Medicines & Healthcare products Regulatory Agency

PBBM

Case study 5

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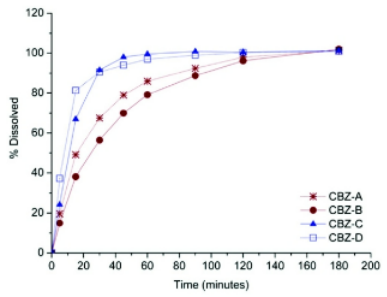
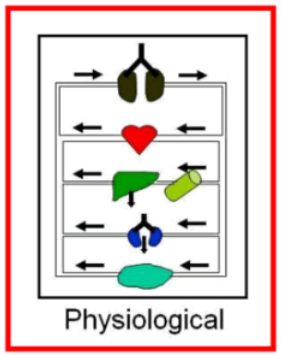
Physiologically-based biopharmaceutics modelling (PBBM)

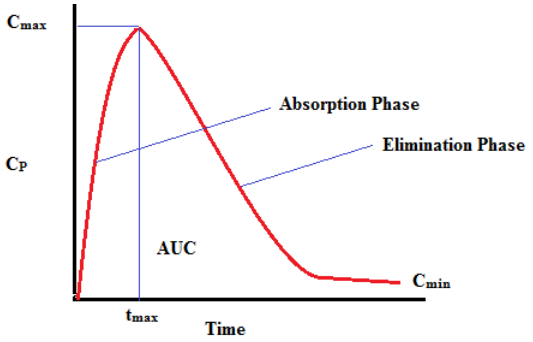
- Physiologically-based pharmacokinetics (PBPK) modelling
- Link between pharmaceutical quality and clinical performance
- Expansion of PBPK to drug product development, manufacturing changes and controls
- In vitro dissolution data provide input to predict absorption



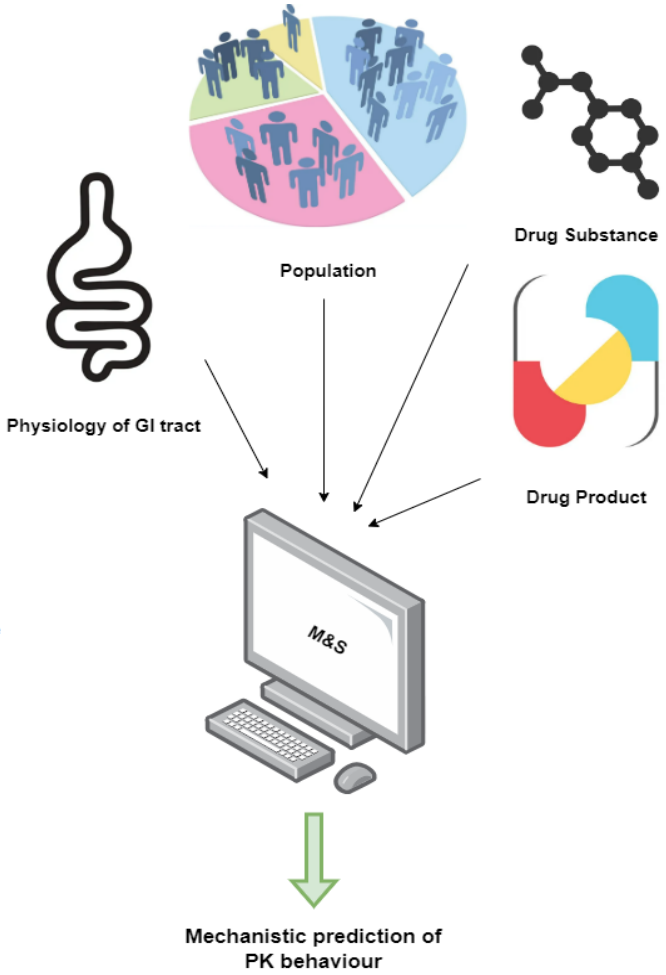
Dissolution modelling



PBPK



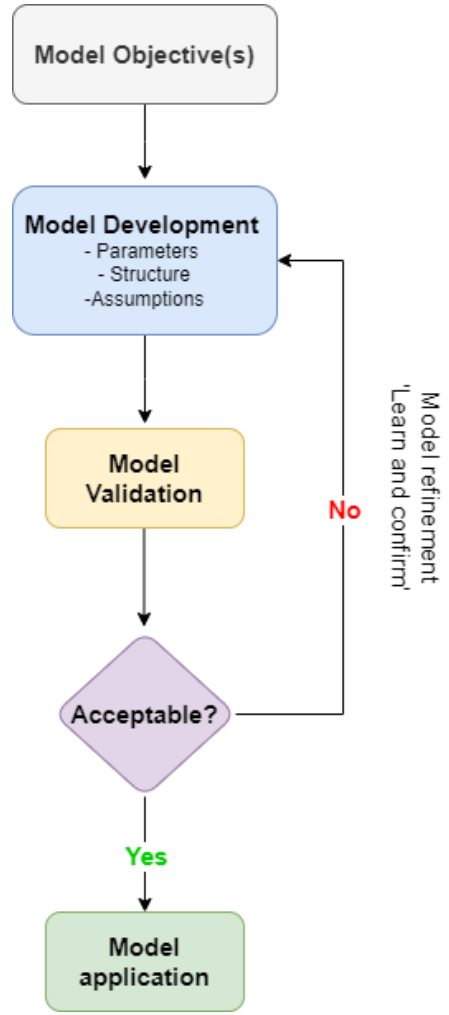
Drug exposure



Mechanistic prediction of PK behaviour

Workflow for the development and evaluation of PBBM

- Model objectives
  - The specific drug product quality issue(s) or question(s) to be addressed by PBBM should be clearly stated
- Model development
  - Focus on in vivo dissolution and absorption
  - Mechanistic absorption modelling with a simplified disposition model
- Model validation
  - Predicting the known
- Model application
  - Predicting the unknown



Drug product

- Background
  - Weak base
  - BCS Class II (i.e., low solubility, high permeability)
  - Immediate-release solid oral dosage form
  - It should be taken with food.

- Issue description
  - Two batches on ICH stability showed OOS results for QC dissolution testing
  - All other stability tests conformed to specifications at shelf life.
  - No root cause could be identified for the OOS results.

BN: X-OOS

Model objective and strategy

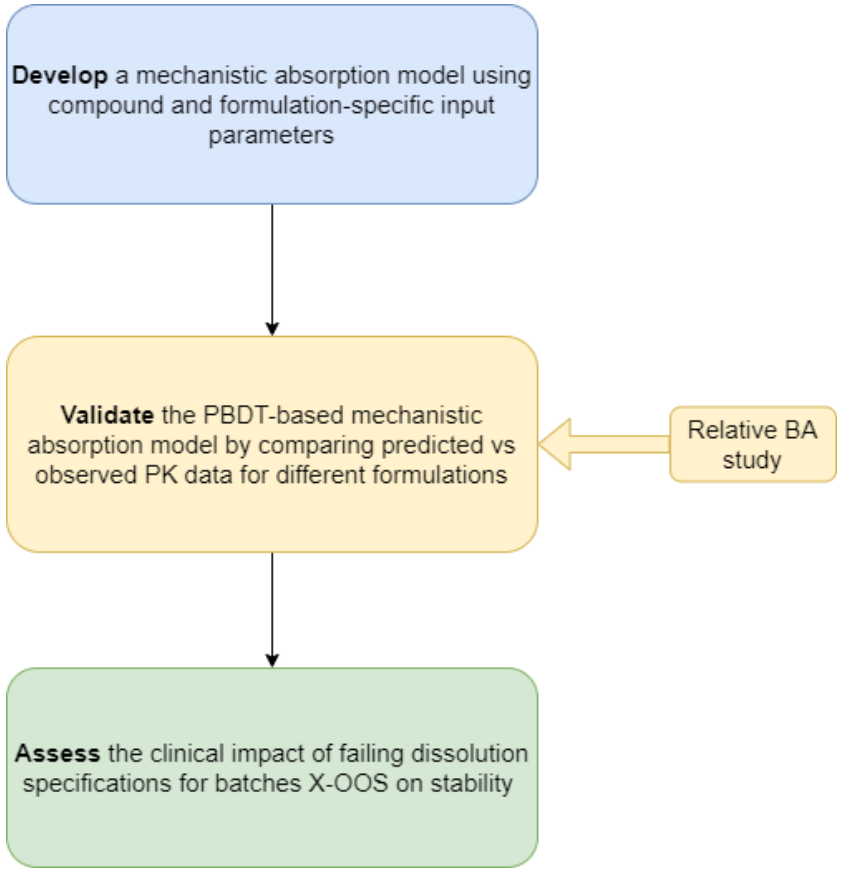
- What is the impact on drug exposure of not meeting the QC dissolution specification?

The mechanistic absorption model was developed using GastroPlus

The data from the virtual crossover trials were exported to Excel after which the between-subject variability was added in Matlab

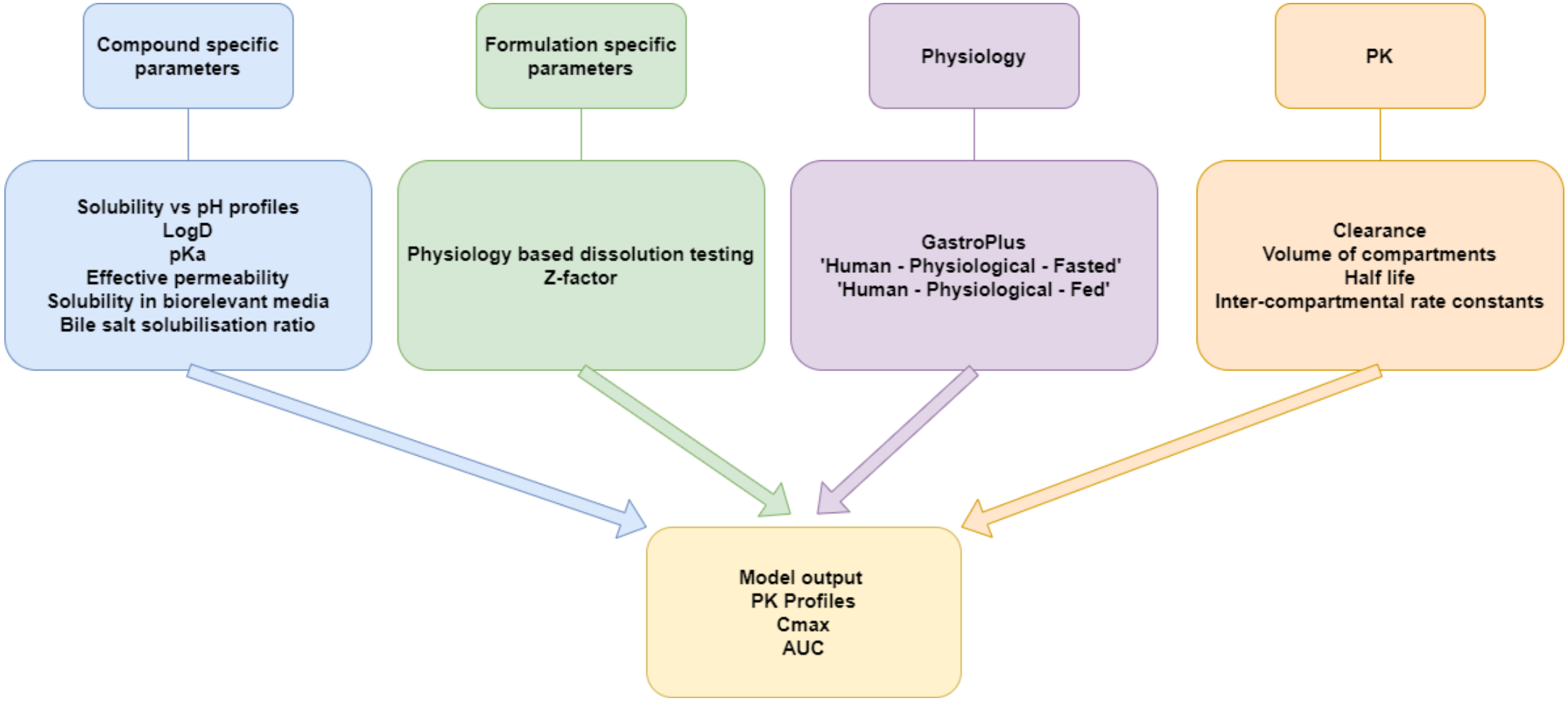
The bioequivalence parameters of the virtual population simulations were calculated in Pharsight Phoenix Built

Software used



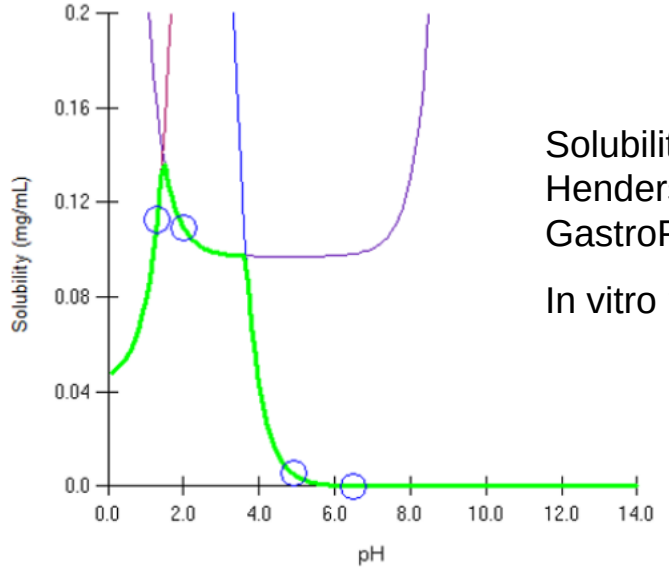
Overview of modelling strategy

Development of the mechanistic absorption model



Compound specific parameters

- Solubility was measured in aqueous and biorelevant media
- The in vitro permeability was not predictive of the in vivo situation due to cellular binding
- The effective permeability predicted by ADMET Predictor was used in the mechanistic absorption model
- Predicted parameters could be accepted but they should be accompanied by a parameter sensitivity analysis.

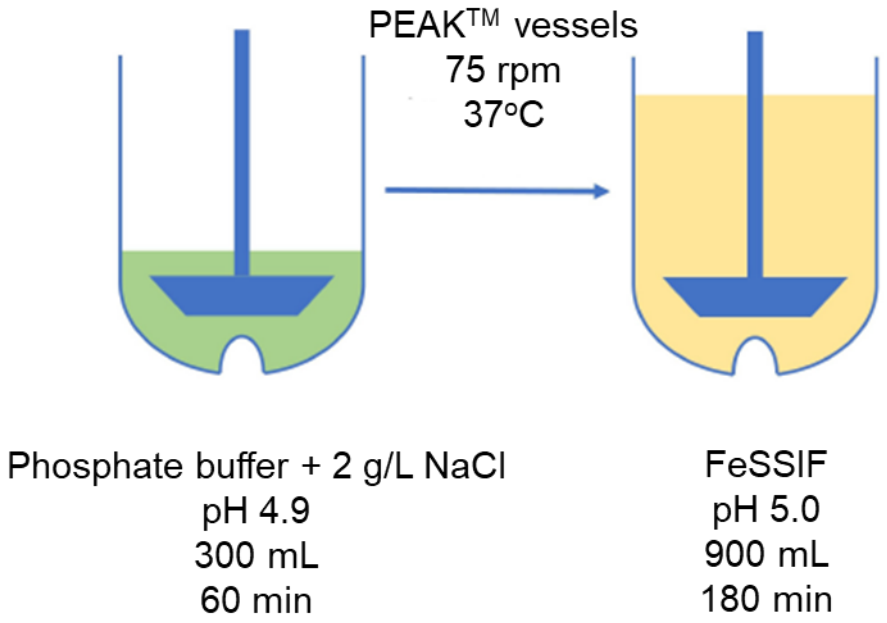


Solubility-pH profile of drug fitted with Henderson-Hasselbalch equation by GastroPlus (green)

In vitro measurements are shown as circles

Dissolution model

- Physiology based dissolution testing (PBDT)
- Two-phase dissolution approach using biorelevant media mimicking the fed state
- Simulation of physiological GI conditions in the fed state
- No clear link between PBDT and the QC method



Physiology based dissolution testing (PBDT) setup

Dissolution data input: z-factor

- A mechanistic way for integration of dissolution includes fitting a z-factor to the dissolution data as proposed by Takano et al. (2006)
- The z-factor (volume $mass^{-1}$ $time^{-1}$) is a composite parameter function of the drug diffusion coefficient, true crystal density, thickness of the unstirred water layer, and the inner particle radius
- More information on how the z-factor was fitted to the data should be provided (e.g., both the rise and plateau of dissolution curves were captured?)
- Limitations of z-factor (e.g., difficulty to be used with micelle-containing media) should be discussed
- Parameter sensitivity analysis on the effect of z-factor on exposure has not been provided
- Justification should be provided on the method selected for dissolution data input
- Clarification should be provided on how a z-factor representative of the fasting state was obtained

Takano et al. (2006); Gray et al. (2020)

Use of the z-factor for dissolution input

- The z-factor can be used as an input option in commercial modelling software

Reference	Use of z-factor
Ding et al. (2015)	Biopharmaceutical model, composed of z-factor dissolution and passive permeation under typical fasted human physiology was applied with the PK model for cancer patients to predict the in vivo performance of immediate-release tablets of galunisertib
Zhu et al. (2016)	Z-factor-based PBPK model for pH-dependent drug-drug interactions
Li et al. (2019)	Justification of biowaiver and dissolution rate specifications for piroxicam immediate-release products based on PBPK
Heimbach et al. (2021)	Establishment of dissolution safe space, within which drug product variants are expected to be bioequivalent to each other

Pharmacokinetics model

- No IV PK data
- A three-compartmental model was derived from low dose oral PK data obtained after dosing a solution in healthy subjects under fed conditions
- Exposure levels expressed as AUC were dose linear up to 700 mg:
  - intestinal absorption is complete
  - possible first-pass effect and metabolism did not become saturated

Model validation

- Model validation was performed using a relative bioavailability study
- Healthy subjects received a single dose of 100 mg under fasted and fed conditions
- A significant positive food effect was observed.

Tablet batches dosed in the relative BA study

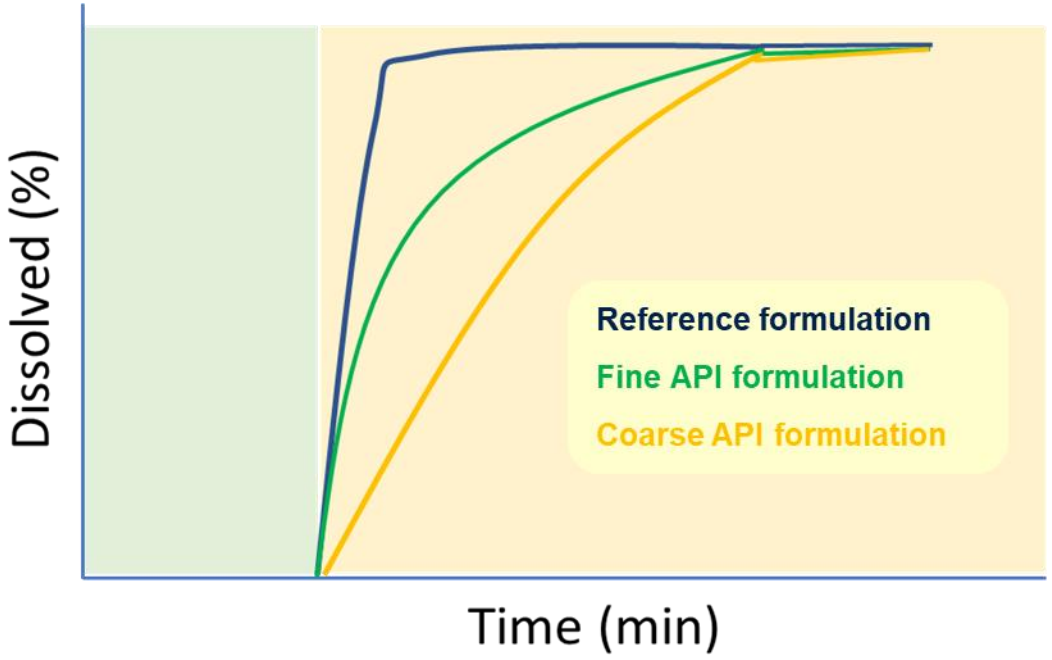
Description	Disintegrant
Reference	Disintegrant 1
Fine API	Disintegrant 2
Coarse API	

Comparing the treatment arms in the relative BA study

Panel A (Fed)	Fine API *vs* Ref	Coarse API *vs* Ref
C_{max}	↓ ~ 10%	↓ ~ 25%
$AUC_{0\text{-}72h}$	↓ ~ 5%	↓ ~ 22%
Panel B (Fasted)	**Fine API *vs* Ref**	**Coarse API *vs* Ref**
C_{max}	↓ ~ 10%	↓ ~ 35%
$AUC_{0\text{-}72h}$	↓ ~ 10%	↓ ~ 35%

90% CI within BE criteria; 90% CI outside BE criteria

Model validation: PBDT data and z-factors



PBDT results for the tablets dosed the relative BA study

Calculation of z-factor for each formulation

Mean simulations for C_{max} and $AUC_{0\text{-}72h}$ under fed and fasted state

Population simulations by incorporating variability

Model validation: population simulations

- Additional information should be provided on how variability was incorporated in the model
- It should be discussed how the variability incorporated in the model affects the upper and lower levels of the geometric mean ratio in the virtual cross-over trials

Examples of parameters included in the population simulations that were varied to mimic the in vivo observed variability

Parameter	CV%	Distribution	Comment
Peff	65	Log-normal	Default value
z-factor	Formulation dependent	Normal	Calculated from PBDT
Subject weight	20/12	Log-normal	According to relative BA study
Length small intestine	10	Log-normal	Default value
Length of caecum	10	Log-normal	Default value
pH stomach	10	Log-normal	Default value
…	…	…	…

Between-subject variability calculated based on the relative BA study

Condition	Parameter	Between-subject CV%
Fed	C_{max}	21%
	AUC	8%
Fasted	C_{max}	27%
	AUC	24%

Bioequivalence calculation at fed state

Overview of 10 virtual crossover trials with 12 subjects under fed conditions simulating relative BA study versus the observed in vivo values

	Treatment B vs A						Treatment C vs A					
	C_{max}			AUC_{0-72h}			C_{max}			AUC_{0-72h}		
	GMR	LL	UL	GMR	LL	UL	GMR	LL	UL	GMR	LL	UL
Trial 1	87.0	78.4	96.4	91.5	85.6	97.7	71.3	62.4	81.5	76.2	70.3	82.6
Trial 2	87.5	76.1	100.7	84.7	80.4	89.2	69.5	58.3	82.7	70.9	61.8	81.2
Trial 3	84.3	73.4	96.8	85.2	79.3	91.4	67.7	56.0	81.9	70.4	61.3	80.8
Trial 4	86.0	77.3	95.7	89.3	82.6	96.6	70.5	62.1	80.1	75.5	68.6	83.0
Trial 5	86.8	75.7	99.5	88.8	85.2	92.5	72.3	64.8	80.6	72.9	67.8	78.2
Trial 6	87.1	79.4	95.5	92.4	88.9	96.0	78.6	71.3	86.6	75.8	70.6	81.4
Trial 7	87.5	75.7	101.2	92.5	89.2	95.9	69.9	59.0	82.8	76.0	70.9	81.5
Trial 8	87.8	76.5	100.9	88.6	84.1	93.3	72.6	61.7	85.4	77.2	69.9	85.3
Trial 9	87.2	77.4	98.2	91.8	87.4	96.4	71.8	62.6	82.4	74.4	69.6	79.6
Trial 10	87.2	79.5	95.6	85.1	80.4	90.1	72.8	62.9	84.1	72.8	66.3	80.0
in vivo	89.6	76.8	94.8	94.8	85.2	105.5	74.8	64.1	87.4	77.3	69.5	86.1
GMR *in silico** / **GMR *in vivo***		0.97			0.94			0.96			0.96	

* The average GMR of the 10 virtual trials was used for the calculation.

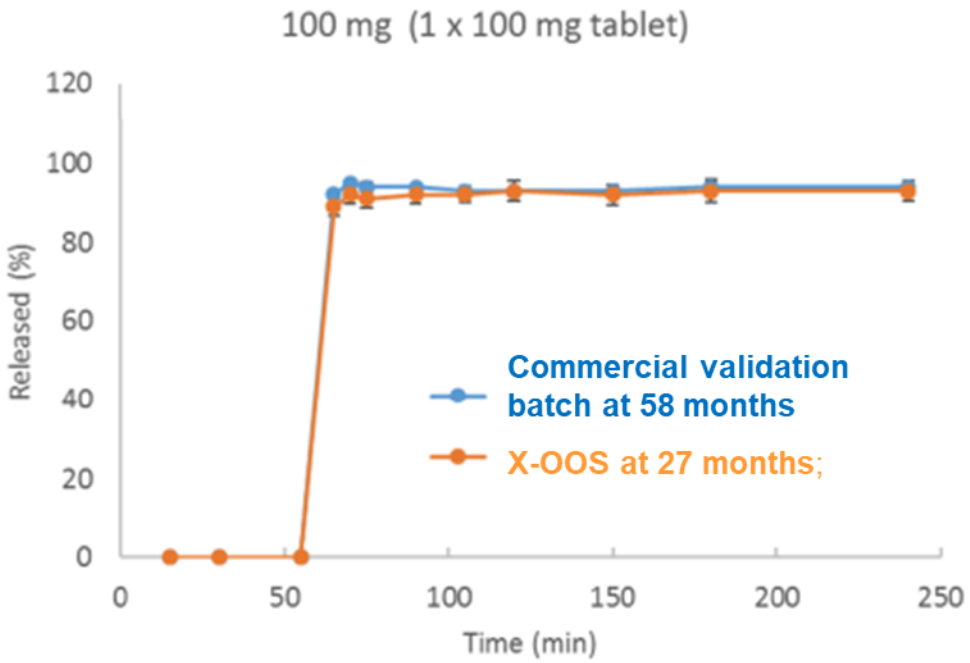
Model application

- Biopharmaceutical impact assessment of not meeting the dissolution specification for batch X-OOS
- A comparison was made with a reference batch on stability which was the commercial validation batch packed in bottles

Commercial validation batch

BN: X-OOS

Model application: PBDT and z-factor



PBDT results at a dose of 100 mg (mean ± SD, n=3)

Calculation of z-factor for each formulation

Mean simulations for C_{max} and $AUC_{0\text{-}72h}$ under fed state

Population simulations by incorporating variability

Model application: population simulations

Overview of 10 virtual crossover trials comparing commercial validation batch vs the X-OOS batch in 30 subjects in fest state at a dose of 100 mg

Virtual trial	Cmax			AUC0-72h		
	GMR	LL	UL	GMR	LL	UL
1	101.5	94.5	109.0	95.4	93.6	97.3
2	95.1	89.0	101.6	98.4	95.4	101.4
3	101.4	94.8	108.4	100.4	97.5	103.3
4	110.1	103.3	117.5	98.6	96.2	101.1
5	108.2	102.0	114.7	96.7	94.5	98.9
6	102.0	97.1	107.1	100.0	97.7	102.5
7	95.5	89.1	102.4	99.9	97.3	102.5
8	102.5	98.5	106.6	97.6	95.4	99.8
9	96.5	89.5	104.0	100.3	97.6	103.0
10	101.8	95.8	108.2	99.7	97.4	102.0

Commercial validation batch

X-OOS

Conclusions

- A mechanistic absorption model was developed using the z-factor calculated by PBDT profiles, as the drug product specific input data
- The model was able to differentiate between tablets that were shown to be BE and non-BE in healthy subjects in the relative BA study
- Virtual BE trials were performed comparing the OOS batch with a reference batch, which were predicted to be BE for both C_{max} and $AUC_{0\text{-}72h}$ under fed conditions
- No impact on drug exposure is expected for X-OOS batch, for which OOS dissolution results were obtained using the QC method during stability testing
- However, no link between the QC method and PBDT was established, and no safe space was demarcated

Take-home messages

- Model objective(s) should be clearly stated
- Predicted parameters can be used when justified, but they should be followed by a parameter sensitivity analysis
- 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
- 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

References

Takano R, et al. Oral absorption of poorly water-soluble drugs: computer simulation of fraction absorbed in humans from a miniscale dissolution test. Pharm Res. 2006;23:1144–56.

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Heimbach T, et al. Establishing the bioequivalence safe space for immediate-release oral dosage forms using physiologically based biopharmaceutics modeling (PBBM): Case studies. J Pharm Sci. 2021;110:3896–906.


Thank You!

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