Physiologically Based Biopharmaceutics Modeling Case Study: Acalabrutinib Capsules

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DISCLAIMER

This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies.

Overview

- Case Study 3: Acalabrutinib Capsules
- Biopharmaceutics of Acalabrutinib Capsules and ADME
- Model Objective & Strategy
- Model Development, Validation, and Application
- Case Study Summary

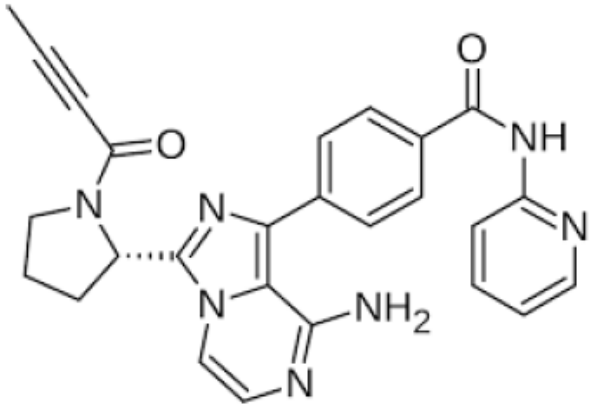
Acalabrutinib Capsules PBBM

A mock case study for Acalabrutinib Capsules based on publicly available data from the following publications:

1. Pepin XJH, Sanderson NJ, Blanazs A, Grover S, Ingallinera TG, Mann JC. Bridging in vitro dissolution and in vivo exposure for acalabrutinib. Part I. Mechanistic modelling of drug product dissolution to derive a P-PSD for PBPK model input. Eur J Pharm Biopharm. 2019 Sep;142:421-434. doi: 10.1016/j.ejpb.2019.07.014. Epub 2019 Jul 12. PMID: 31306753.
2. Pepin XJH, Moir AJ, Mann JC, Sanderson NJ, Barker R, Meehan E, Plumb AP, Bailey GR, Murphy DS, Krejsa CM, Andrew MA, Ingallinera TG, Slatter JG. 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. Eur J Pharm Biopharm. 2019 Sep;142:435-448. doi: 10.1016/j.ejpb.2019.07.011. Epub 2019 Jul 12. PMID: 31306750.
3. Zhou D, Chen B, Sharma S, Tang W, Pepin X. Physiologically Based Absorption Modelling to Explore the Formulation and Gastric pH Changes on the Pharmacokinetics of Acalabrutinib. Pharm Res. 2023 Feb;40(2):375-386. doi: 10.1007/s11095-022-03268-0. Epub 2022 Apr 27. PMID: 35478298.

Biopharm Properties & ADME Highlights

- BCS class II drug
- MW 465.5 g/mol
- Density= 1.34 g/mL
- $f_{u,p}$=2.6%
- Intrinsic solubility=48 µg/mL at pH 8
- Log P=2.0
- pKas in the physiological range: 3.5 (B), 5.8 (B)

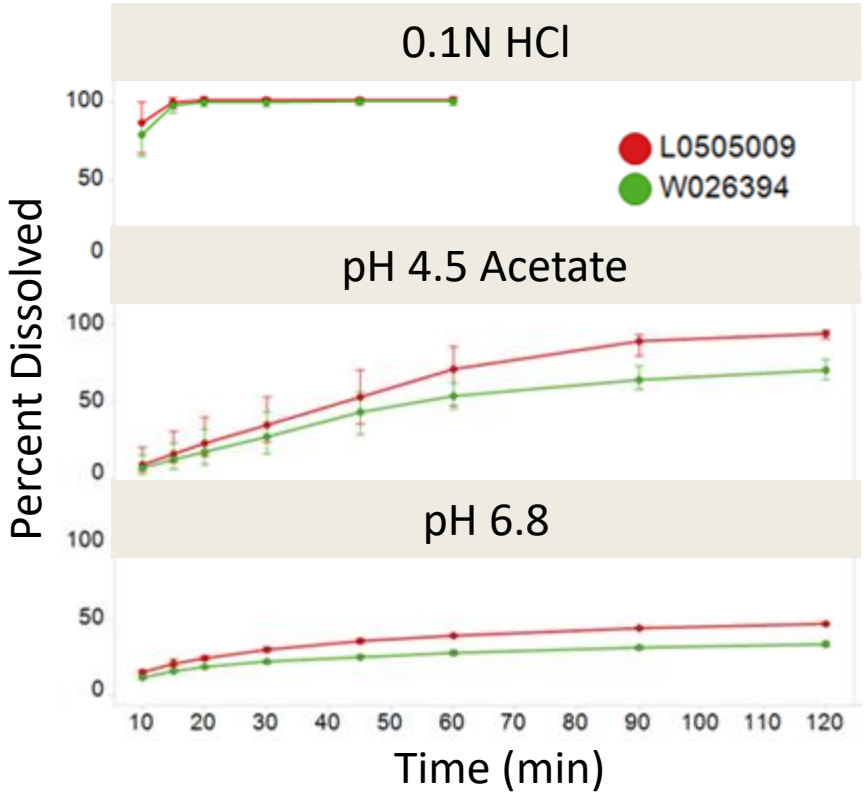


Absorption	T_{max}: 0.9 hrs; Absolute BA: 25%
Distribution	Protein binding: 97.5%; volume of distribution at SS: 101 L
Metabolism	Predominantly by CYP3A to form ACP-5826, a major active metabolite
Elimination	$t_{1/2}$: 1 hr
Dose proportionality	Dose proportional increase in exposure across a dose range of 75 to 250 mg

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/210259s009lbl.pdf

PBBM Objective

Scientific Question: Do differences in dissolution at higher pH impact in vivo behavior of W026394 and L0505009?



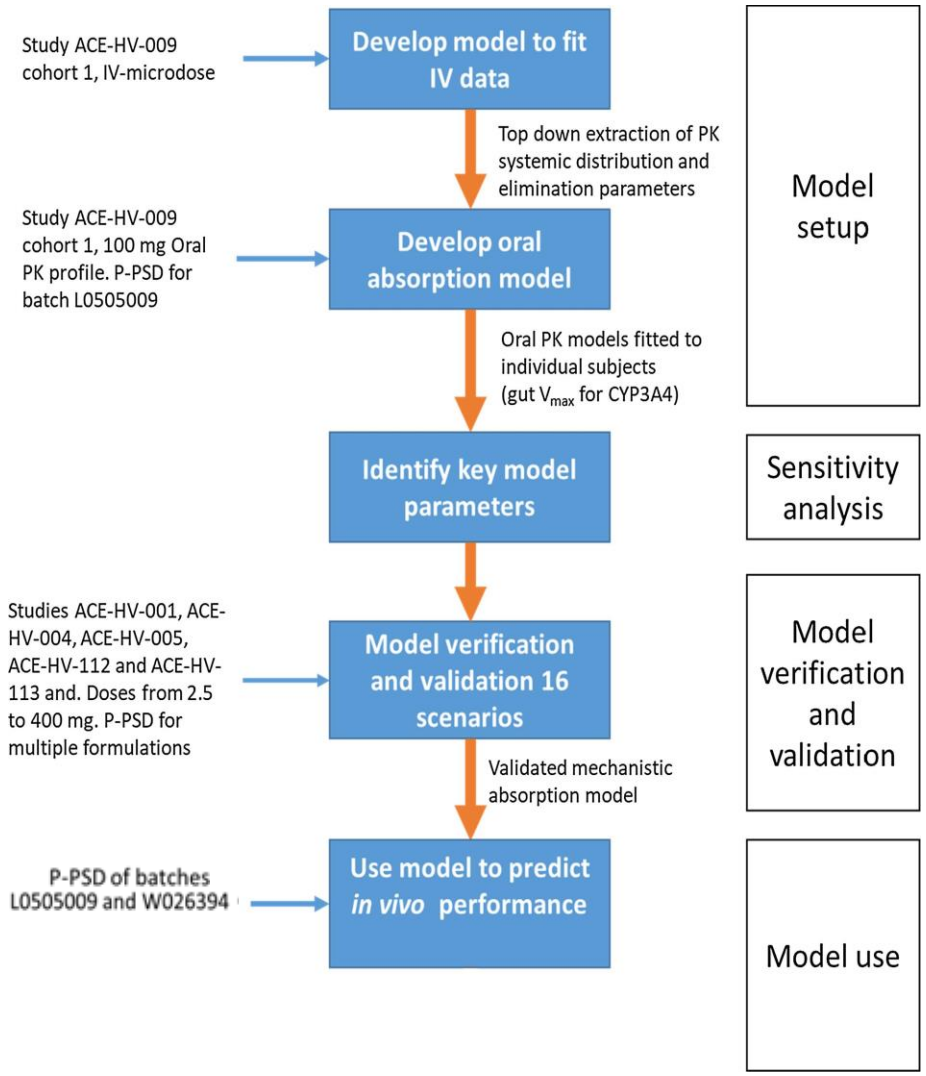
PBBM Objective

Scientific Question: Do differences in dissolution at higher pH impact in vivo behavior of W026394 and L0505009?

Considerations:

1. *Both batches dissolve fast in low pH conditions, but fail f2 at higher pH*
2. *Both batches were dosed in clinic in parallel studies*

PBBM Strategy

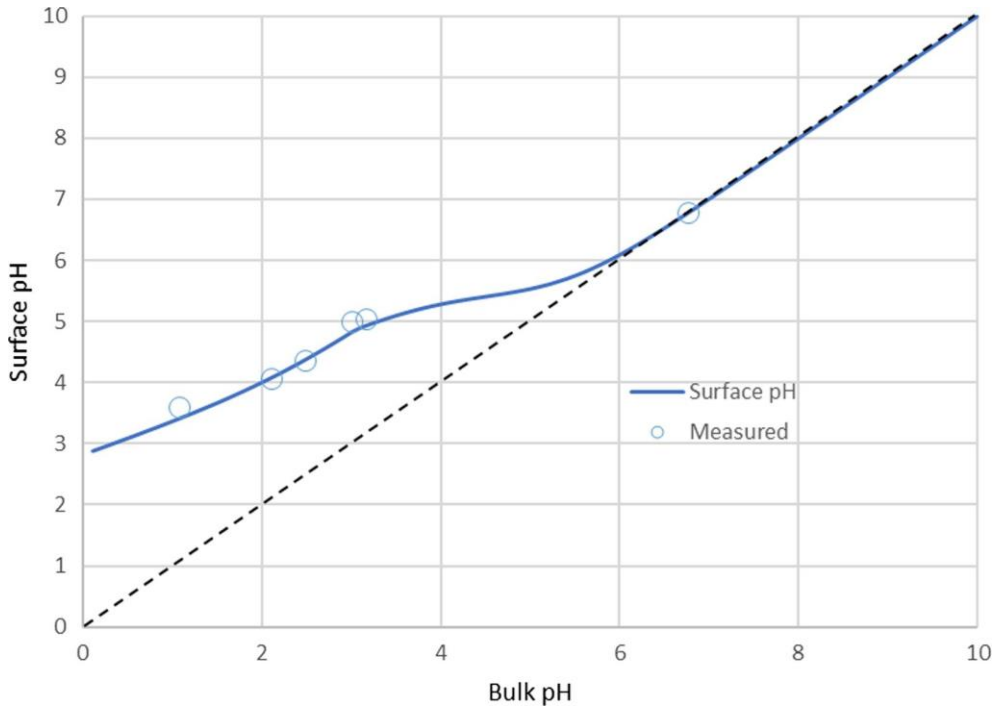


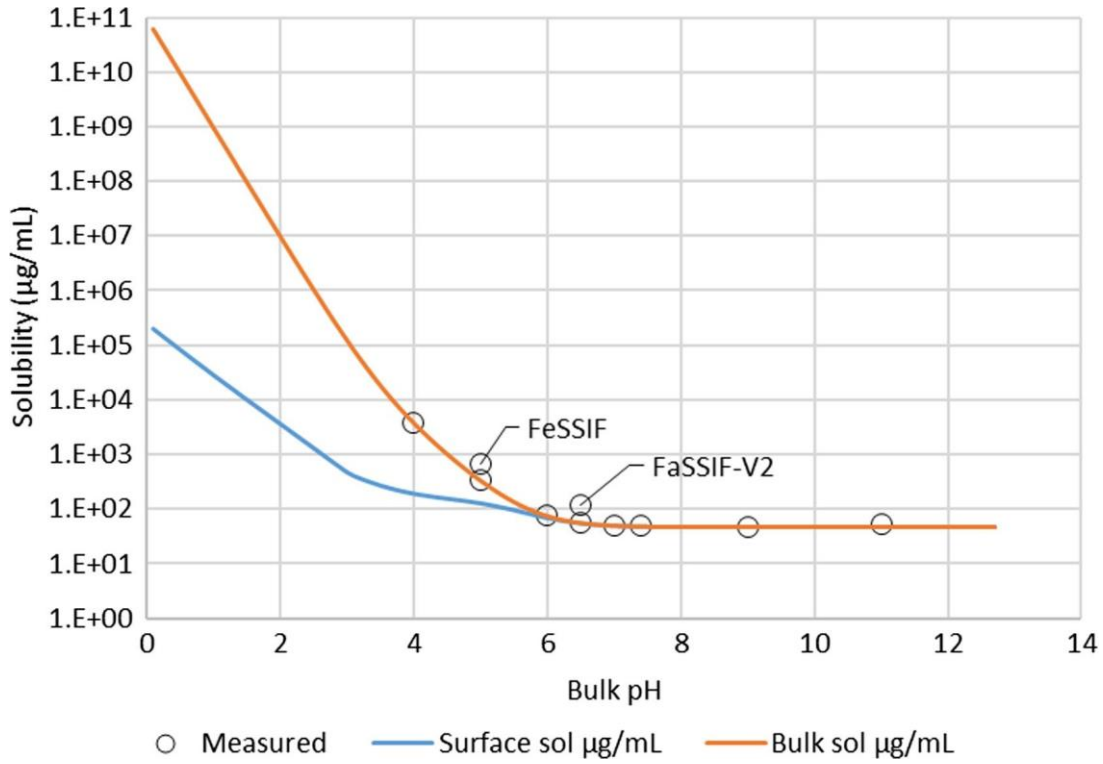
1. Top-down analysis of absolute bioavailability study where 8 subjects were dosed with 100 mg acalabrutinib capsules and an IV microdose at oral dose t_{max}.
2. Build oral absorption model with P-PSD.
3. Identify parameters most influential to acalabrutinib PK.
4. Validate model's ability to reproduce clinical observations obtained in 16 different scenarios from 5 independent clinical studies.
5. Predict in vivo performance of two batches with differing in vitro dissolution profiles.

Modified from Pepin XJH, et al. Eur J Pharm Biopharm. 2019 Sep;142:435-448.

Model Inputs:

Solubility, Precipitation, Dissolution



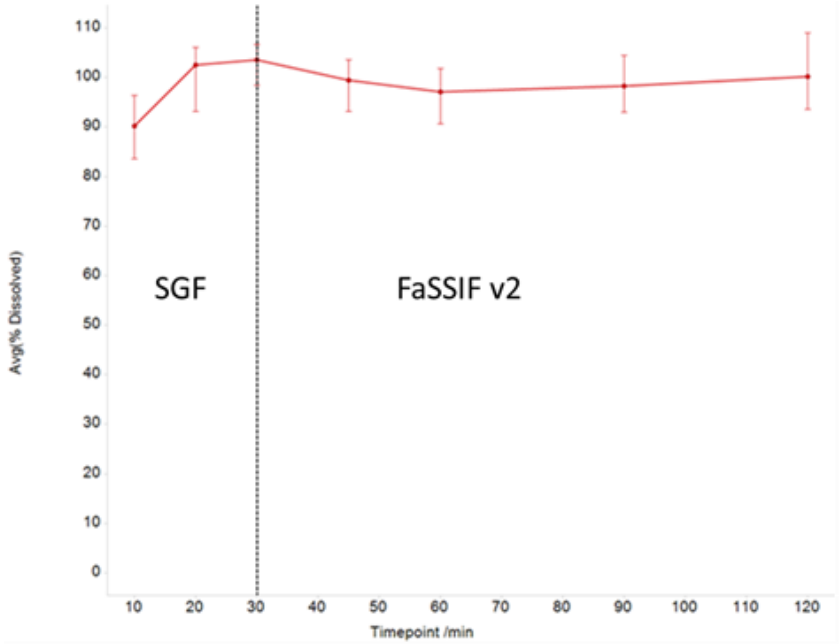


Full bulk pH solubility profile for acalabrutinib entered in PBBM, but stomach pH adjusted to acalabrutinib surface pH

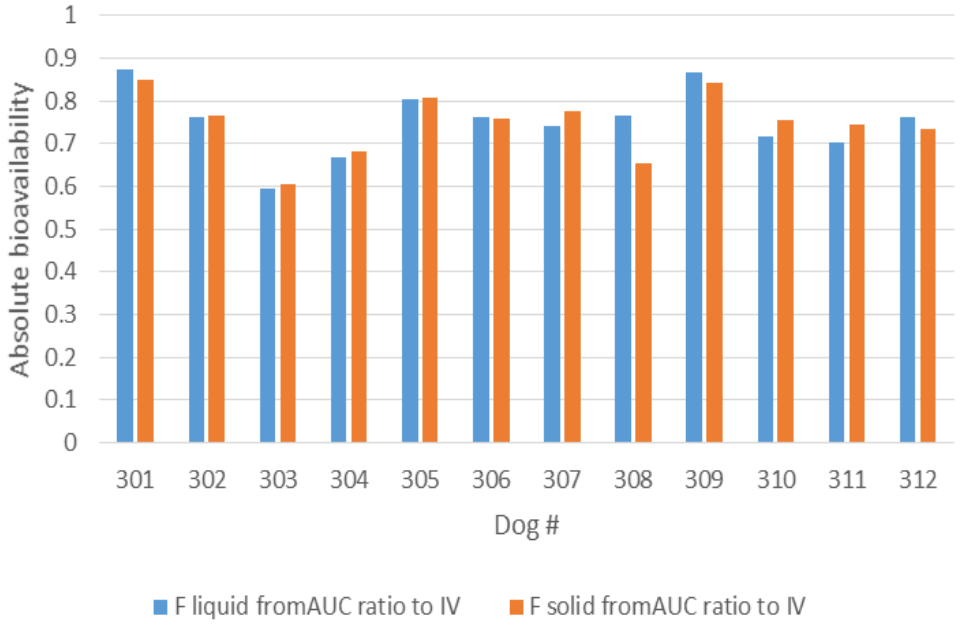
Model Inputs:

Solubility, Precipitation, Dissolution

Biorelevant pH shift dissolution of acalabrutinib 100 mg capsule, 250 mL SGF pH 1.8 for 30 minutes followed by addition of 250 mL of 2X FaSSIF v2 pH 6.9, USP 2, 50 rpm



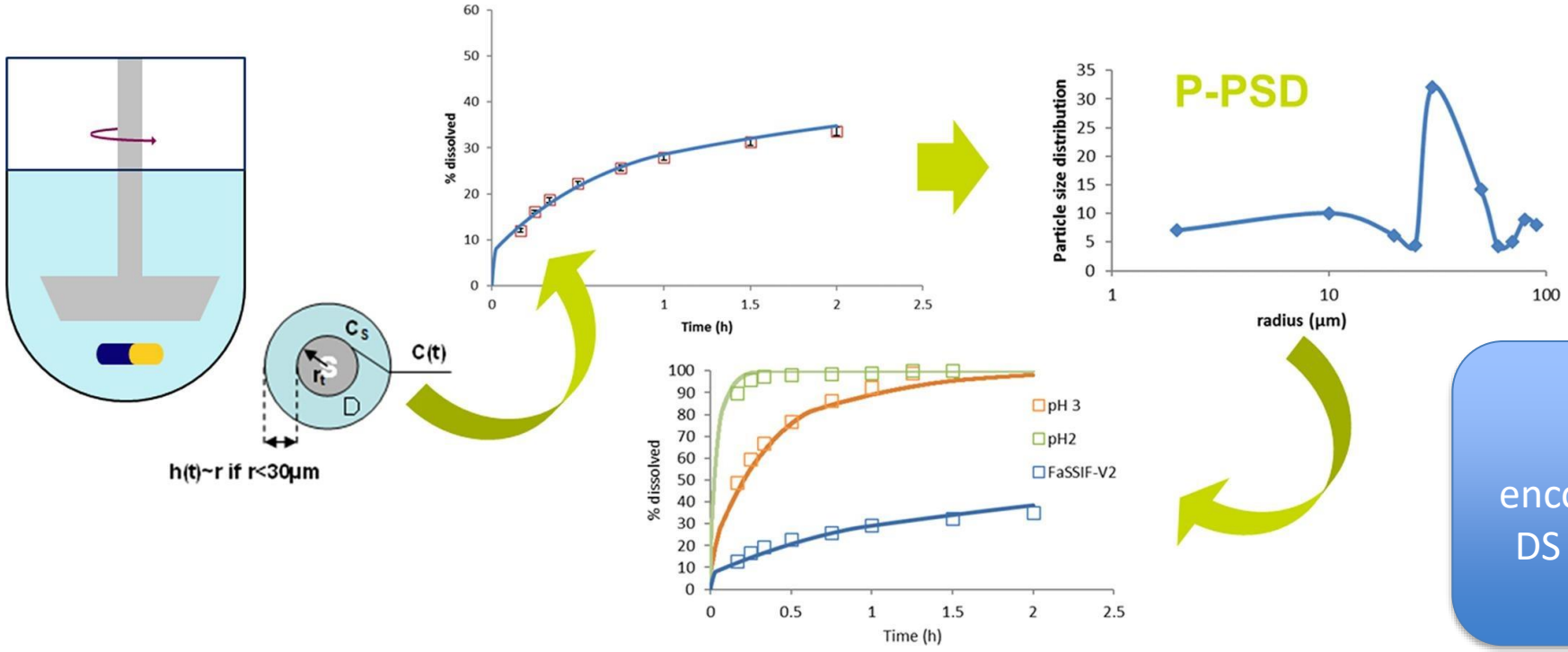
Absolute bioavailability of 100 mg oral solution and solid formulation representative of the intended commercial formulation in dogs



Propensity for precipitation investigated in vitro (*rapid pH shift model*) and in vivo (*in dogs*)

Model Inputs:

Solubility, Precipitation, Dissolution



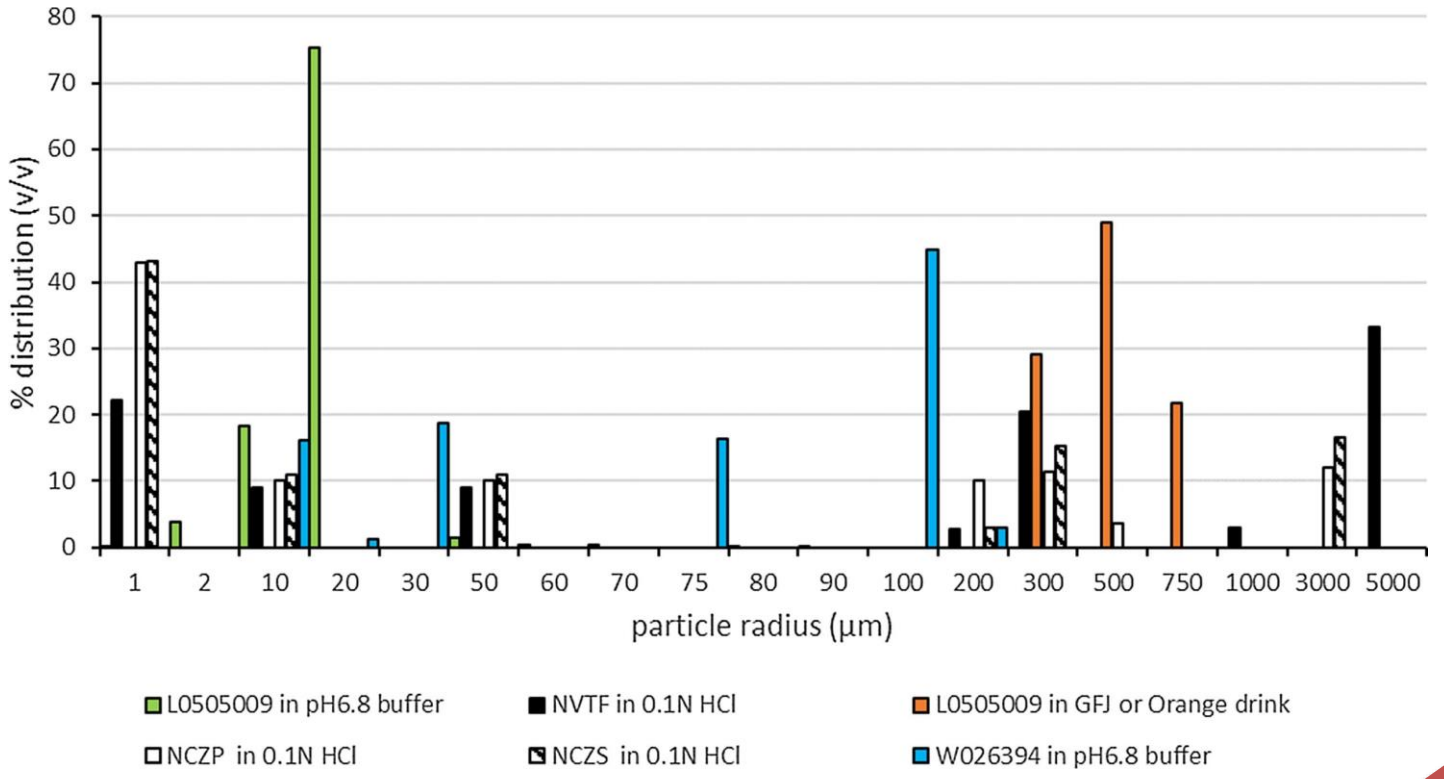
P-PSD is a creative approach that encompasses the effect of DS and DP properties on drug dissolution

Considerations:

- Prediction ability of P-PSD needs to be validated in several pH media to be considered acceptable
- Use appropriate number of in vitro dissolution data points to capture profile
- When fitting P-PSD, use fewest number of bins

Model Inputs:

Solubility, Precipitation, Dissolution

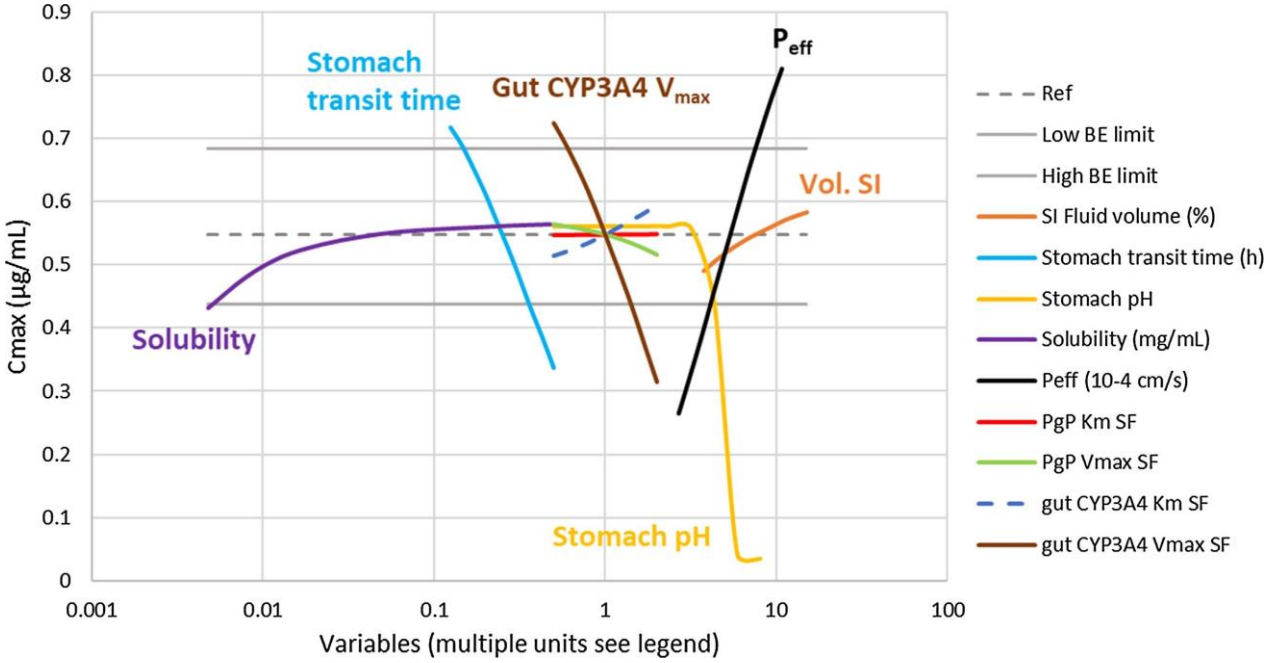


Batch	Radius mean	CV%	min	max	Study	Dissolution Profiles used
L0505009	122.4	78.8	9.9	332.7	HV-005, HV-112	pH 1, 3, 4.5, 6.8
W026394	152.3	74.7	8.1	329	HV-113	pH 1, 3, 6.8
NCZS	148.7	92.1	5.4	604	HV-001	pH 1
NVTF	193.6	64.5	26.1	502.6	HV-004	pH 1

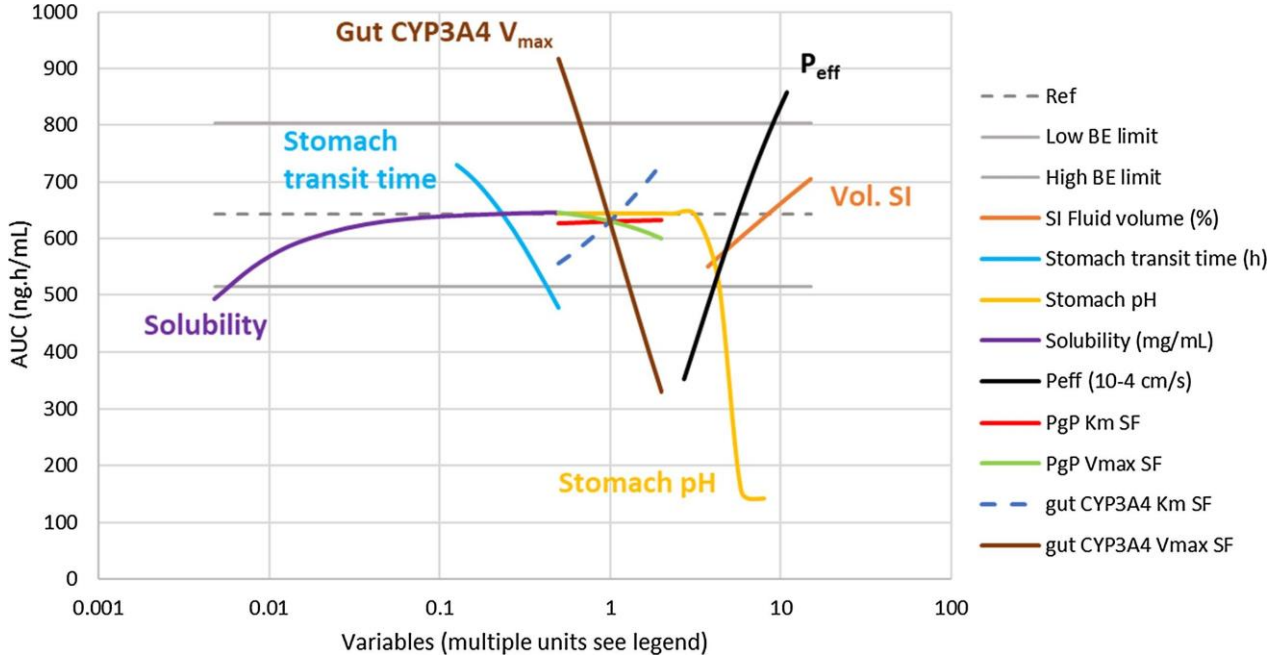
P-PSD 'extracted' using different dissolution conditions.

Model Development:
Sensitivity Analysis

Cmax



AUC



System parameters most influential are:

Stomach pH and Stomach transit time

- Stomach pH adjusted to surface pH
- Stomach transit time fit to individual based on lag times observed in PK profile

Drug parameters that are most influential are:

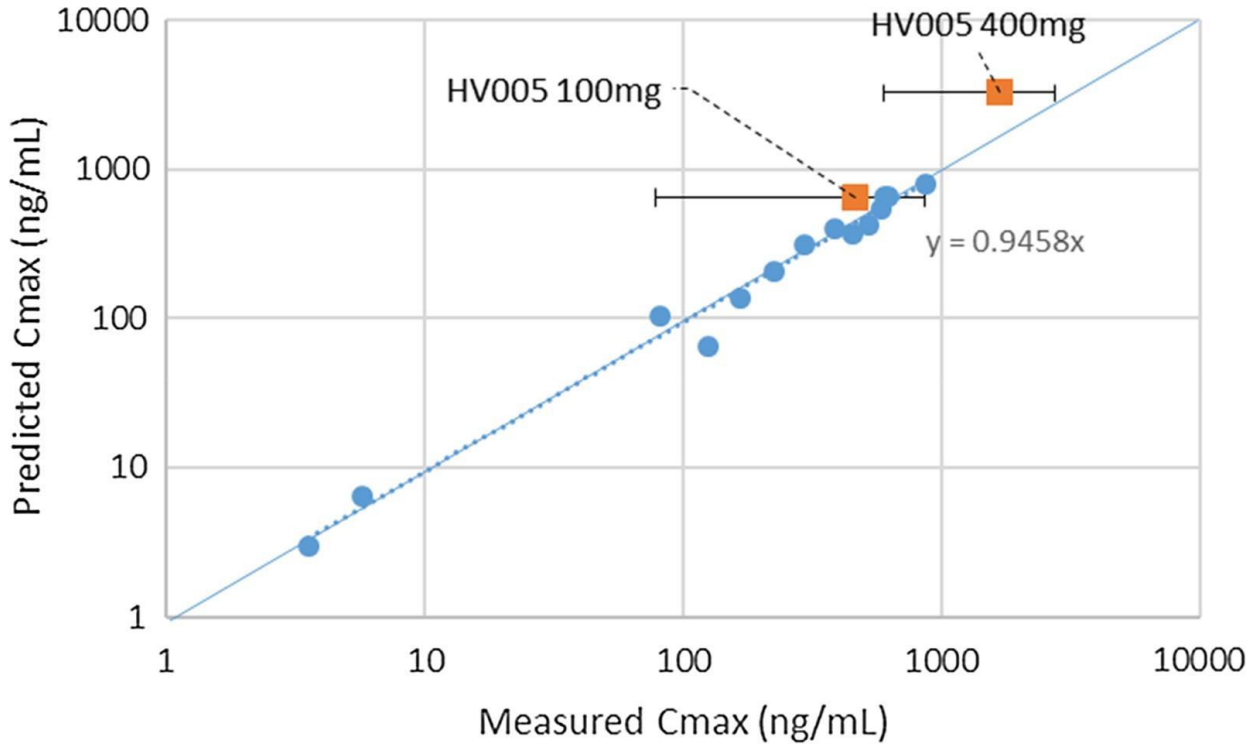
Permeability and gut CYP3A4 Vmax scaling factor

- Permeability based on MDCK-MDR1 in vitro experiment
- V_{max} for gut CYP3A4 individually fitted

Model Validation:

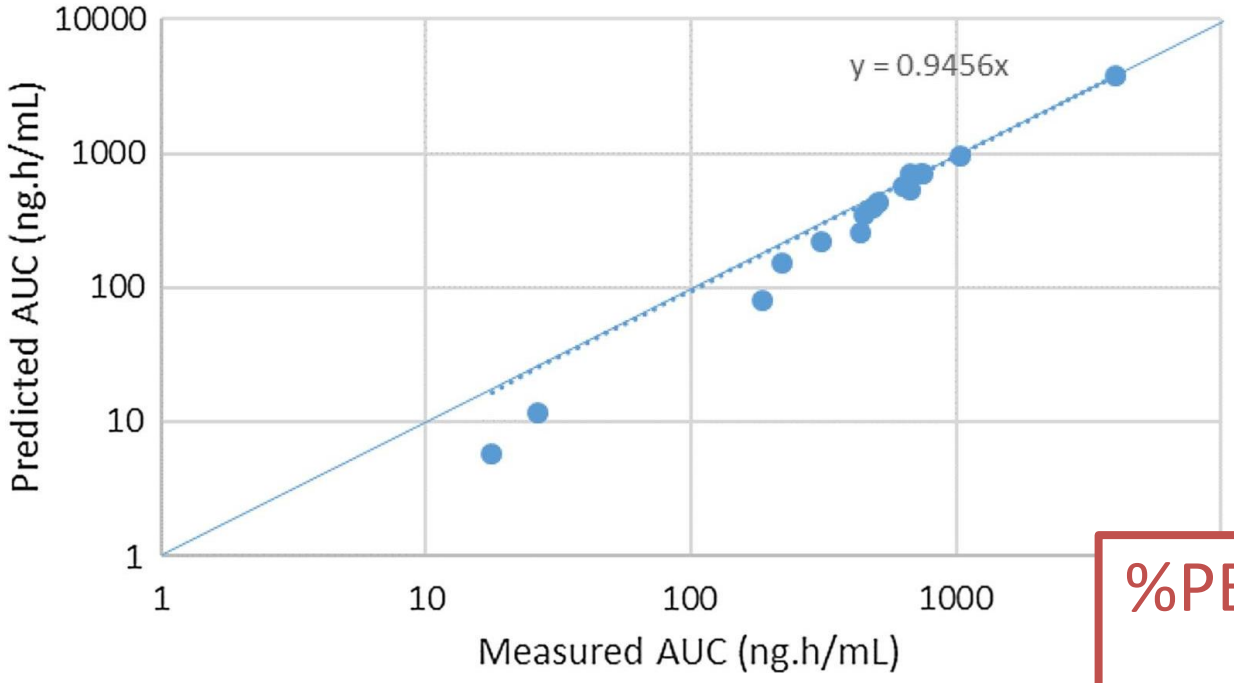
Ability of ACE-HV-009 eight subject population to provide adequate mean values for $AUC_{0\text{-}t}$ and C_{max} for different clinical populations, with different formulations and/or dose or administration schemes

Model Validation: C_{max}



AFE and AAFE (omitting ACE-HV-005) are 0.92 and 1.17 respectively

Model Validation: $AUC_{0\rightarrow t}$



%PE for a few individual studies >20%

AFE and AAFE are 0.72 and 1.39 respectively

Model Application:

Predict PK for acalabrutinib batches W026394 (test batch) in comparison to L0505009 (reference batch) in 8-subject population.

C_{max} and $AUC_{0\rightarrow t}$ ratios predicted close to 1 and 90% confidence interval is comprised between the BE limits of 0.8-1.25

No within subject variability

Case Study Summary

Considering the totality of evidence, the risk of bioinequivalence for batches W026394 and L0505009 due to dissimilar dissolution at high pH is **LOW**

Case Study Summary

Application of model for future use is limited:

- Model predictions on individual level using only 8 subjects. *Is 8-subject data set a suitable representative for the population? Able to capture variability seen in clinic?*

Recommendations for PBBM Submission

- All modeling files with detailed modeling report (see 2020 FDA Guidance *The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls*)

- Information regarding the formulation(s) and manufacturing process(es) for batches used in development and validation of PBBM

- Biopharmaceutics Risk Assessment*

Thank you!