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Expanding BCS Class 3 Waivers for Generic Drugs to Non-Q1/Q2 Products

PBPK 2021: Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches

Day 2 Session 1: Oral PBPK as alternative BE approach, risk assessment/biowaiver

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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

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Background

- The FDA and the EMA allow biowaivers of clinical bioequivalence (BE) studies for BCS Class 1 (highly soluble and highly permeable) drugs and for some BCS Class 3 (highly soluble and not highly permeable) drugs.
- There is an unmet need for a robust, predictive *in vitro* model for evaluating the effects of excipients on drug permeation.
- This work is based on FDA Contract 75F40119C10127: "EXPANDING BCS CLASS 3 WAIVERS FOR GENERIC DRUGS TO NON-Q1/Q2 Products"
- Contractor: Absorption Systems LLC

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Objectives

Aim 1: Qualification of a proprietary model, the *in-vitro* Dissolution Absorption System (IDAS), for assessment of excipient effects on drug permeation (focus of this talk)

Aim 2: Impact of different combinations of excipients in solid oral dose forms (tablets and capsules) on drug dissolution and permeation, measured simultaneously using IDAS

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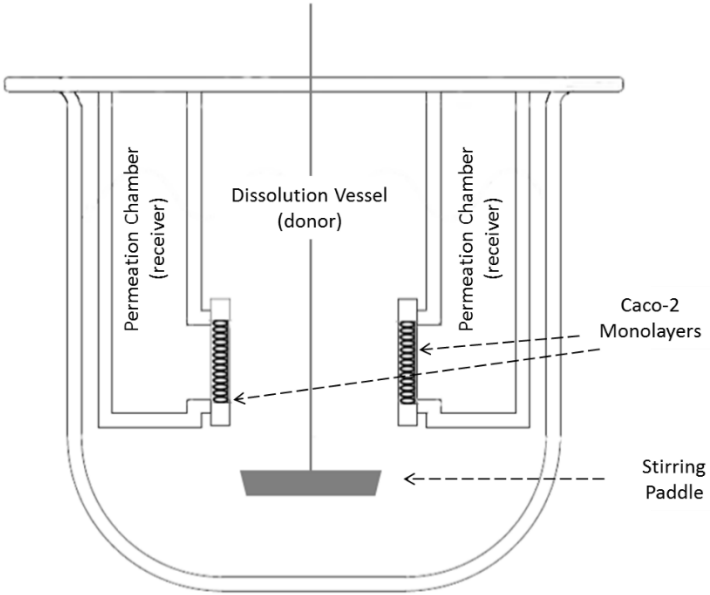
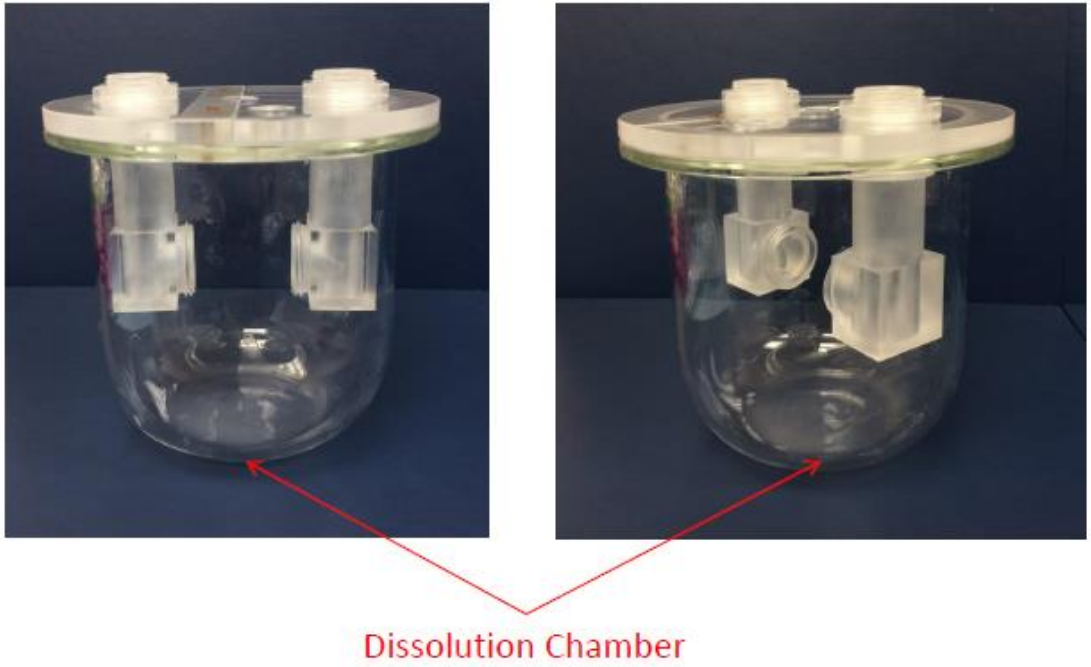
IDAS Overview





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Methods

- Developed a single LC-MS/MS analytical method for the quantification of five model drugs:
  - Acyclovir (Class 3, clinical data on excipient effects)
  - Cimetidine (Class 3, clinical data on excipient effects)
  - Ranitidine (Class 3, clinical data on excipient effects)
  - Atenolol (Class 3, cell monolayer integrity marker)
  - Minoxidil (Class 1)
- Used IDAS to evaluate the permeation of the pre-dissolved model drugs (co-dosed as a cassette) in the absence and presence of 15 excipients (one at a time), each at three concentrations

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Test Excipients

Excipient	Concentration (mg/mL)		
	Low	Mid	High*
Povidone K30	0.0500	0.200	0.800
Hydroxypropyl methylcellulose 2910 (4000 mPa·s)	0.0125	0.0500	0.210
Hydroxypropyl methylcellulose 2910 (15 mPa·s)	0.0125	0.0500	0.210
SLS	0.0375	0.150	0.300
PEG-400	0.260	1.11	4.23
Lactose monohydrate	0.500	2.00	8.00
Microcrystalline cellulose	0.390	1.55	6.21
Magnesium stearate	0.100	0.400	1.60
Croscarmellose sodium	0.0450	0.180	0.720
Sorbitol	1.25	5.00	20.0
Dibasic calcium phosphate dihydrate	0.160	0.640	2.54
Silicon dioxide	0.0400	0.160	0.640
Pregelatinized starch	0.113	0.453	1.81
Talc	0.0400	0.400	4.00
Mannitol	0.170	0.682	2.73

*** In general (with some exceptions), the High test concentration is equal to the highest amount of a given excipient in an immediate-release solid oral dose form (according to the FDA Inactive Ingredients Database), dissolved in 250 mL; the Mid concentration is generally 25% of the High; and the Low concentration is generally 25% of the Mid**

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Functional Class(es) of Test Excipients

Excipient	Functional Class(es)
Povidone K30	Disintegrant, dissolution enhancer, binder
Hydroxypropyl methylcellulose 2910 (4000 mPa·s)	Binder, dispersing agent
Hydroxypropyl methylcellulose 2910 (15 mPa·s)	Binder, dispersing agent
SLS	Anionic surfactant, lubricant
PEG-400	Solvent, lubricant
Lactose monohydrate	Filler/diluent
Microcrystalline cellulose	Filler/diluent, disintegrant
Magnesium stearate	Lubricant
Croscarmellose sodium	Disintegrant
Sorbitol	Filler/diluent
Dibasic calcium phosphate dihydrate	Filler/diluent, binder
Silicon dioxide	Glidant
Pregelatinized starch	Binder, disintegrant, filler/diluent (at higher amounts)
Mannitol	Filler/diluent, sweetener, plasticizer, tonicity agent
Talc	Lubricant, glidant, anti-caking agent, diluent

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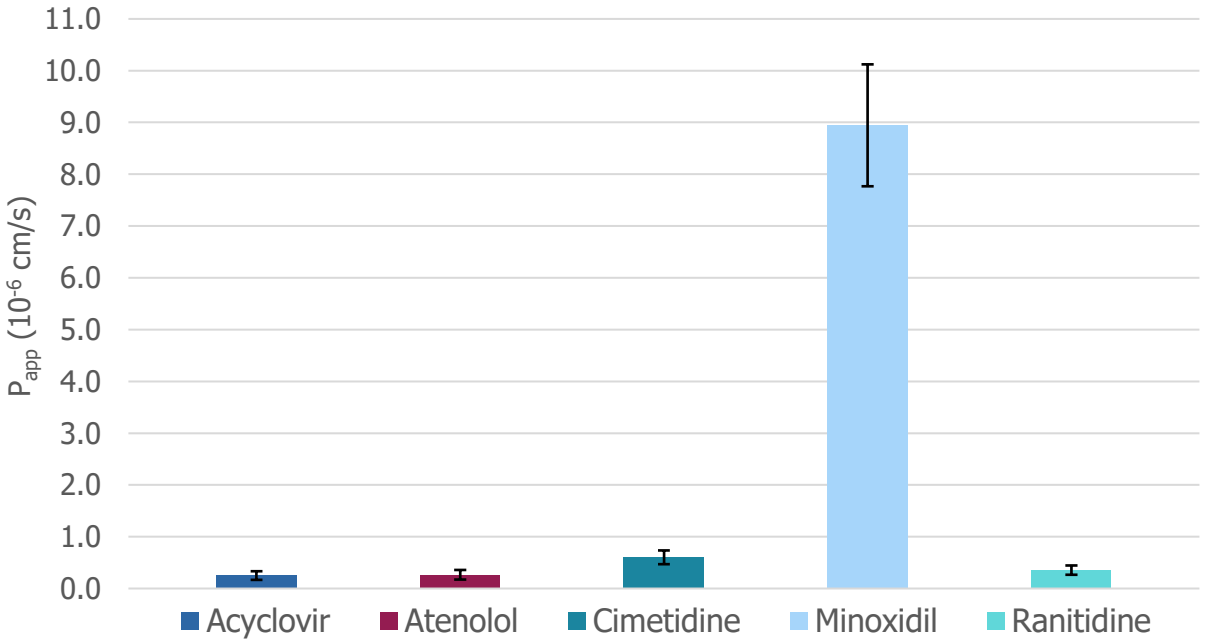
Permeation of Model Drug Cassette +/- Excipients

- Excipient treatments performed with n=3/6 replicates
  (3 dissolution vessels, 6 permeation chambers)
- Apparent permeability coefficient (P_{app}) and AUC were calculated
  - Note that in this *in vitro* system, the receiver concentration of the model drug is constantly increasing over time.

P_{app} of Negative Controls Run in Parallel with Excipients



Each bar represents all negative controls (no excipients) for one of the model drugs run in parallel with test excipients (mean ± standard deviation, n=66)

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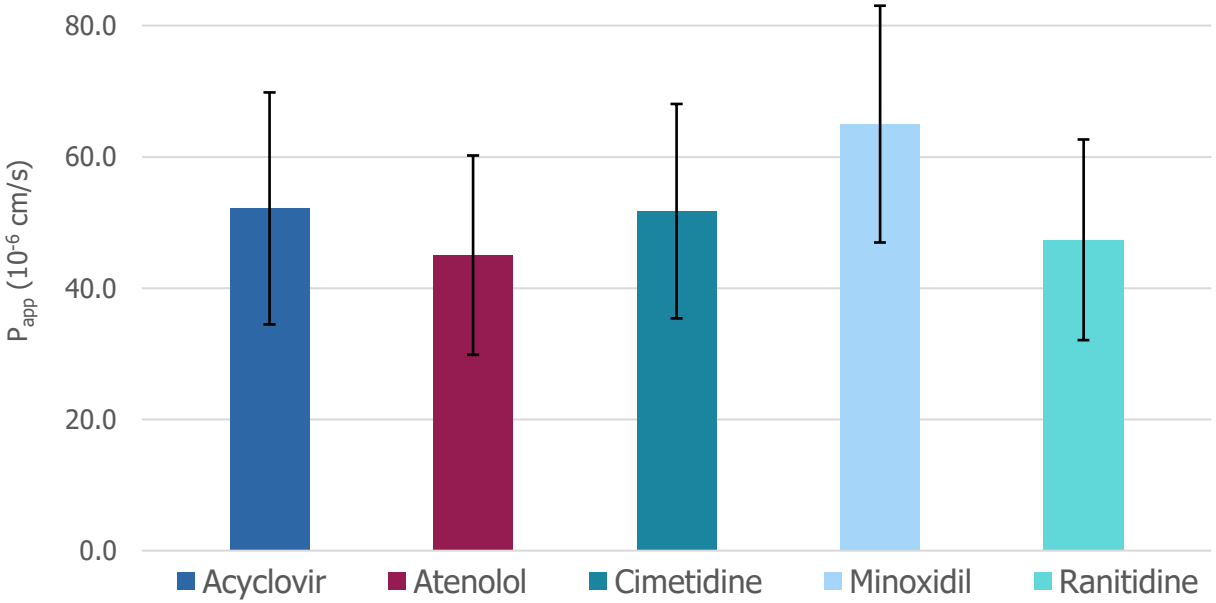
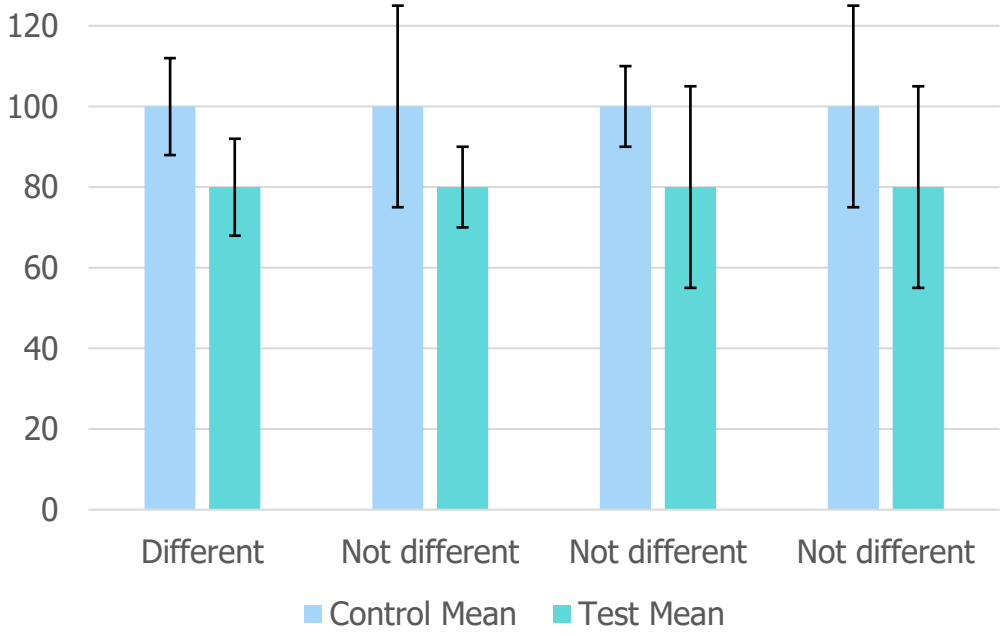
P_{app} of Positive Controls Run in Parallel with Excipients



Each bar represents all positive controls (SLS at 0.6 mg/mL) for one of the model drugs run in parallel with test excipients (mean ± standard deviation, n=36)

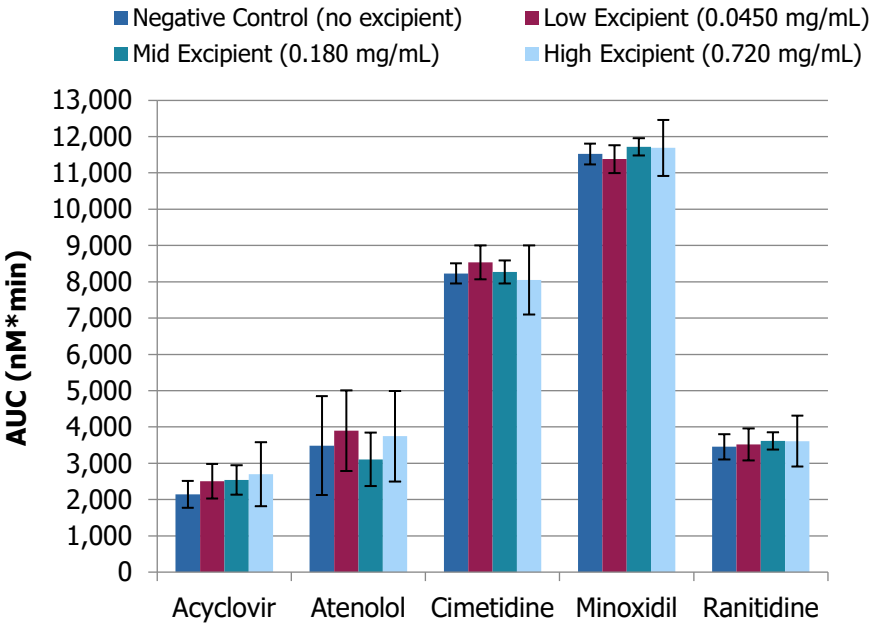
How to Identify Effects of Excipients on Permeation?



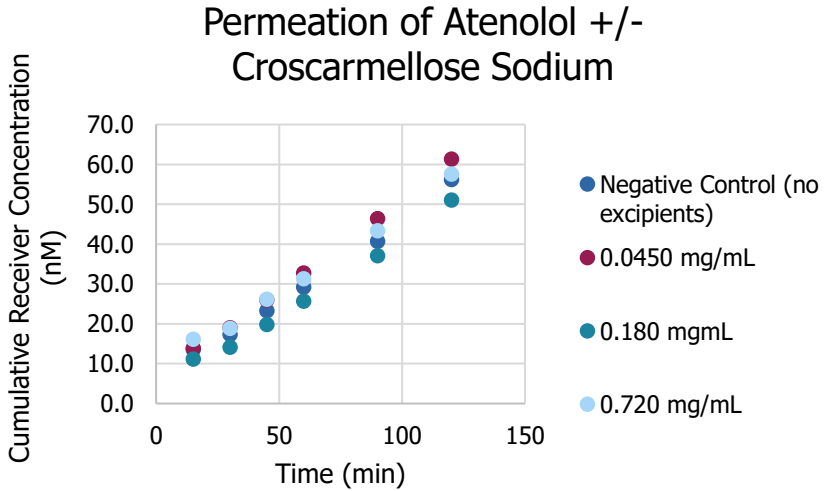
- The criterion of two standard deviations above and below the mean (encompassing approximately 95% of the values in a set of data, assuming normal Gaussian distribution) is used to identify a potentially meaningful effect of an excipient treatment.
- In other words, a test mean differing from that of the negative control by less than two times the standard deviation of either treatment (the excipient or the negative control) is considered "no effect."

Note: In this slide, error bars represent 2 standard deviations

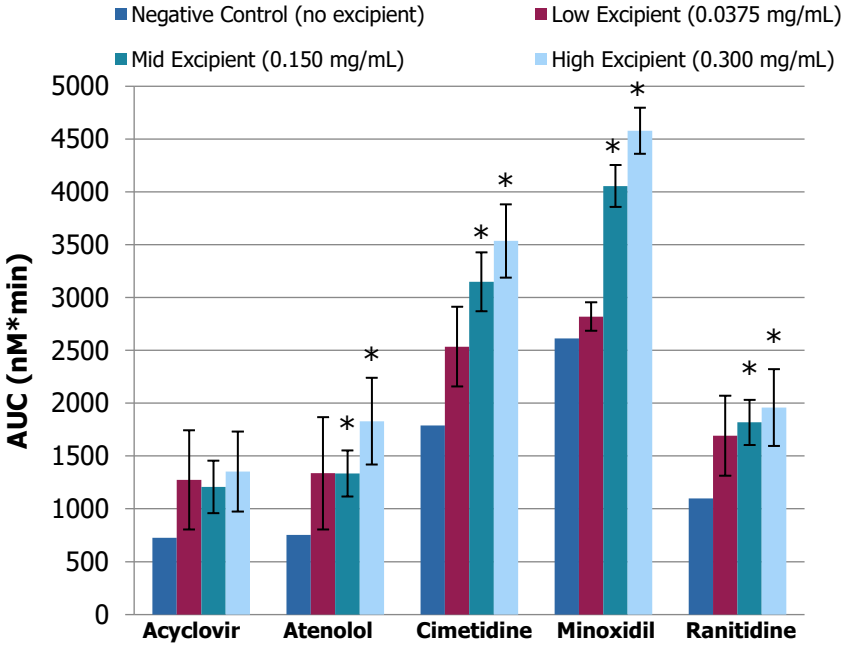
No Effect of Croscarmellose Sodium on AUC of Model Drugs

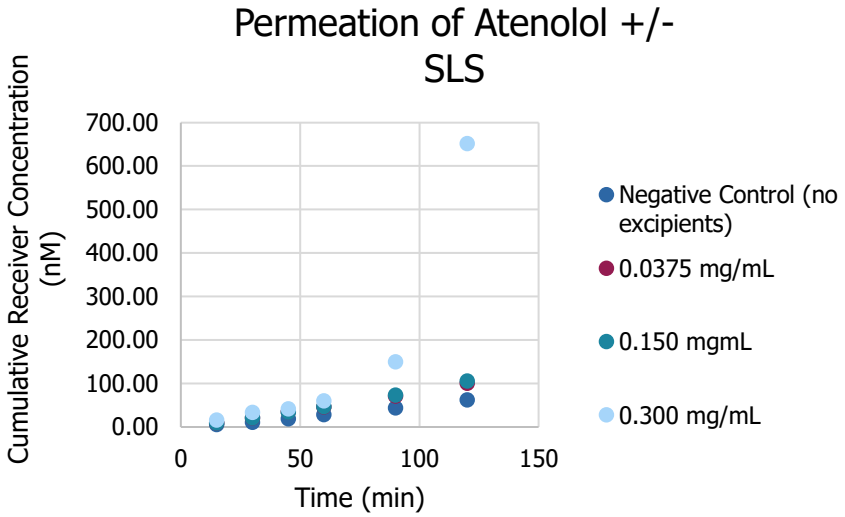


Data represent mean ± standard deviation, n=6



Effects of SLS on AUC of Model Drugs





Data represent mean ± standard deviation, n=6

* Both the mean of the test treatment and the mean of the negative control were outside the range of two standard deviations of the other.

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Results with Class 3 Model Drugs

Effects	Excipients	Change in Permeation
None	Hydroxypropyl methylcellulose (two viscosities), microcrystalline cellulose, croscarmellose sodium, talc, mannitol, silicon dioxide	No effects on permeation of any model drugs
Spotty	Povidone K30	Decrease in permeation of acyclovir and ranitidine
	Magnesium stearate	Decrease in permeation of acyclovir
	Lactose, calcium phosphate, pregelatinized starch, PEG-400	Increase in permeation of cimetidine and ranitidine
Inconsistent	Sorbitol	Effects on permeation of all model drugs, but different directions in two tests
Consistent	SLS	Dose-dependent increase in permeation of all model drugs

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Summary of Results and Implications

1

Caco-2 cell monolayers in IDAS were less sensitive to excipients than in Transwells, a format in which the cells are overly sensitive to excipients. This may be due to the geometry (vertically oriented cell monolayers) and more effective mixing (apical surface of the cell monolayer exposed to the dissolution chamber, which is agitated by a paddle).

2

Most of the excipients tested had little or no effect on the permeation of Class 3 drugs, suggesting that expanding biowaivers to non-Q1/Q2 formulations within a certain range for a Class 3 drug biowaiver may be possible. This could have important consequences for the development and regulatory approval of generic drugs.

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Next Steps

Extend these *in vitro* findings to marketed oral drug products and research formulations with clinical data

In vitro data to be used to predict *in vivo* performance in combination with a physiologically based pharmacokinetic (PBPK) model

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Thank You

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