Use of Modeling and Simulation Tools as Alternative BE Approaches for BCS IV and High-Risk Products: Generic Industry Perspective

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Session 4: Implementation of the M13A Guidance: Lessons Learned and Advances for Immediate Release Products

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Content of the presentation

- **ICH M13A BE guidance**
  - Generic industry perspectives, opportunities, challenges
- **High-risk products**
  - Definition
  - Types of formulations
  - Requirements of fasting and fed BE
- **Alternative BE approaches**
  - PBPK modeling (workflow)
  - Typical model input parameters
  - Validation approaches
  - Challenges in developing PBPK for high-risk products
- **Case examples on the use of PBBM**
  - **1** # Waiver of fed BE arising from different formulation principles between reference and test
  - **2** # BCS IV reformulations & use of modeling to avoid repeated BE
- **Research areas & conclusion**

ICH M13A – Generic industry view

General perspectives	Opportunities	Looking forward
• Harmonized guidance across lead geographies, synchronized the BE approaches across agencies • Clarity on BE studies based on product risk (high and low risk) • Clarity on various aspects (male/female in BE, subjects removal for BE calculations, study designs) • Details on study related aspects (designs, subjects, inclusion/exclusion)	• Reduction of studies (multiple market RLDs in same study, three period with two comparator products) • USA – reduction of fasting and fed as per label recommendation and based on complexity of product • Details on potency correction – can be applied in exceptional cases for more than 5% difference	• ICH M13B – revised criteria with respect to formulation proportionality, dissolution similarity (RSD limit 8%, lower 90% CI of bootstrapped f2 ≥ 46) • ICH M13C - for HVD and NTI drugs (differences are evident among USFDA, EMA & HC)

High-risk products as per M13A

- Where the drug substance characteristics in combination with the complexity of the formulation design or manufacturing process lead to an increased likelihood that in vivo performance will be impacted differently by varying gastrointestinal (GI) conditions between the fasted and fed conditions
- Fasting BE may not be extrapolated to fed BE or vice versa and thus both studies are required
- BE needs to be conducted in both fasting and fed BE states irrespective of the labelling with regard to food intake, if safety permits
- Complex formulation / manufacturing methods: solid dispersions, microemulsions, co-processed drug substances, lipid-based formulations, nanotechnologies, or other specialized technologies, which may increase solubility / dissolution rate of the API

Amorphous Solid Dispersions (ASDs)

- Molecular dispersion of API within a polymeric matrix
- Formulation approach: HME / spray drying
- Exposure depends on polymer used

Lipid based formulations / microemulsions

- Simple oil based or formulated with mixtures of oil, surfactant, cosolvent
- Can be micro / nano emulsions
- Undergoes digestion process in GIT

Nano-formulations

- Size reduced in nano-range to facilitate more solubilization / dissolution rate
- May be added with additional excipients for targeting or to escape transporters

Why does high-risk products require fasting and fed BE

Amorphous Solid Dispersions (ASDs)

- Compositional differences between Reference and Test in terms of polymer may cause different extents of food effect
- Use of pH independent (e.g. HPMC) vs pH dependent (HPMC AS or phthalate) can cause different solubilizations in GIT in fasting and fed
- Supersaturation or kinetic solubility in absence or presence of food components may be difficult to predict
- IVIVC often is challenging for ASDs due to complexities of solubilization and absorption

Lipid based formulations / microemulsions

- The extent of solubilization / dissolution rate is dependent on the formulation components
- Oil based formulation may not be dispersed whereas combination of oil, surfactant and cosolvent may yield very rapid dispersion
- Unlike other formulations, presence of additional pathways, e.g. digestion, lymphatic absorption may be challenging to predict

Nano-formulations

- Solubility or dissolution rate can be sensitive towards particle size (e.g. nano or microns range)
- Typically, along with size reduction, other components are also added (viscosity enhancers, surface coated polymers) which may behave differently in fasting and fed conditions
- May undergo other types of absorption pathways (e.g. paracellular) depending on size
- Interactions with food may be different nano formulations (e.g. enhanced surface area)

Fasting vs Fed BE – differences among different formulations

Drug	Formulation A		Formulation B	
	Formulation principle	Observed food effect	Formulation principle	Observed food effect
ABT-102 *(Othman et al., 2012)*	Melt extrusion solid dispersion	No significant impact of food on bioavailability	Spray dried formulation	Cmax and AUC increased by 11% and 17% respectively
Itraconazole *(Rudolph et al., 2025)*	Sempera®, Hypromellose-based ASD	Positive food effect	Tolsura®, hypromellose phthalate based ASD	Negative food effect
Tacrolimus *(FDA Prograf Label, FDA Envarsus XR Label)*	Immediate release ASD	Mean AUC and Cmax were decreased 37% and 77%, respectively	Extended release ASD	Mean AUC and Cmax were decreased 55% and 22%, respectively
Dasatinib *(FDA SPRYCEL Label, FDA PHYRAGO Label)*	Sprycel, conventional immediate release	High-fat meal resulted in a 14% increase in the mean AUC of dasatinib	Phyrago, ASD	A 30% reduction in Cmax was observed with no change in AUC
Enzalutamide *(FDA XTANDI Label)*	Capsule, microemulsion	No impact on AUC but Cmax reduced by 15%	Tablets, solid dispersion	No impact on AUC observed

- Presence of different polymer in ASD may cause different food effect. Moreover, ASD vs conventional crystalline formulation may cause difference in food effect
- Formulation principle (IR or MR) can also cause different or similar food effect so as ASD vs microemulsion
- ***Thus, the behavior of high-risk formulations is difficult to predict on food effect***

High-risk formulations: Food for thought ??

Does the following situation quality for fasting or fed BE waiver?

Amorphous Solid Dispersions (ASDs)

Lipid based formulations / microemulsions

Q1 & Q2 with Innovator composition

Same manufacturing process & grades of excipients

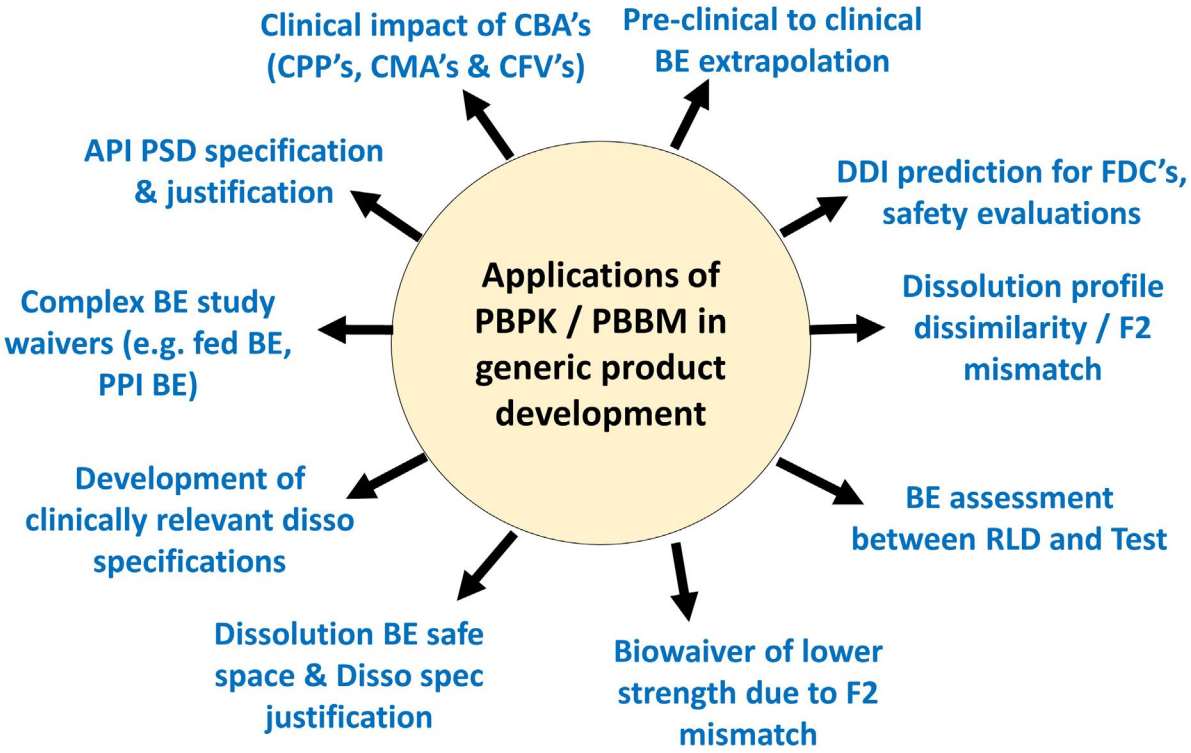
Biopharmaceutics risk assessment (e.g. same solubility of pre-mix, in presence of excipients, kinetic solubility)

Multimedia dissolution (pH 1.2, 4.5, 6.8 and biorelevant fluids)

PBBM to justify bioequivalence using virtual BE approach ?

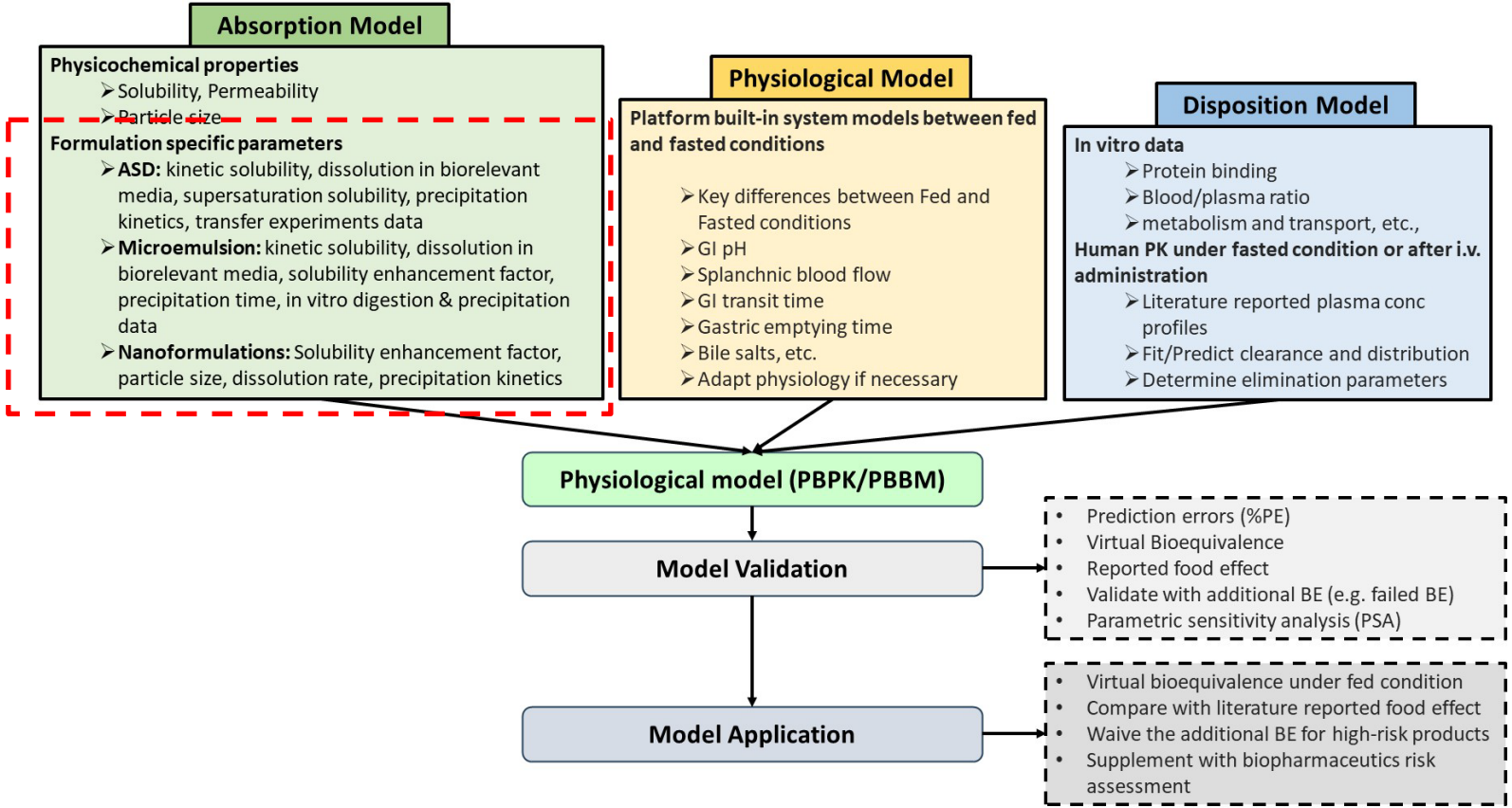
Possibility of waiver ??

Applications of modeling in generic product development

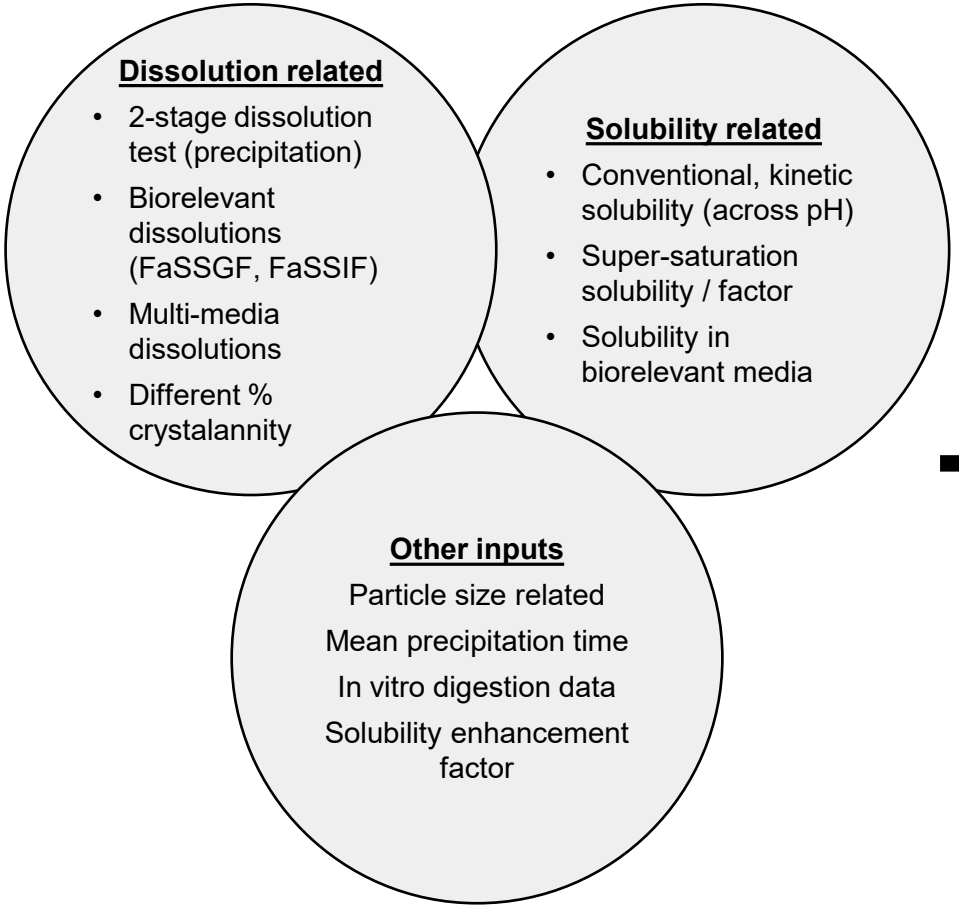


Yuvaneshwari K, Kollipara S, Ahmed T, Chachad S. Applications of PBPK/PBBM modeling in generic product development: An industry perspective. J Drug Deliv Technol. 69, 2022, 103152

PBPK model workflow for high-risk compounds



PBPK models for high-risk compounds – model specific inputs



Data from complex systems

- TNO TIM dissolution data (bio-accessible fraction)
- ASD models (artificial stomach duodenum)
- Dissolved species (micelles, nano-precipitated material) consideration
- Dissolution + permeability systems

PBPK models for high-risk compounds – Validation approaches & challenges

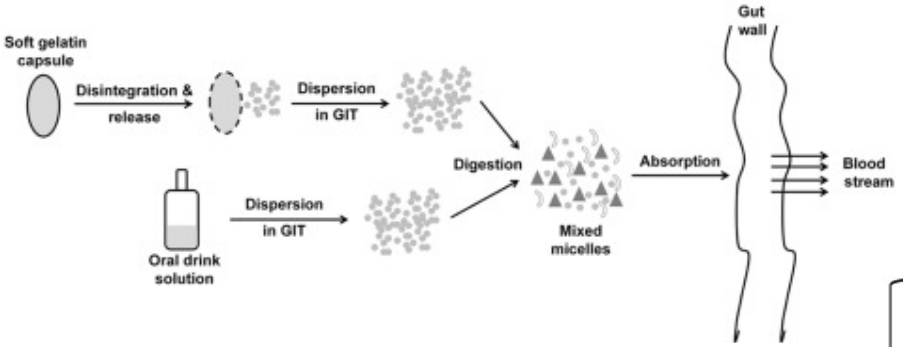
Validation approaches

- Validation with conventional formulations data (e.g. literature based)
- Fasting and fed conditions (e.g. food effect)
- Pilot and pivotal formulations data (virtual bioequivalence)
- Failed BE study (for model credibility analysis)
- PPI study data (if available)
- Parametric sensitivity analyses (understand factor impacting in vivo behavior)
- Role of biopharmaceutics risk assessment (to supplement PBBM)

Challenges to apply PBBM

- IVIVC is not always evident for ASD's and microemulsions
- Dissolution may not be factor governing in vivo behavior)
- Specific in vitro test (e.g. kinetic solubility may be relevant)
- Specific formulation behavior (microemulsions – in vivo digestion may govern in vivo behavior together with in vitro dissolution)
- pH dependent polymers in the ASD (non-Q1/Q2 may have more challenges)

IVIVC for specific lipid based formulations



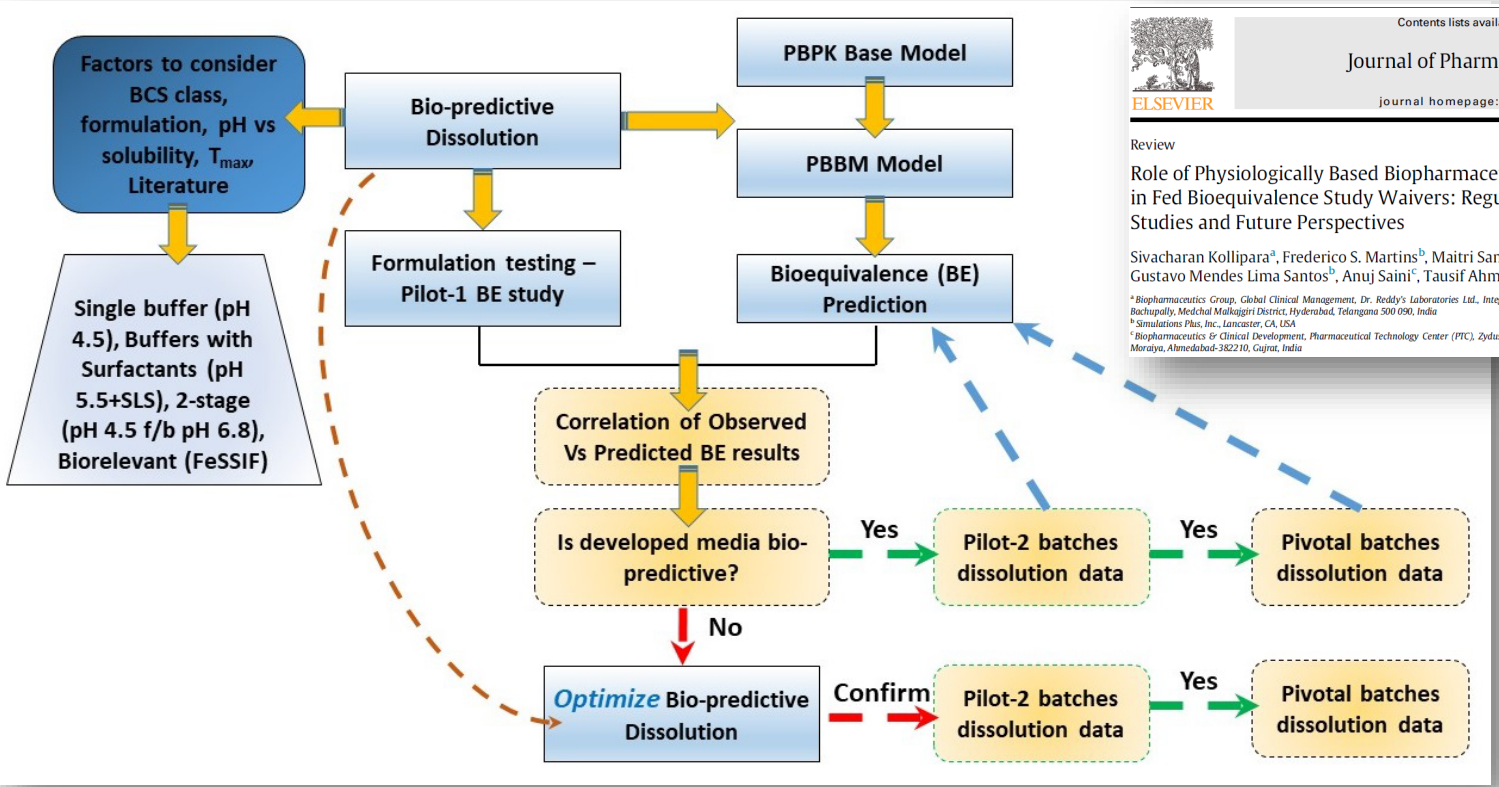
In vivo processes after lipid formulations ingestion

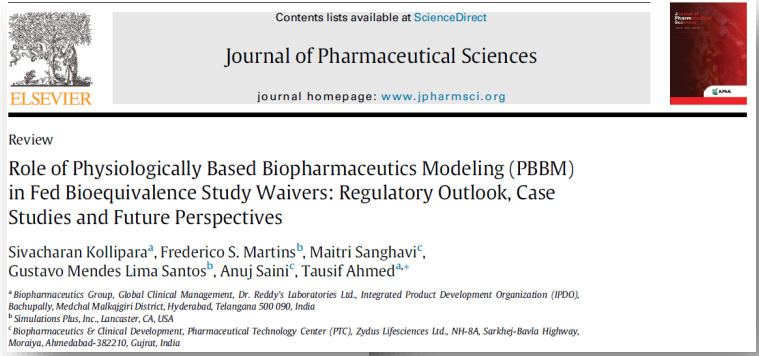
Potential IVIVC approaches

		Dissolution (Biorelevant media such as fasted and fed gastric/ intestinal)	Dispersion/Precipitation (Biorelevant media such as fasted and fed gastric/ intestinal)	Lipolysis (In standard and biorelevant buffers)	*ex vivo* permeability (In standard models such as rat, dog or humans)
In vitro	Study				
	Data	• % Drug released *vs* time profile for in case of softgel capsules	• % Solubulized or precipitated drug *vs* time • Extent of solubulized drug for different formulations	• % Solubulized drug *vs* time • Extent of solubulized drug for different formulations	• Permeability values for dispersed formulations • Permeability values for lipolytic products
In vivo	Study	*In vivo* pharmacokinetic data from dogs / humans / rats / monkeys / rabbits for selected formulations			
	Data	• Fraction drug absorbed *vs* time • AUC and C_{max} values obtained for various formulations			
IVIVC outcome		• ***Establish relationship (IVIVC Equation, R^2 value)*** • ***Correlation between rank ordering of the formulations from in vivo and in vitro studies***			

Kollipara S, Gandhi RK, Pharmacokinetic aspects and in vitro–in vivo correlation potential for lipid-based formulations. Acta Pharm Sin B. 4(5), 2014, 333-349

Case study # 1: Role of modeling approaches in fed BE waivers





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Review

Role of Physiologically Based Biopharmaceutics Modeling (PBBM) in Fed Bioequivalence Study Waivers: Regulatory Outlook, Case Studies and Future Perspectives

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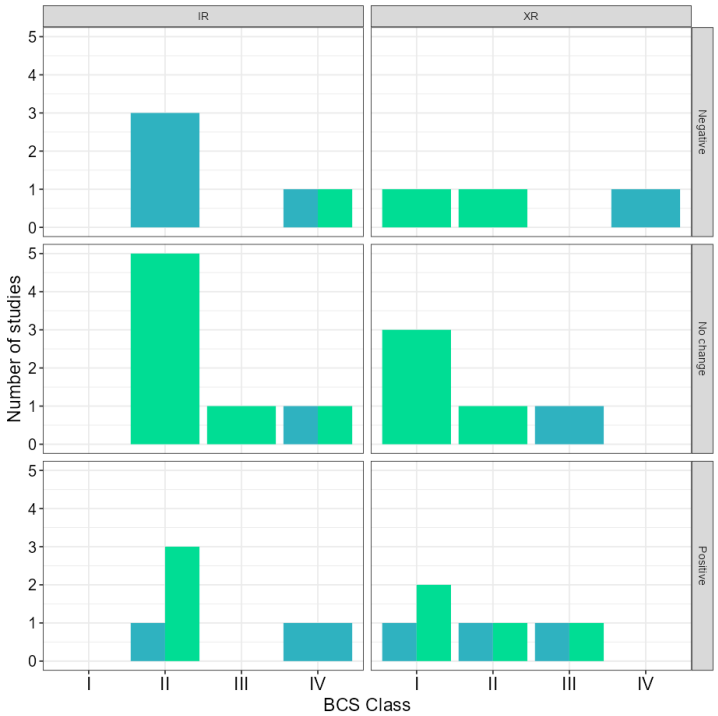
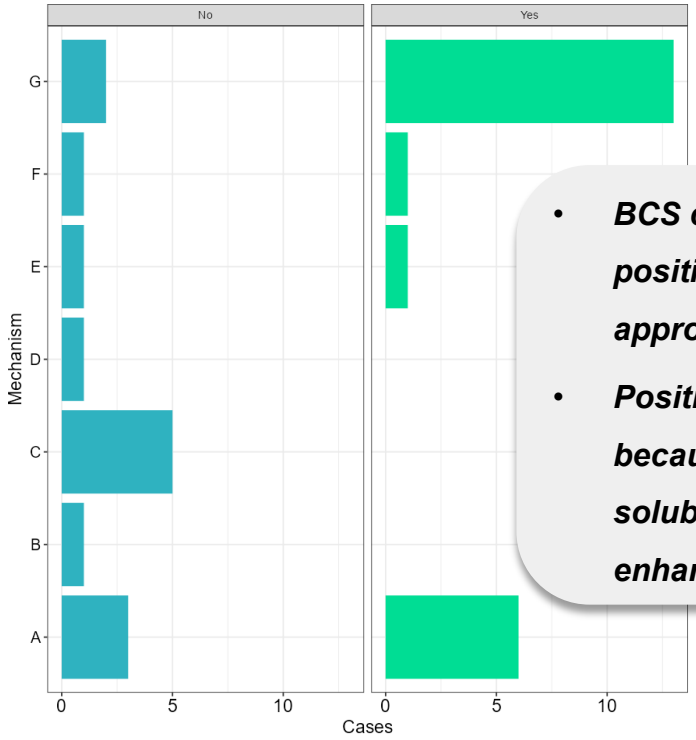
Kollipara et al. Role of Physiologically Based Biopharmaceutics Modeling (PBBM) in Fed Bioequivalence Study Waivers: Regulatory Outlook, Case Studies and Future Perspectives, Journal of Pharmaceutical Sciences, Volume 113, Issue 2, 2024, Pages 345-358

Case study # 1: Role of modeling approaches in fed BE waivers





- ***BCS class I, II molecules and positive food effect is predicted appropriately***
- ***Positive food effect resulting because of solubility/dissolution rate enhancement is predicted***

PBBM model predictability
No
Yes

A:Enhancedsolubility/release, B:Reducedsolubility, C:Delayed emptying, D:Chelation, E:Degradation, F:Transporter inhibition, G:No food effect.

Kollipara et al. Role of Physiologically Based Biopharmaceutics Modeling (PBBM) in Fed Bioequivalence Study Waivers: Regulatory Outlook, Case Studies and Future Perspectives, Journal of Pharmaceutical Sciences, Volume 113, Issue 2, 2024, Pages 345-358

Case study # 1: Role of modeling approaches in fed BE waivers

- ***Reference has micronized API, Test is solid dispersion***
- ***Fed BE study waiver is obtained based on biopharamceutics justification, VBE***
- ***Biopharmaceutics risk assessment (multimedia dissolutions)***

Model Development

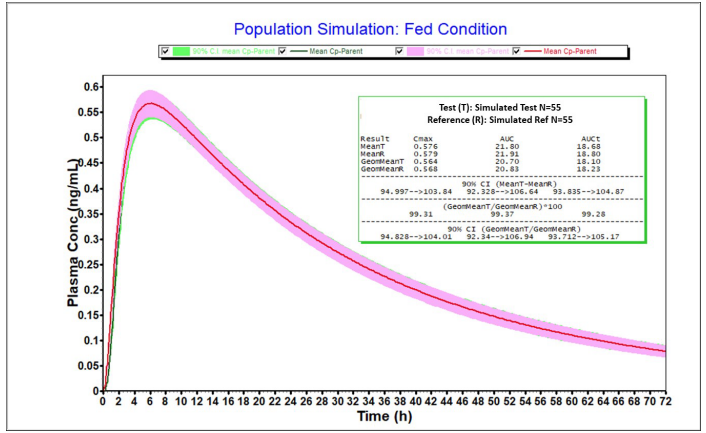
Physicochemical Properties (Experimental, Structure based, Literature) → Disposition Parameters (Literature) → Physiology (Gastroplus – Fasting, Fed)

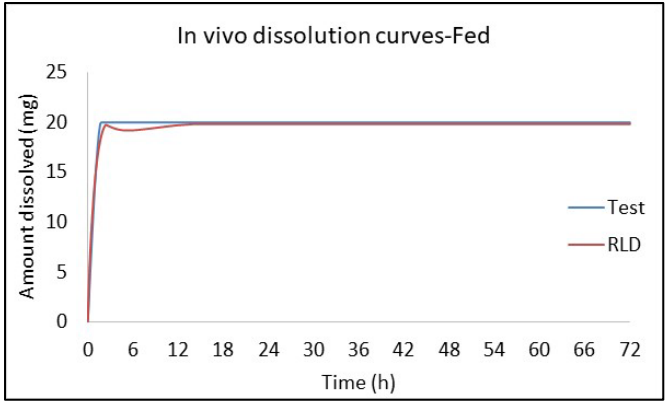
Model Validation

Exposures of Reference, Test – Fasting Condition → Virtual BE Simulations → T/R, 90% CI within 80-125%, matching with Clinical data

Model Application

Exposures of Reference, Test – Fed Condition → T/R, 90% CI within 80-125% → Food effect (Fed/Fast) 1) RLD (literature vs simulated) 2) RLD Vs Test





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Case study # 1: Role of modeling approaches in fed BE waivers

Biopharmaceutics risk assessment

General properties

- BCS II (low solubility, high permeability)
- pH independent low solubility
- Good oral bioavailability for solid dosage form
- No food effect was observed

Formulation

- Similar excipients between reference and test except surfactant
- Micronized API compensated with ASD
- Fasting bioequivalence
- Literature supports that ASD can circumvent food effect
- Pilot studies data (fed BE was never a risk)

Characterization

- Multimedia dissolutions: with and without surfactants have shown similarity as f2 is more than 50
- No risk of precipitation was seen for both reference and test

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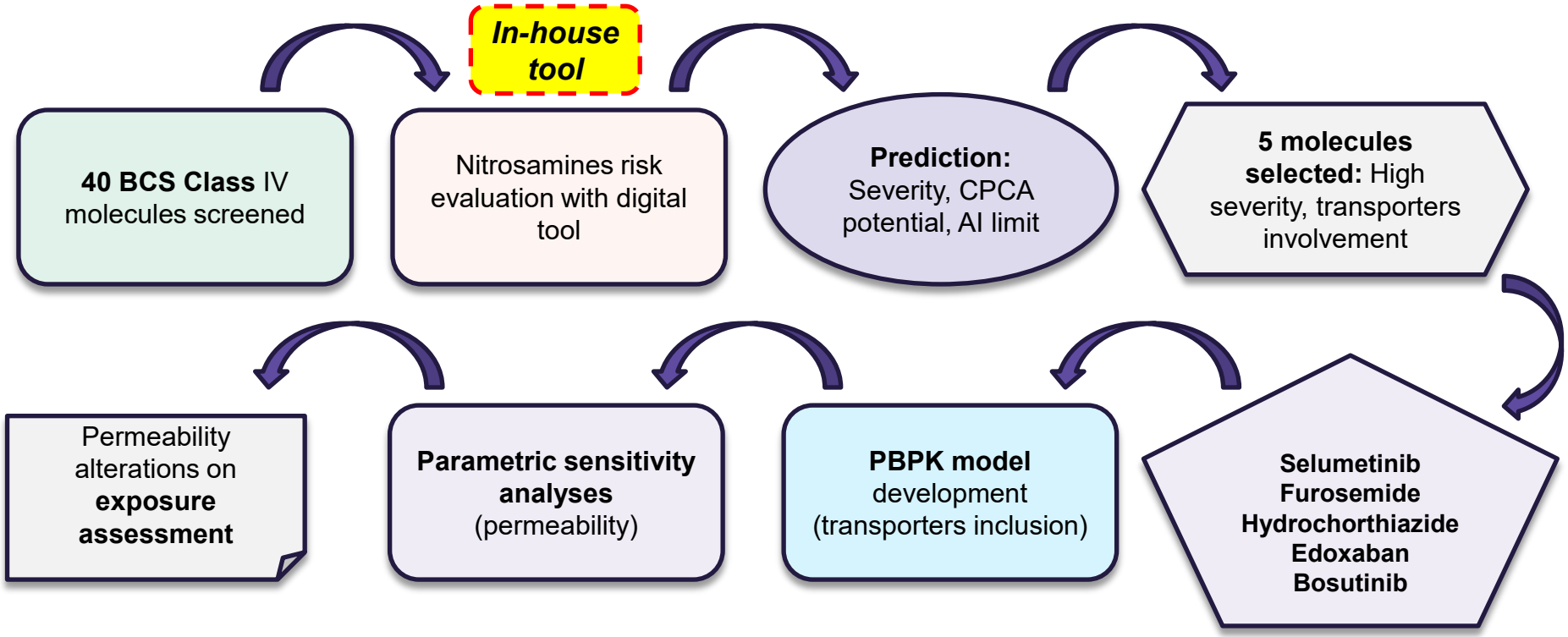
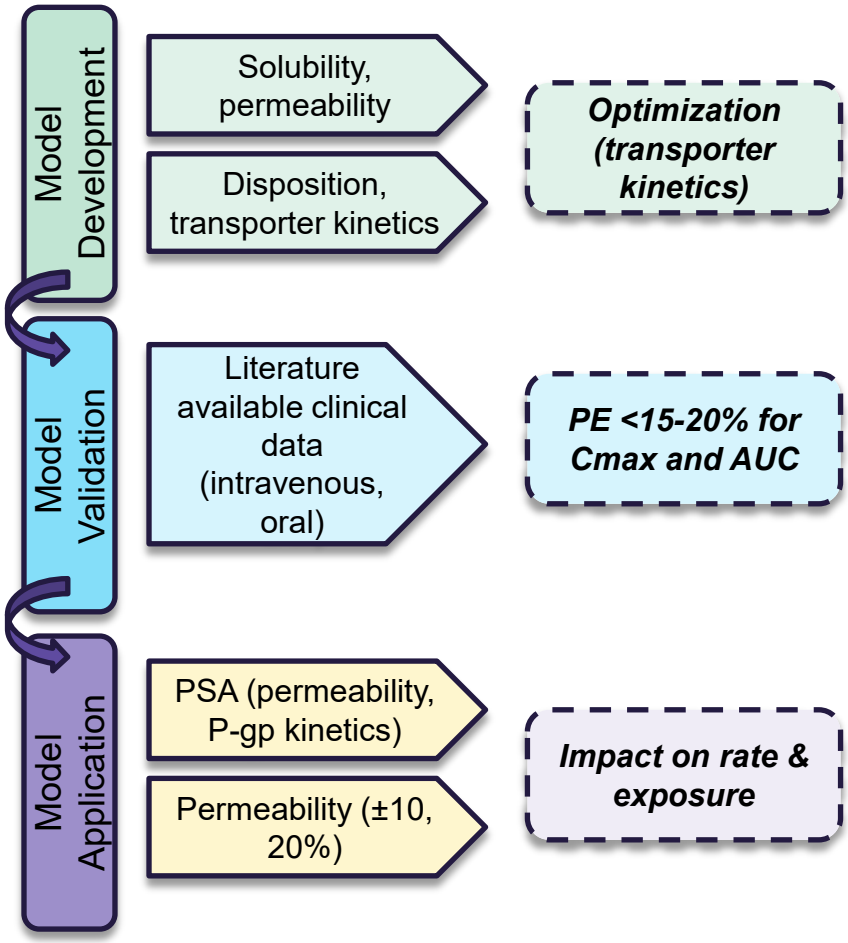
Case example # 2: Reformulation of BCS IV products, avoidance of repeat BE



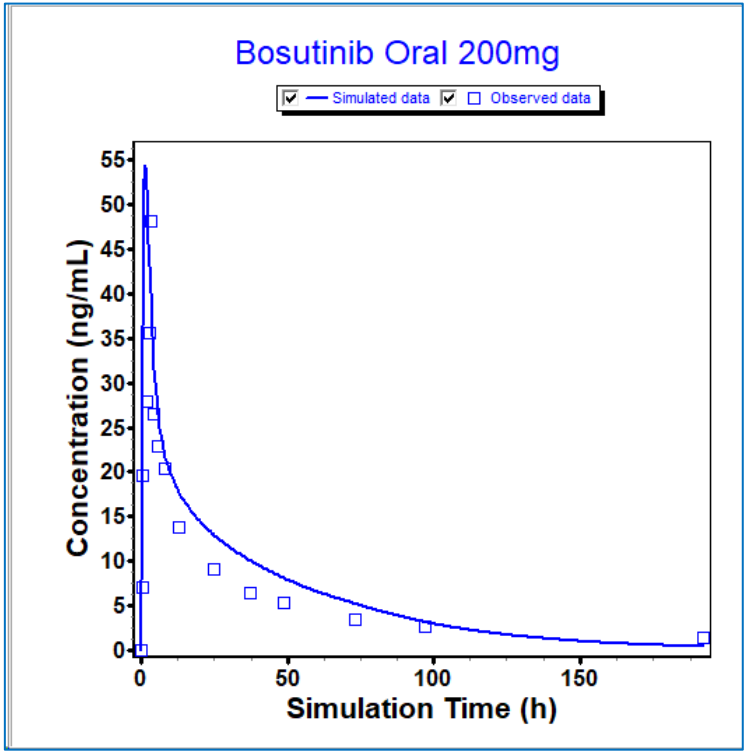
Case example # 2: Reformulation of BCS IV products, avoidance of repeat BE

Compound	Transporters involved	Transporters type
Bosutinib	**P-gp**	**Efflux**

- Objective primarily is to assess the impact of excipients on the absorption

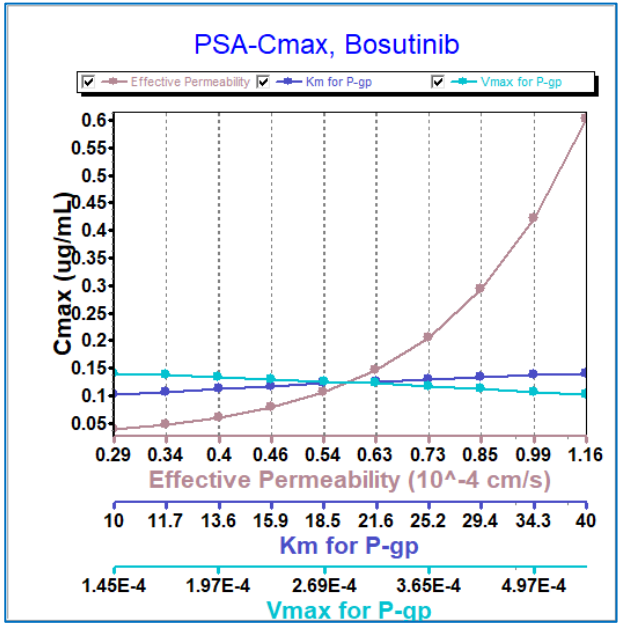


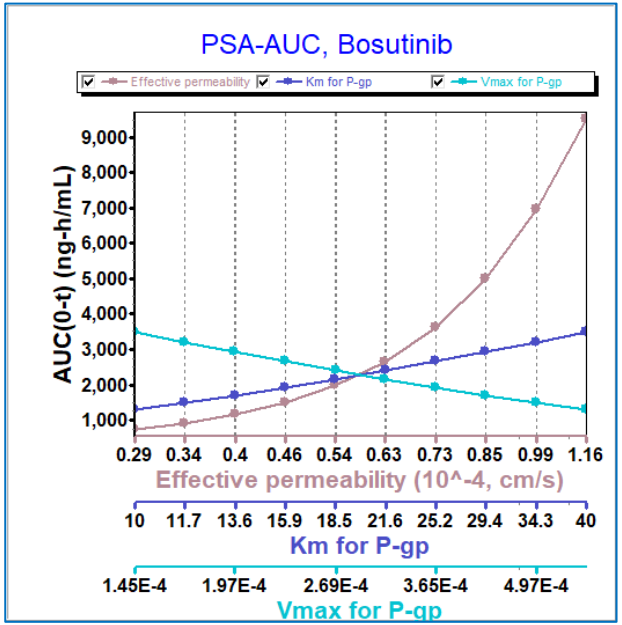
Case example # 2: Reformulation of BCS IV products, avoidance of repeat BE



- PBPK model was successfully developed and validated against pharmacokinetic data
- Models captured PK data well with acceptable prediction errors for C_{max}, AUC parameters (<20%)
- Model was further validated across additional doses

Case example # 2: Bosutinib PSA analysis

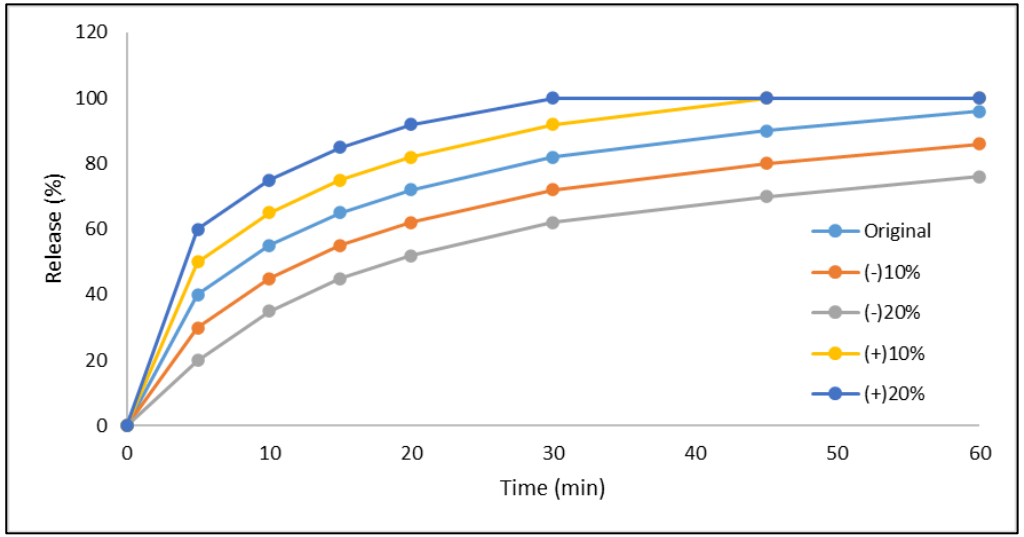




Permeability	C_{max} T/R	AUC T/R
+10%	122.3	120.5
-10%	80.9	82.0
+20%	148.2	143.7
-20%	64.8	66.4

- V_{max} and K_m of P-gp didn't show impact on C_{max} and AUC parameters
- Permeability (within ±20%) showed impact on both C_{max} and AUC parameters
- Any additional excipient causing differences in permeability, attention needs to be paid

Case example # 2: Impact of dissolution on Bosutinib



Dissolution	Cmax T/R	AUC T/R
-10%	89.28	92.23
+10%	105.95	105.15
-20%	76.33	81.34
+20%	110.95	108.83

- Dissolution has impact on T/R ratio's and a reduction by 20% has impacted C_{max} and AUC T/R ratios based on the modeling
- Dissolution safe space will be considered for target formulation development and the bio-predictability will be validated against actual in vivo data
- Any alterations of excipients that is causing differences in permeability, solubility and dissolution rate may impact in vivo performance

Potential research topics for focus

- Development of in vitro methods that can simulate the in vivo behavior of high-risk formulations
- Use of specialized (or complex) in vitro systems for predicting in vivo behavior of high-risk formulations
- Development of in vitro tests other than dissolution (e.g. kinetic solubility, supersaturation assay, lipid digestion assay)
- Validation approaches for PBBM / PBPK models for high-risk formulations
- Alternative BE approaches (e.g. biopharmaceutics risk assessment, modeling) to potentially waive off additional study (fasting or fed) for high-risk formulations

Conclusions

- ICH M13A has paved way for harmonization across the regulatory agencies on conduct of BE studies. Advantages of this harmonized study includes conducting BE studies with multiple comparator products in same study
- High risk products may require fasting, and fed BE studies due to complexity of formulations and the fact that BE in one condition (fasting/fed) may not be extrapolated to another
- Approaches like PBPK modeling can be “alternative BE” methodology to obtain BE wavier for high-risk compounds. However, attention needs to be paid on model development, validation and identification of biopredictive dissolution method
- For high-risk products, apart from dissolution, other in vitro parameters like kinetic solubility, precipitation time and supersaturation may govern the in vivo exposures
- PBPK modeling continues to evolve as alternative BE approach for high-risk products and knowledge sharing among academia, industry and regulatory is essential to develop further expertise in this direction

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Thank You

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