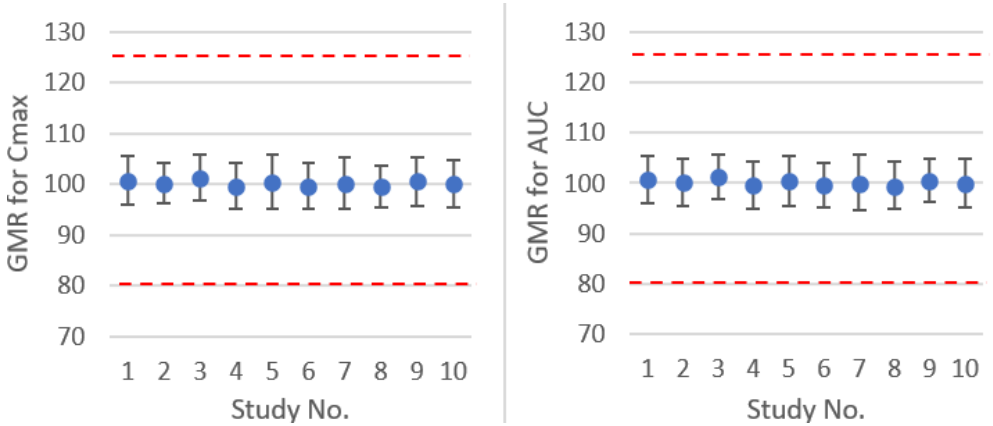
Case study 2

VBE results

- In line with fed pivotal study

C_{max} T/R ratio 104.05% (97.88-110.61%)

AUC T/R ratio 99.43% (97.88-101.00%)

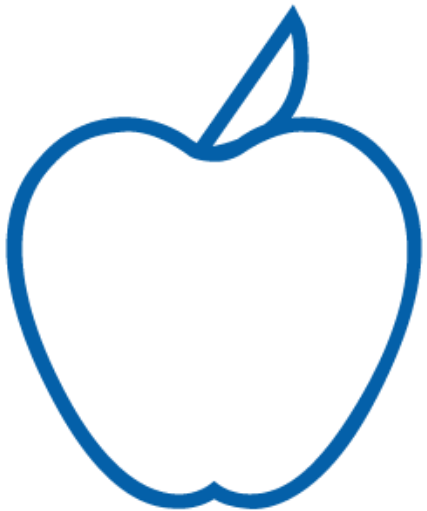


Model deficiencies according to HA

- Not appropriately validated → should use batches with different release rates/preferably non-BE batch
- No in-house experimental data on solubility (SGF, FaSSIF, FeSSIF)
- Not enough biorelevant dissolution methods

Conclusion

- **PBPK Modeling to Support Risk Assessment** & **Waiver of Fed BE Studies**
  - Useful for internal decision making in drug development
  - Regulatory applications – difficult to have properly validated models



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- IVIVC group

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Thank you

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