Advantages of PBBM and PKPD modeling to define dissolution safe space

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Please note: this presentation, including questions from the audience, is being recorded and may be made available.

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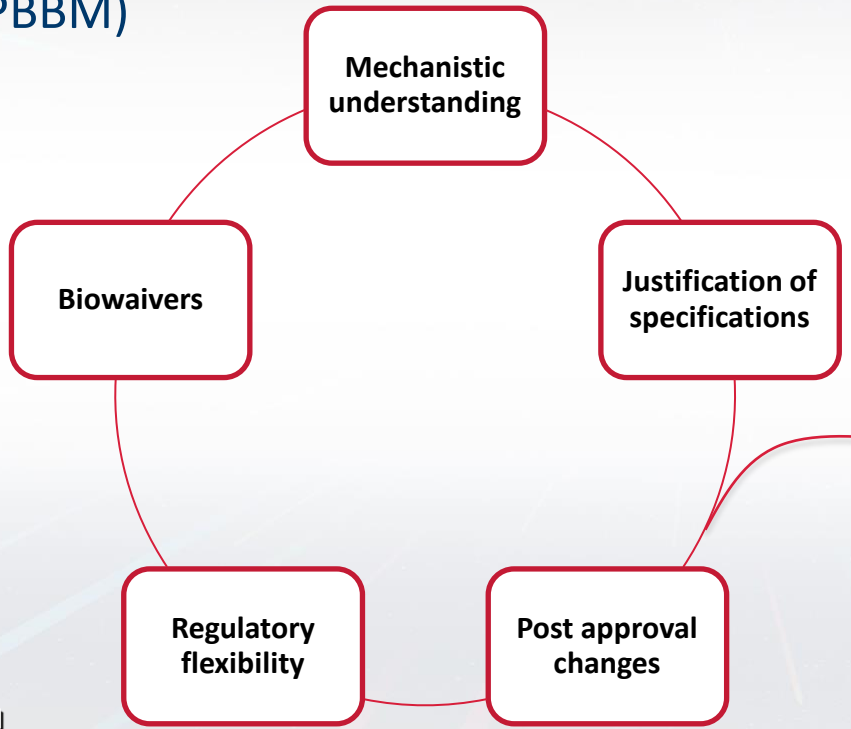
PBBM in the pharma industry

- Various benefits of Physiologically-based biopharmaceutics models (PBBM)



- Increase product value:
  Efficacy, safety, right drug load and release rate
- Reduce production waste
- Seamless manufacture
- Avoid unnecessary human testing

Why PBBM and PKPD ?

- PBBM links drug product quality attributes to in vivo exposure
  - In vitro dissolution
  - Polymorphic impurities
  - Manufacturing process and material attributes (through dissolution)
  - In vivo degradation
  - Effect of excipients on solubility, dissolution, precipitation or on the GI function

PBBM allows a safe space definition where all drug product batches are anticipated to be bioequivalent to one another

Typically, virtual bioequivalence studies are conducted with standard, or reference scaled BE criteria, to conclude on bioequivalence

Why PBBM and PKPD ?, cont.

- PKPD links drug product exposure to efficacy and toxicity
  - They are based on observed efficacy data vs exposure (clinical endpoint or biomarkers of efficacy)
  - They can be mathematical relationships based on observations or mechanistic models based on the understood mechanism of action and cell signaling pathways

PKPD models allow to define an effective (and safe) space where all the batches are anticipated to have the same pharmacological efficacy without additional toxicity

Larger than BE effective spaces may be accessible through PKPD modeling

Combination of PBBM and PKPD links product quality attributes to efficacy/safety

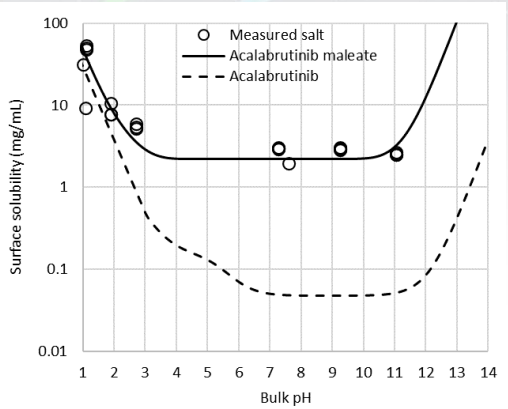
2 case studies

- Case 1 : Acalabrutinib maleate tablet (AMT)
  - PKPD and PBBM were used to determine drug product dissolution space in the target patient population

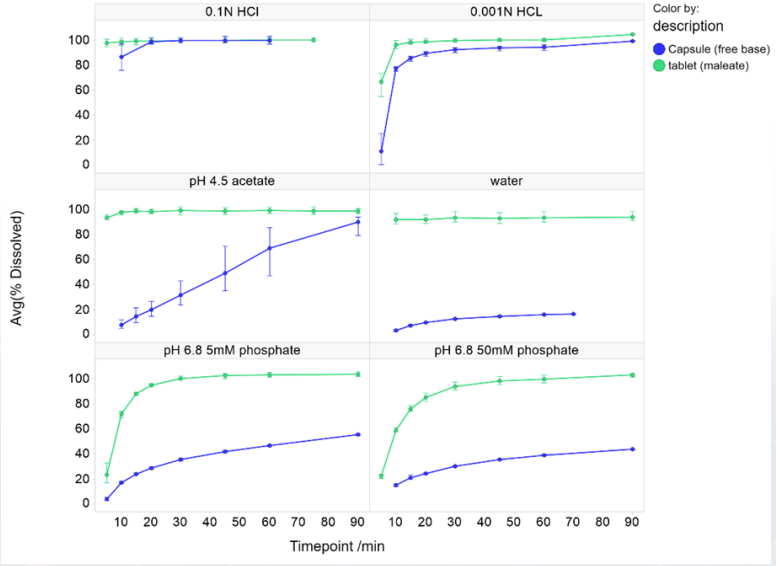
- Case 2 : Drug X-salt tablet
  - PKPD model was developed for this poorly absorbable drug in combination to PBBM to evaluate the risk for delayed tablet disintegration

Case 1 : Acalabrutinib maleate tablet (AMT)

- Project information
  - Acalabrutinib free base is associated with label restriction for patients undergoing acid reducing agent (ARA) treatment
  - 20-40% hematological cancer patients are estimated to take ARAs
  - Acalabrutinib maleate increases surface solubility compared to the free base leading to faster and complete dissolution in all media

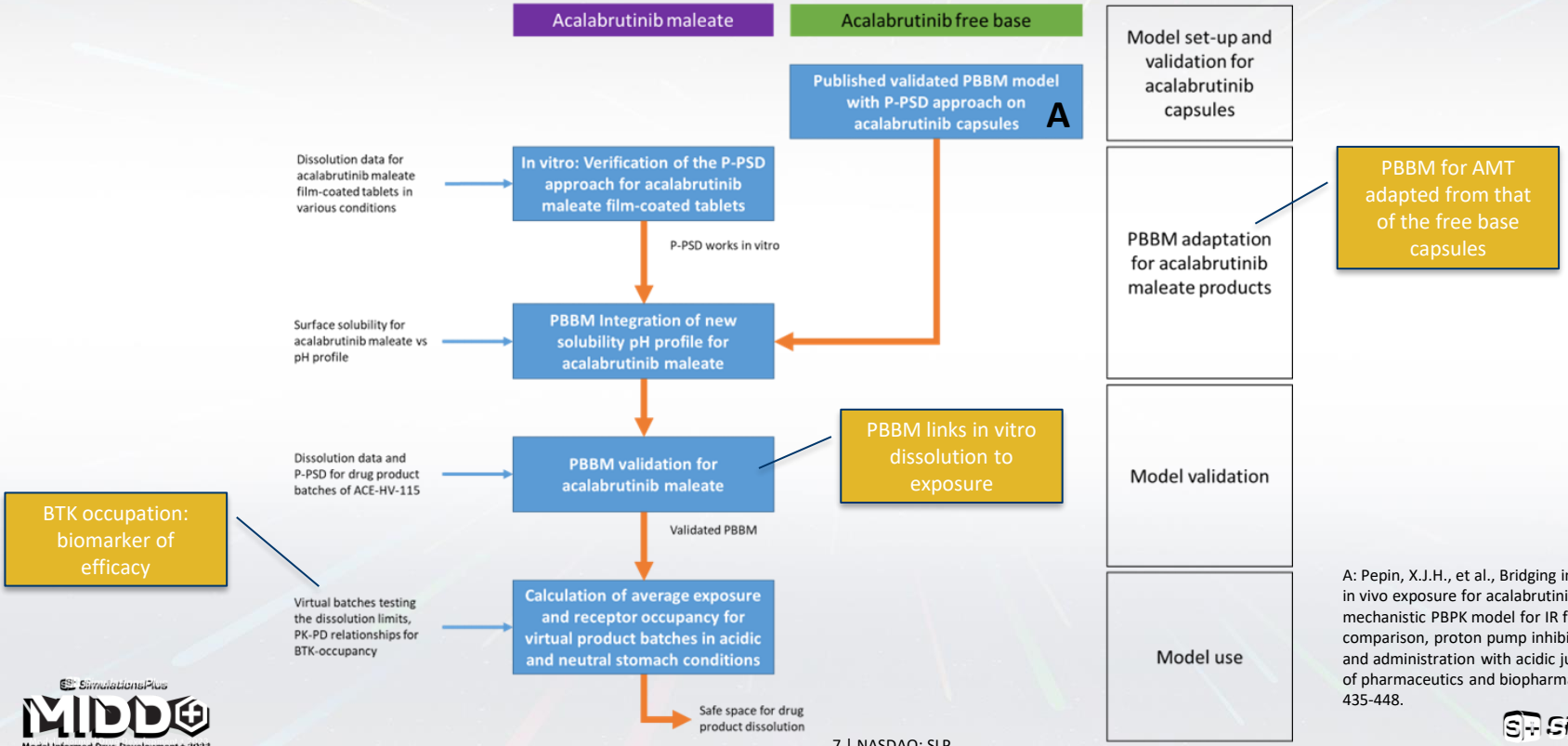


- Model purpose
  - Justify proposed dissolution specification for AMT



AMT : Modeling strategy

– Objective : Justify the dissolution acceptance criterion for AMT

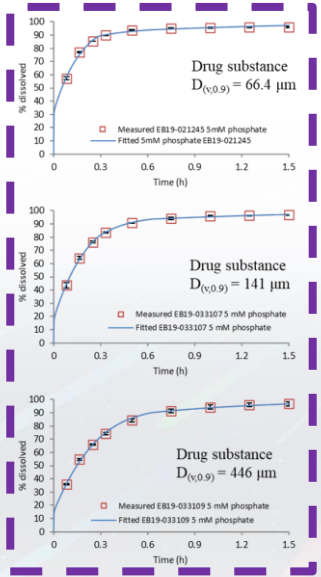


A: Pepin, X.J.H., et al., Bridging in vitro dissolution and in vivo exposure for acalabrutinib. Part II. A mechanistic PBPK model for IR formulation comparison, proton pump inhibitor drug interactions, and administration with acidic juices. European journal of pharmaceutics and biopharmaceutics, 2019. 142: p. 435-448.

AMT : PBBM adaptations from free base

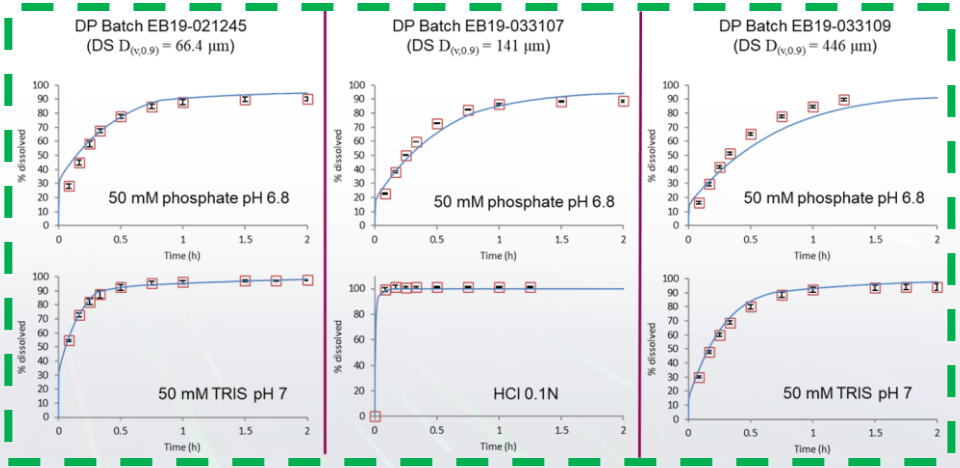
- Use surface solubility vs pH and crystal density for acalabrutinib maleate
- Use P-PSD approach on AMT batches after verification that they are predictive of other conditions (see below)
- Super-saturation identical between AMT and free base capsules: No precipitation
- All post dissolution processes are identical (same model as that of free base)

1-QC dissolution method
P-PSD extraction



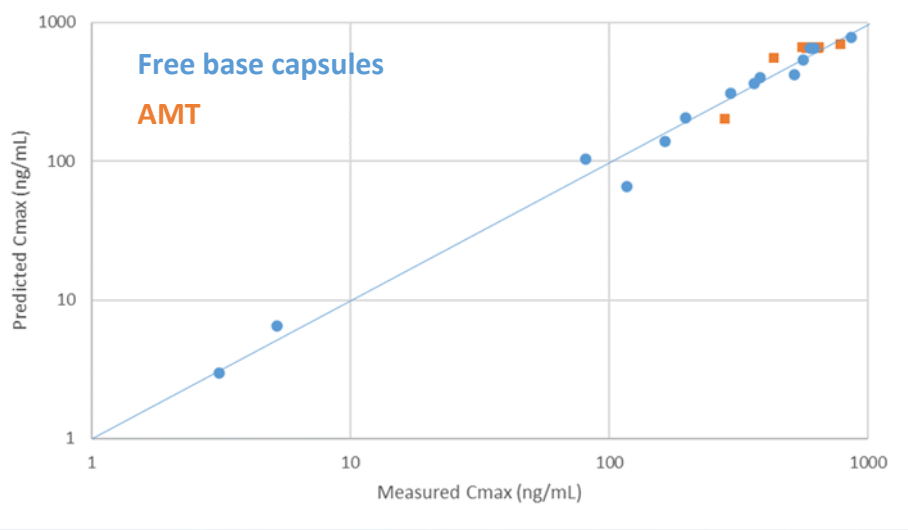
2-P-PSD verification: dissolution prediction in other media

AFE=1.02, AAFE= 1.06

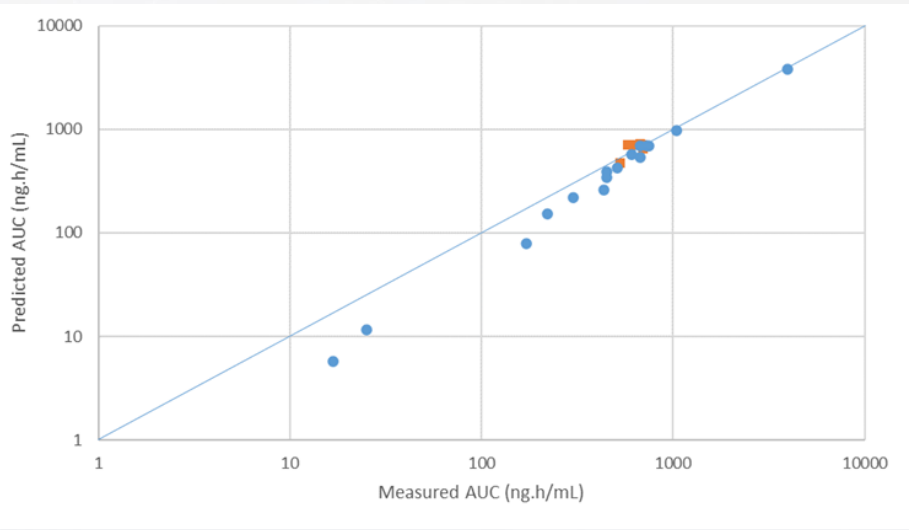


AMT : PBBM validation

AFE = 1.01
AAPE = 6.7%



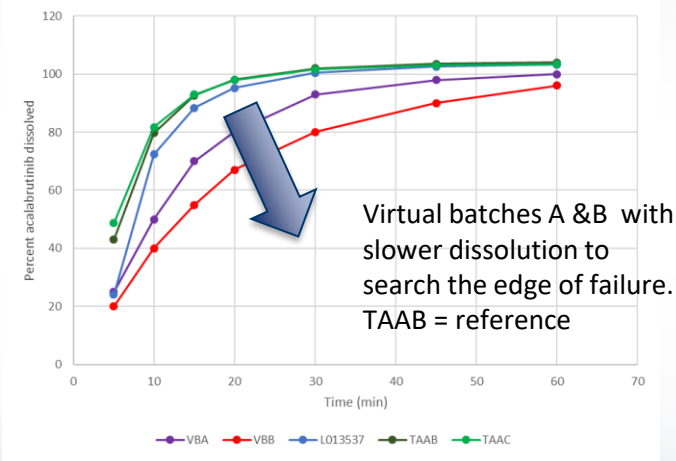
AFE = 1.05
AAPE = 8.5%



Acceptable model prediction performance across studies with no adjustment of the disposition parameters

AMT : PBBM use

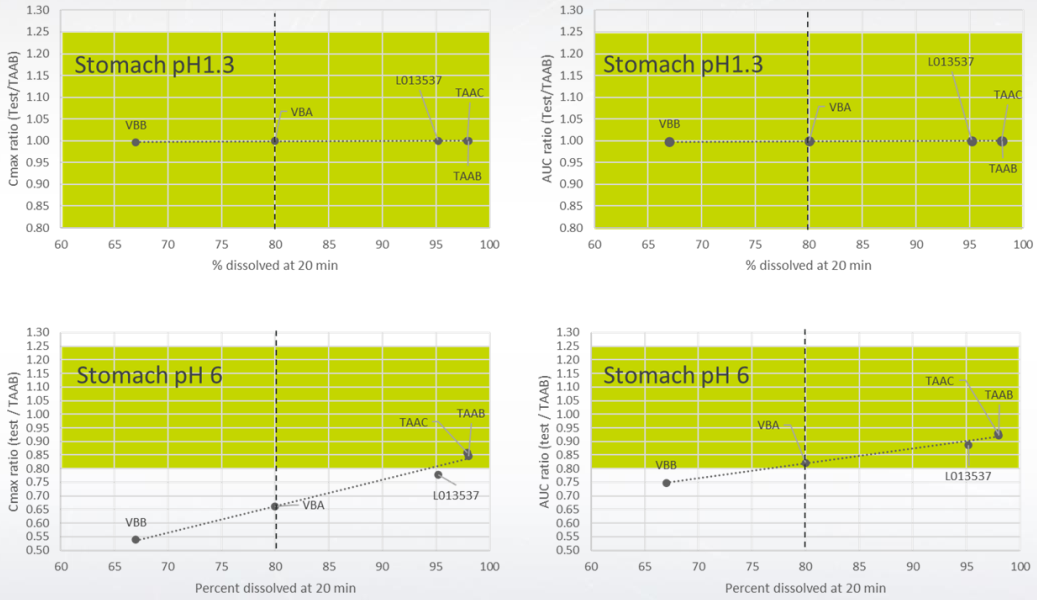
In vitro dissolution with QC method



Virtual batches A &B with slower dissolution to search the edge of failure.
TAAB = reference

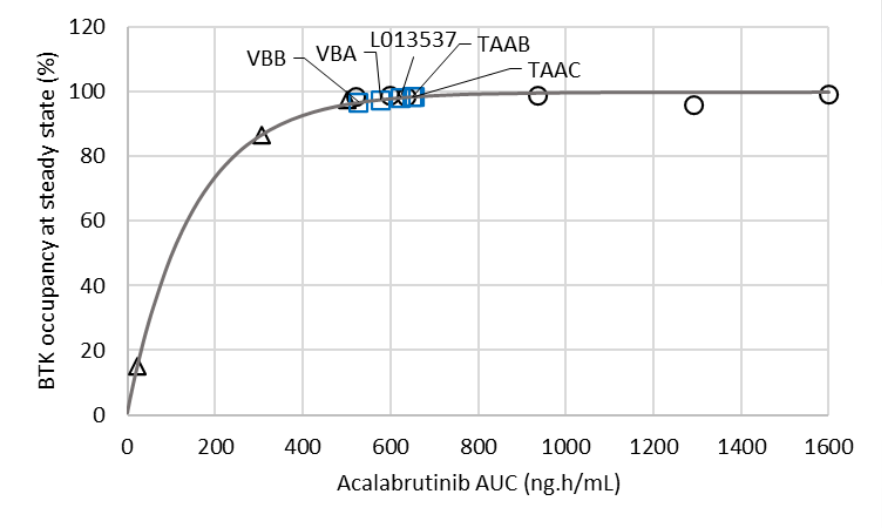
VBA: Virtual batch A
VBB: Virtual batch B

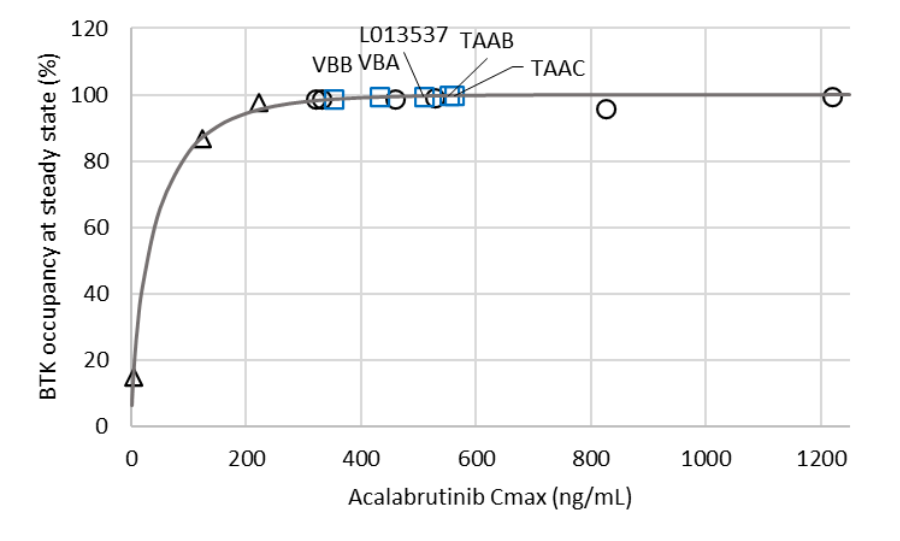
VBA and VBB bioequivalent to reference in acidic stomach conditions



VBA and VBB with PPI not BE to reference (in acidic conditions)

AMT : PBBM + PKPD model

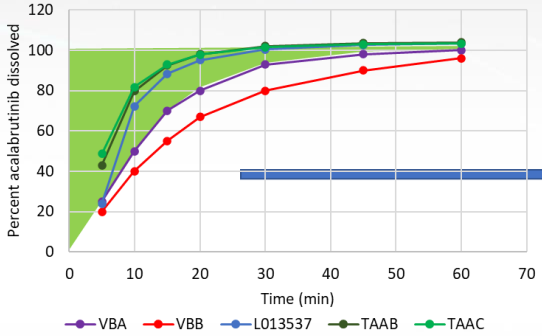


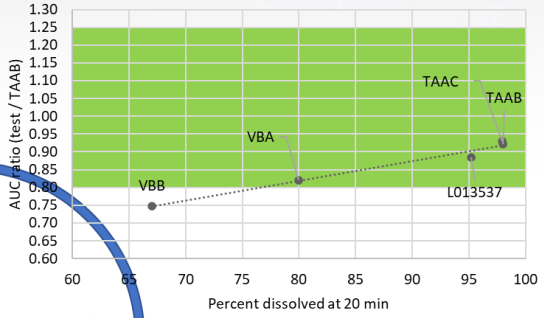


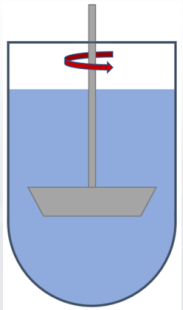
BTK-occupancy vs AUC or vs Cmax, show that exposure to VBA or VBB in neutral stomach conditions are anticipated to be safe and effective : Similar target engagement compared to pivotal efficacy study

Acalabrutinib maleate tablet: conclusions

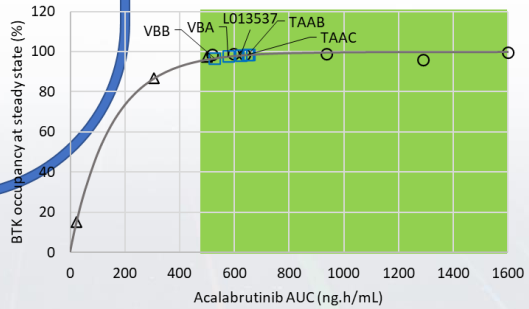
– VBA was used to delineate dissolution safe space identified using PBBM and PKPD







DP dissolution Specification

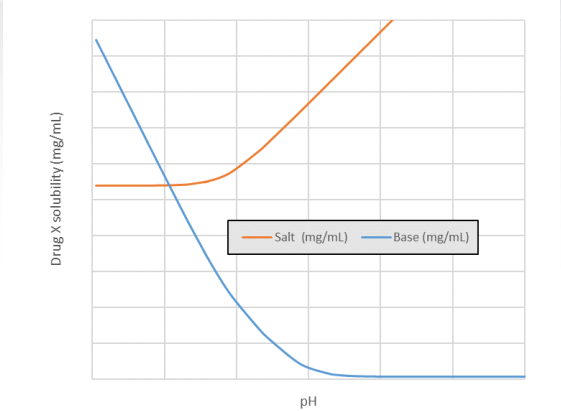


Q=80% 20-30 minutes is anticipated to be safe and effective for 100 mg AMT

Oral solution was administered in the clinic and proved BE to the tablet (upper bound of safe space)

Case 2 : Drug X-salt

- Project information
  - Drug X is minimally absorbed from the GI tract and plasma concentrations are below LOQ.
  - Drug X salt solubility is high compared to free base
  - Systemic PK observable for main drug X inactive metabolite “M”
  - Drug X is locally acting in the gut
  - Existence of a biomarker “B”, which concentration is measurable in the feces as a direct result of the pharmacological action of Drug X
  - Existence of clinical data for M systemic concentration and existence of clinical PD data. All data were associated to batch dissolution
  - Drug substance shows evidence of precipitation
- Model purpose
  - Drug product dissolution shows variability of tablet disintegration upon storage @ high temperature : How does a worst-case delayed dissolution impact drug X efficacy ?



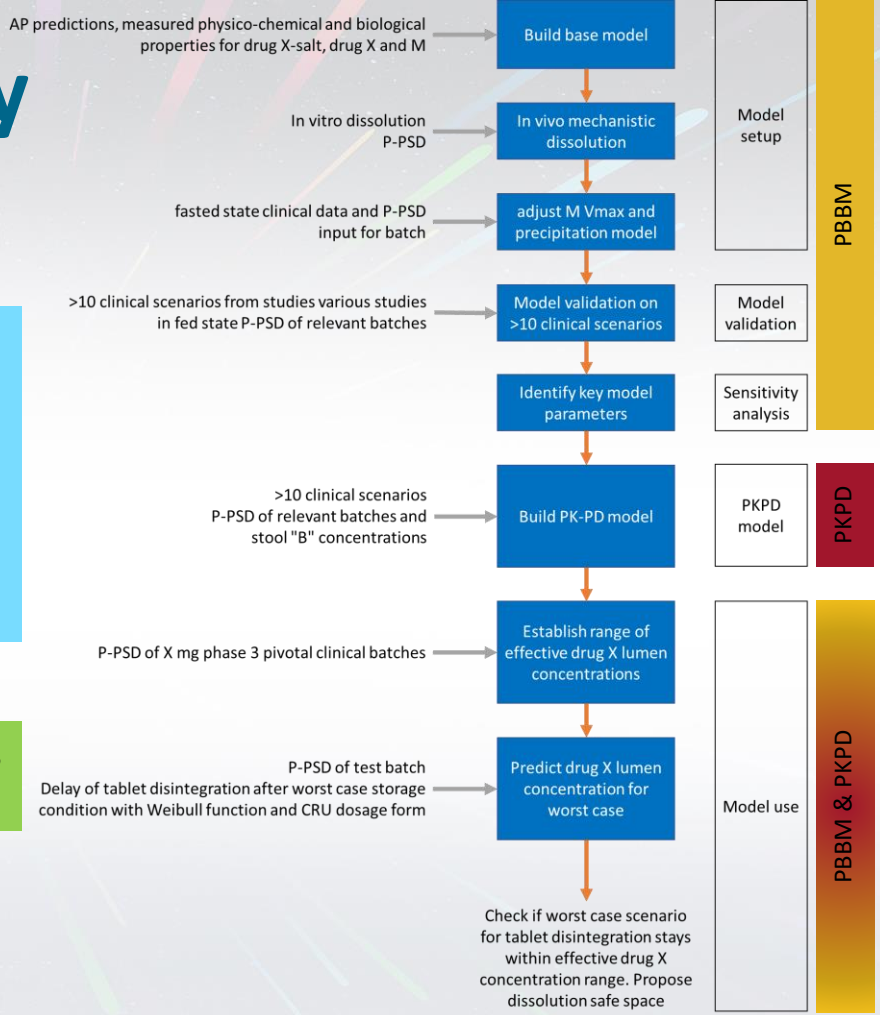
Drug X: Modeling strategy

Biopharmaceutics risk analysis

3 types of formulations
- Salt in additional formulation (SAF)
- Tablet with salt
- Tablet with free base

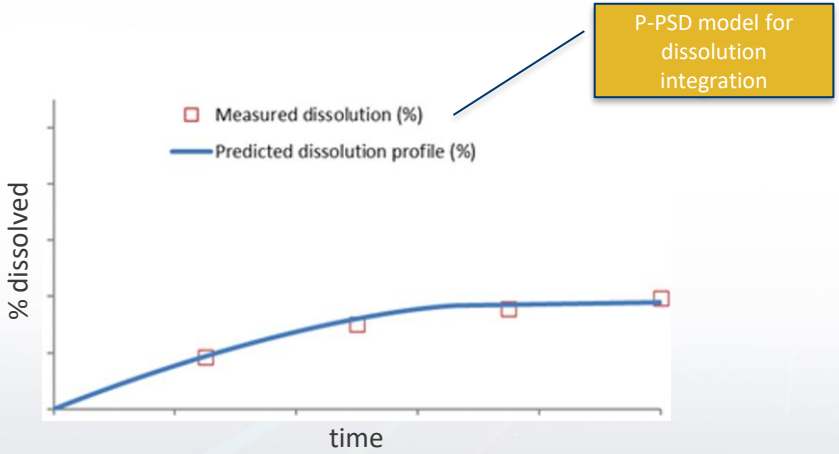
Clinical data for M systemic PK (mostly sparse)
Clinical data for drug X efficacy (stool biomarker)

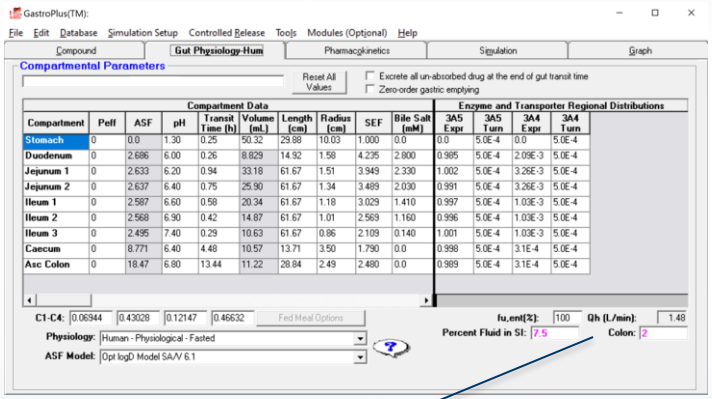
In parallel to the PBBM effort, route cause analysis for tablet delay in dissolution.



Input data and model parameters

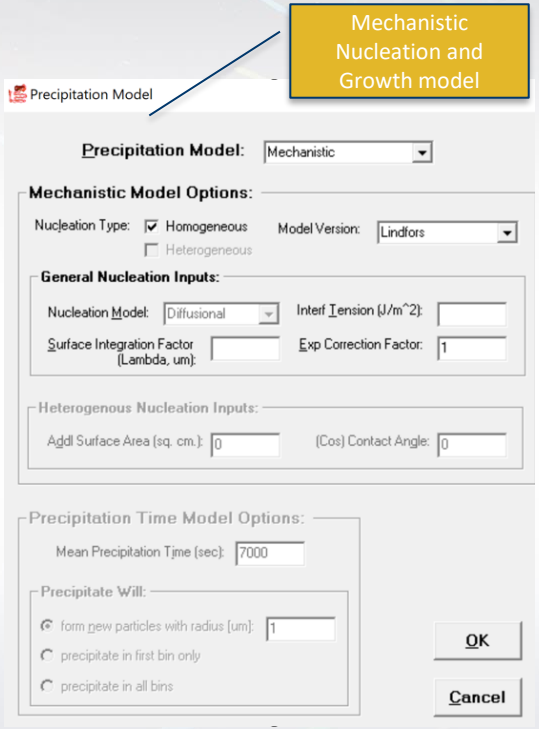
Mix of in vitro measured values and ADMET Predictor® values for physico-chemical and biopharmaceutics properties of drug X and inactive metabolite M



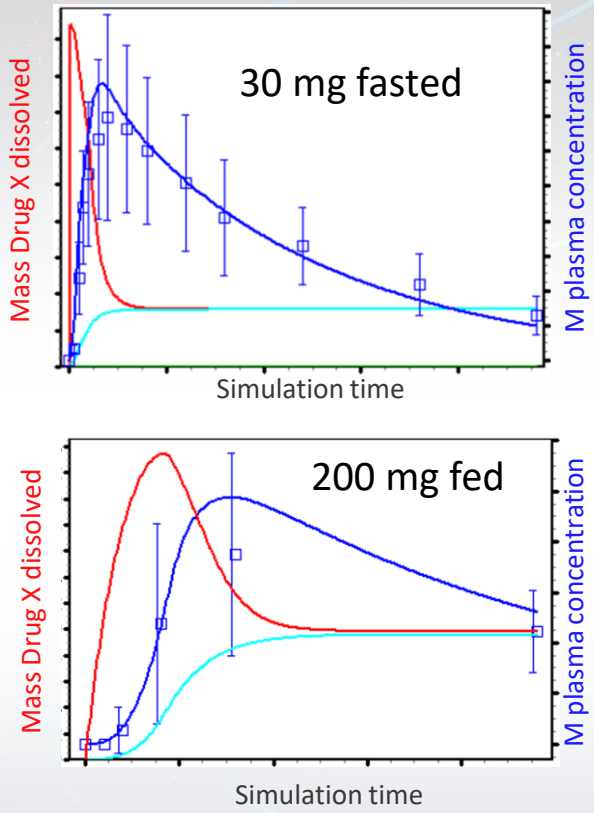


Luminal volumes representative of MRI studies (wort case for dissolution)

Drug X Precipitation



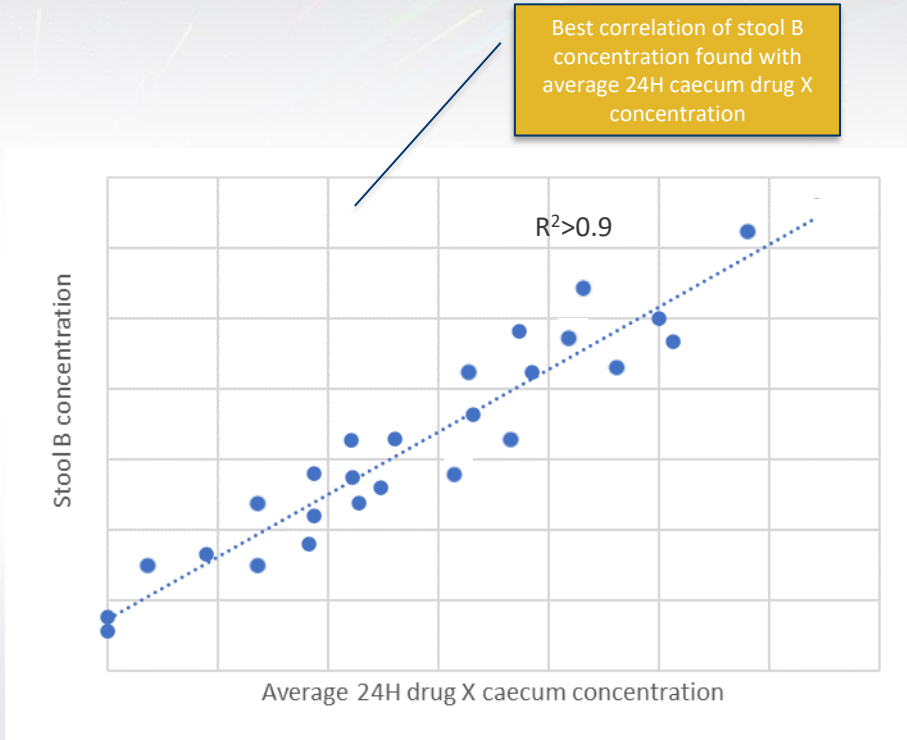
1 set of parameters for MNG model can account for effect of prandial state, dose and formulation on precipitation



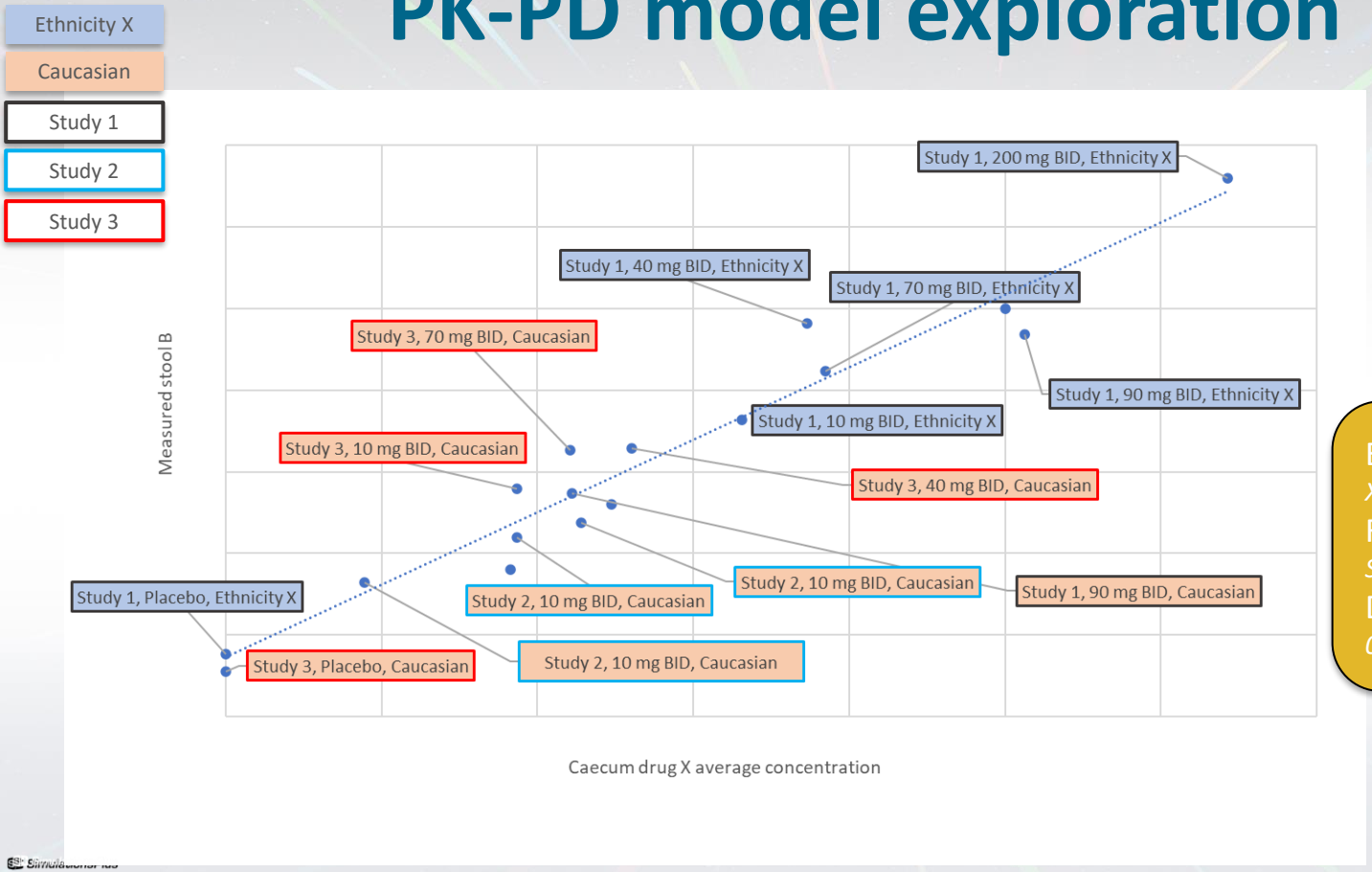
PK-PD model

- Calculation of luminal drug X concentrations in all the GI tract for given clinical scenarios
  - Administration schedule
  - Dose
  - Formulation
  - Population characteristics

- Correlation with biomarker B concentrations in the stool
  - B stool concentration demonstrates drug efficacy



PK-PD model exploration



Ethic differences

X or Caucasian

Formulation differences

SAF, Salt tablet, free base tablet

Dose differences

0-200 mg

PK-PD model exploration : Dose & formulation

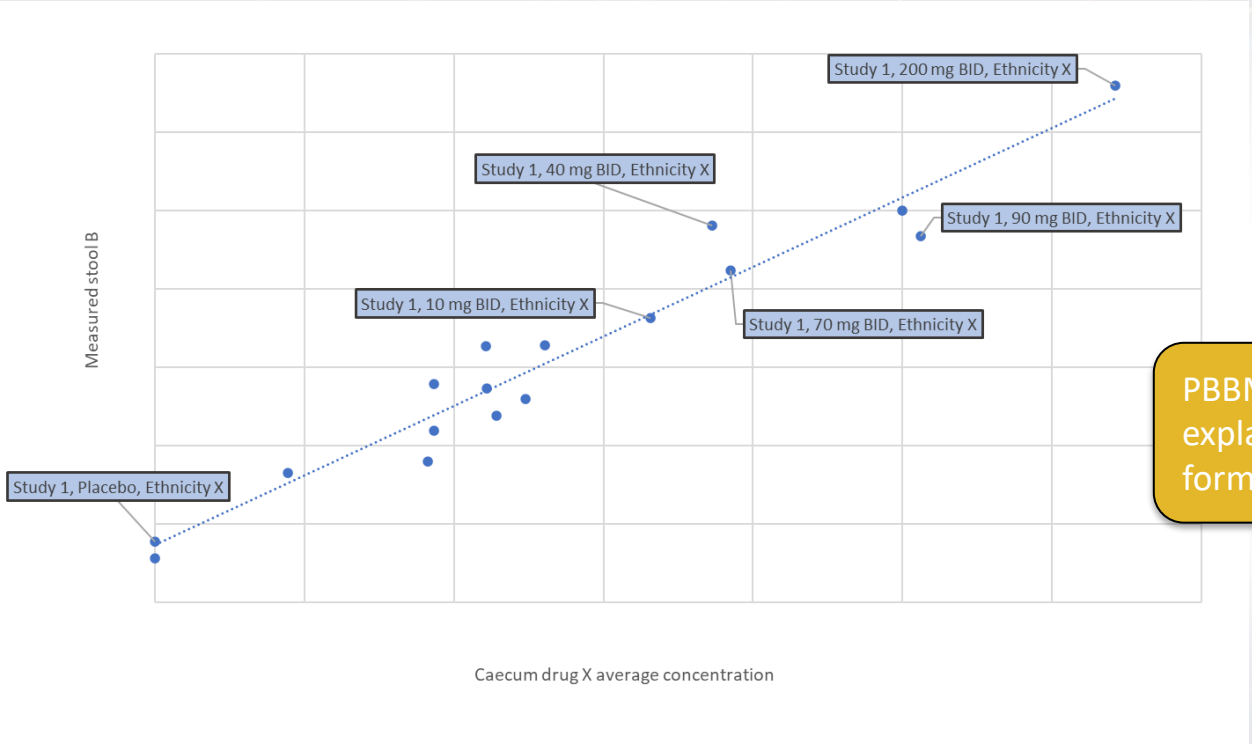
Ethnicity X

Caucasian

Study 1

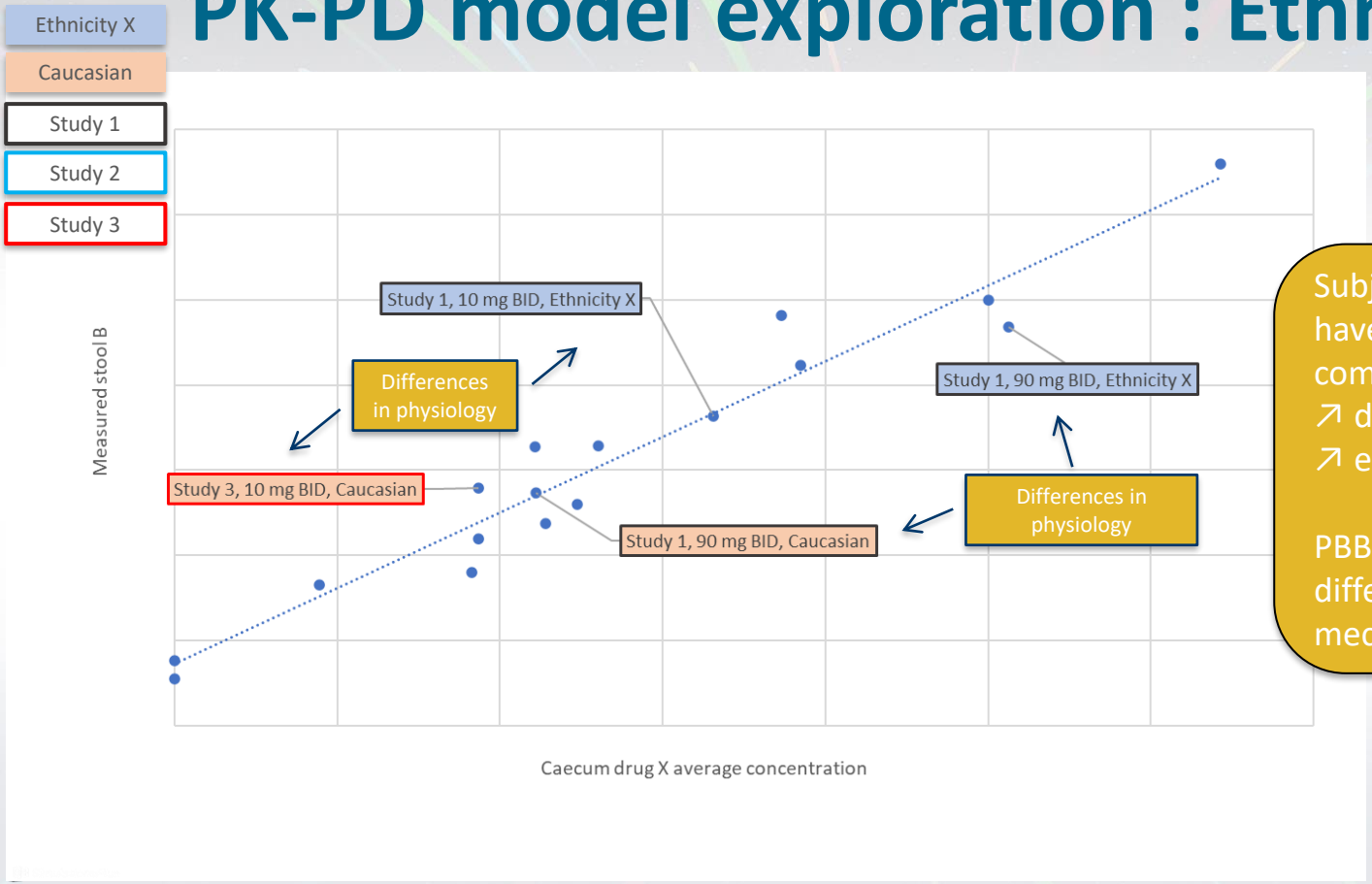
Study 2

Study 3



PBBM+PKPD model explain dose and formulation differences

PK-PD model exploration : Ethnicity



Subjects from ethnicity X have smaller caecum compared to Caucasian
↗ drug X concentration
↗ efficacy

PBBM comprised these differences and provided for mechanistic understanding

PK-PD model exploration : formulation

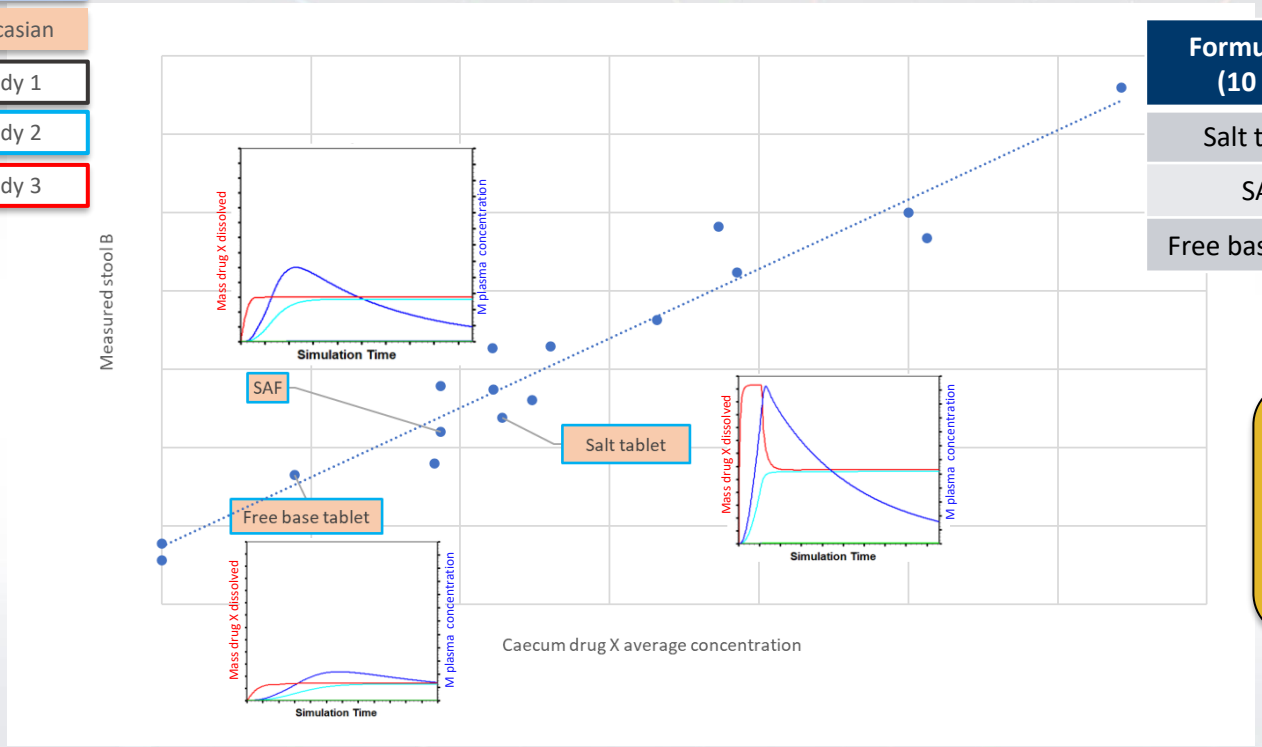
Ethnicity X

Caucasian

Study 1

Study 2

Study 3



Formulation (10 mg)	Supersaturation & precipitation	Dose dissolved
Salt tablet	Yes	X mg
SAF	No	X/2 mg
Free base tablet	No	X/4 mg

PBBM+PKPD model mechanistically explain observed formulation differences in efficacy

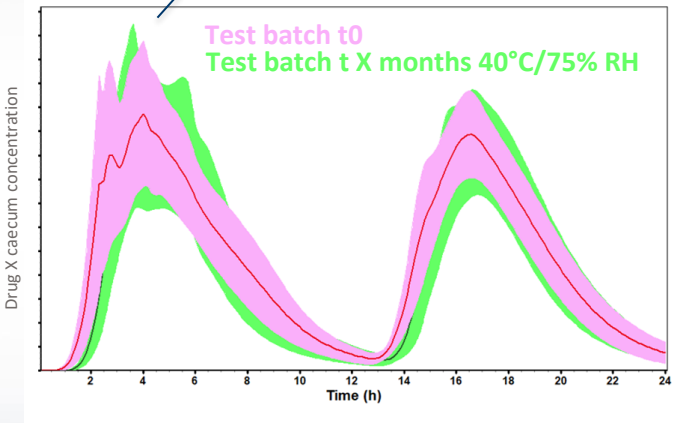
Root cause analysis for slowed dissolution

- 2 hypotheses
  - A: Salt disproportionation to the free base
  - B: Disintegrant degradation due to exposure to heat
- Analysis
  - Spectral methods ruled out salt-disproportionation
  - Existing data with salt tablet batches spiked with free base provided a different profile evolution for dissolution
  - Literature already reported disintegrant susceptibility to heat exposure
  - Photographic evidence of slower disintegration during dissolution

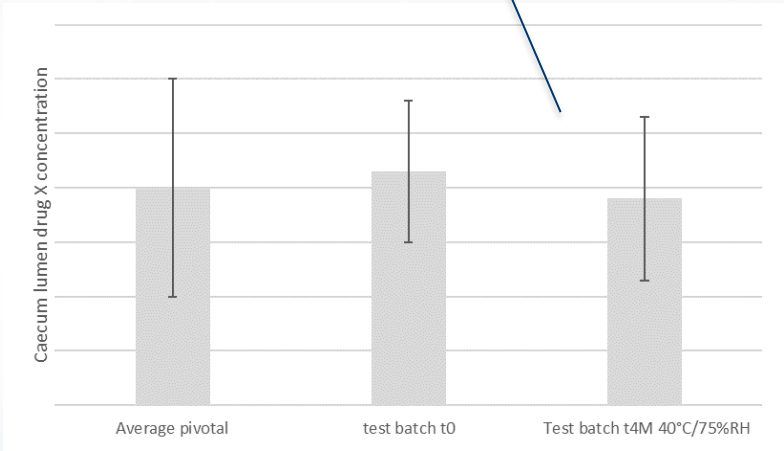
Tablet slower disintegration confirmed and tested in the PBPK-PKPD model

Model use

Population simulation of 24H caecum drug X concentration from fresh and aged test batch



24H average caecum drug X concentration from fresh and aged test batch comparable to pivotal clinical references



Delay in disintegration is anticipated not to lead to differences in drug X efficacy
Dissolution data for test batch and historical batch dissolution data used to propose a safe space and justify proposed specification

Take-home messages

- PBBM allows to mechanistically link product quality attributes to exposure and is widely used to bridge formulations and support other manufacturing and control changes
- PKPD models coupled to PBBM allow to expand the product quality safe space beyond that offered by bioequivalence testing
- PKPD models coupled to PBBM allow to use efficacy biomarkers to further validate the PBBM and provide mechanistic explanation to differences in efficacy related to population characteristics, dose or formulation differences. This is particularly useful for non- (or poorly-) absorbed drugs, for which systemic PK is not available

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Q&A

Questions & Answers