Application of Physiologically Based Pharmacokinetic (PBPK) Modeling in Generic Drug Evaluation

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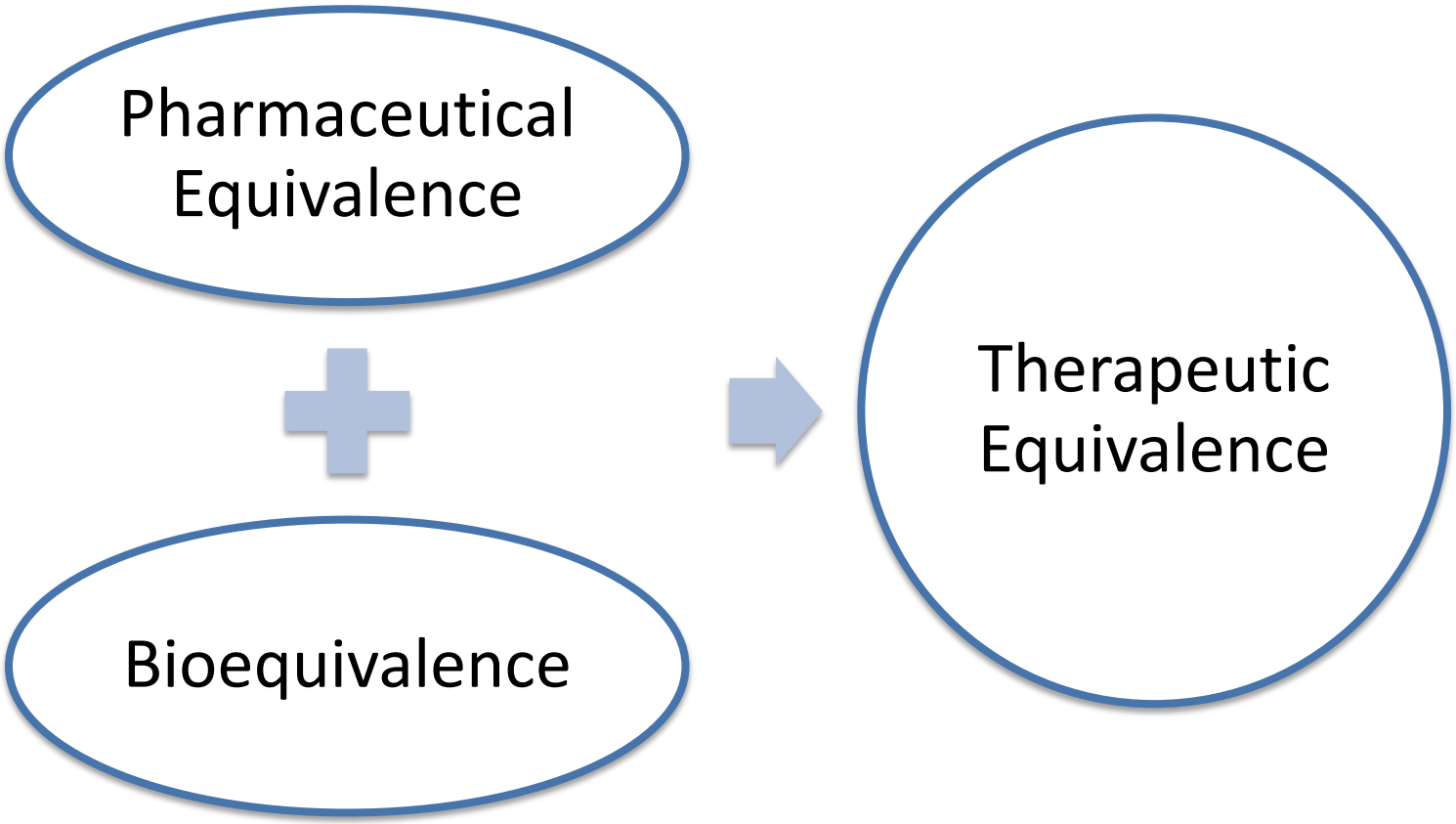
Disclaimer

The views expressed in this presentation are those of the speaker and not necessarily those of the Food and Drug Administration (FDA).

Outline

- Update on PBPK modeling and simulation in OGD
- Case examples of mechanistic oral absorption modeling and simulation
- Challenges and Opportunities

The Science of Equivalence



PBPK modeling for oral dosage forms

Modeling and Simulation of Biopharmaceutical Performance

X Zhang[1] and RA Lionberger[1]

Biopharmaceutical performance refers to the influence of pharmaceutical formulation variables on *in vivo* performance. New drug product success depends on formulation design for sufficient bioavailability for clinically desired dosing. Regulatory interest in biopharmaceutical performance includes batch-to-batch consistency, acceptability of postapproval changes, and evaluation of bioequivalence (BE) for generic drug products. This Commentary summarizes biopharmaceutical modeling and simulation in the US Food and Drug Administration (FDA) Office of Generic Drugs (OGD) for orally administered generic drugs.

Clinical Pharmacology & Therapeutics (2014); 95 5, 480–482.

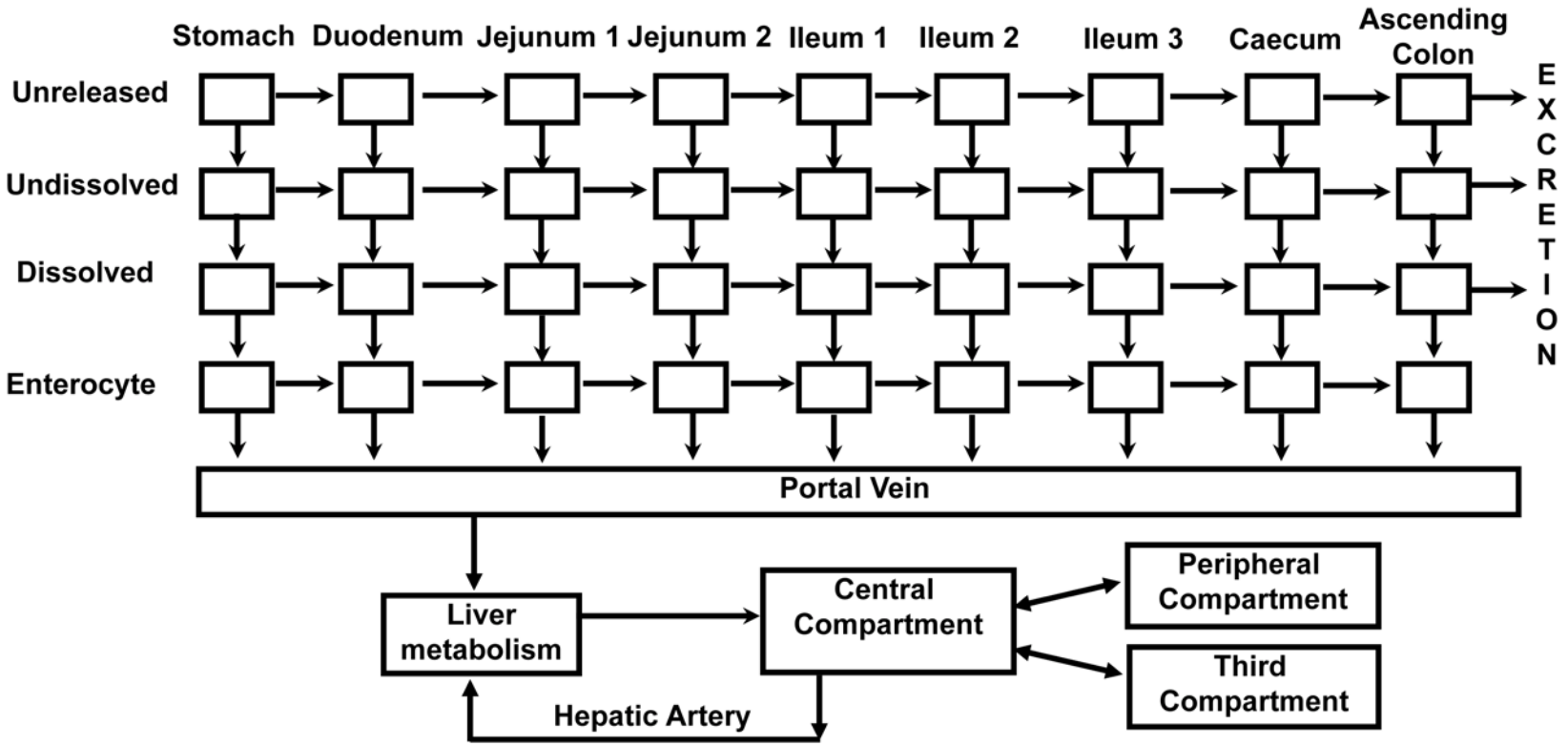
PBPK modeling for non-oral dosage forms

- Dermal absorption
- Ocular delivery
- Complex drug products
- Nasal delivery
- Pulmonary delivery
- Any others not included in the above topics (BAA)

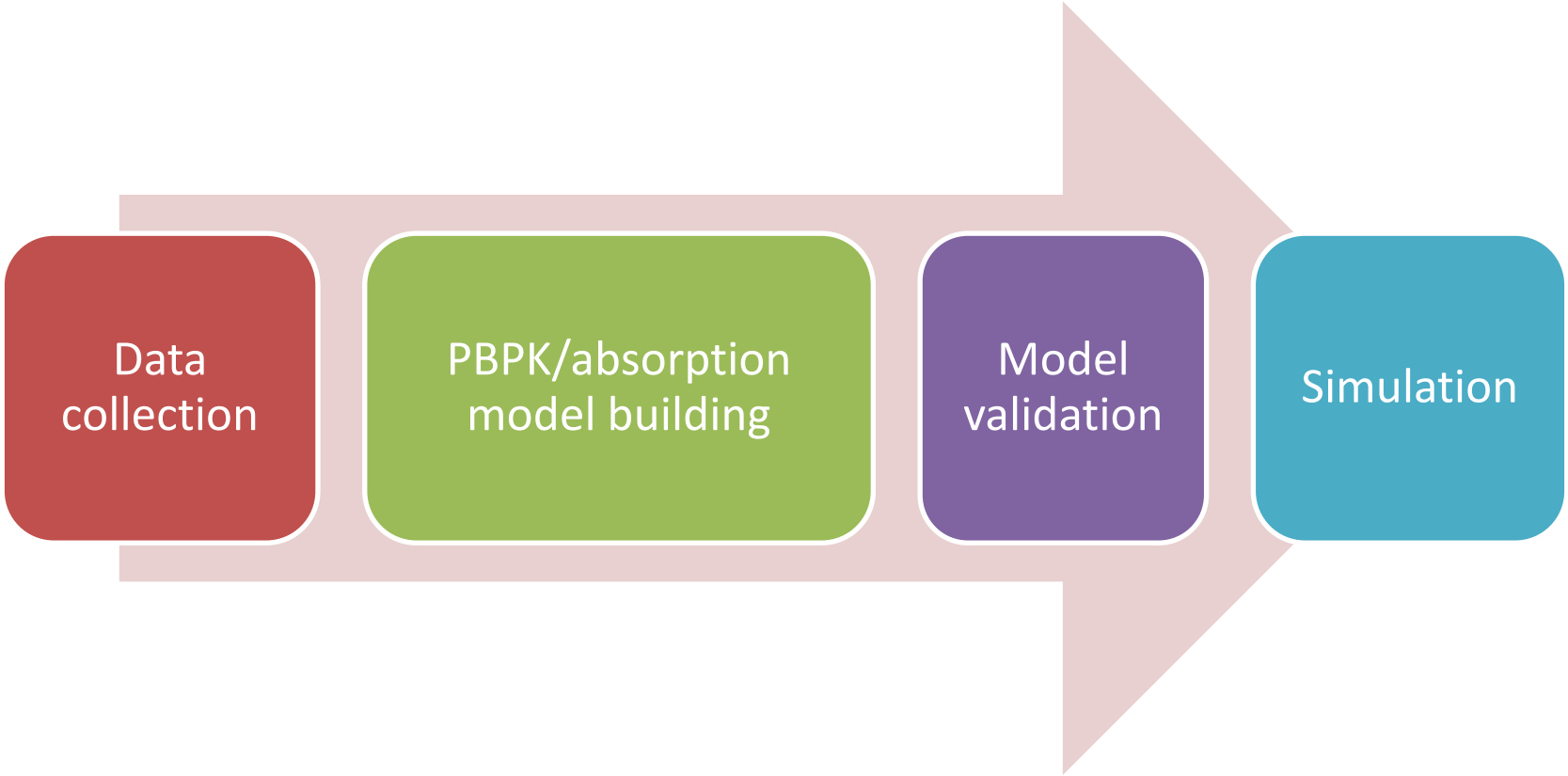
GDUFA Regulatory Science:
http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm370952.htm

Case examples of using PBPK modeling and simulation for BE assessment

ACAT Model in GastroPlus



General Procedure



Case study #1: Amphetamine salts oral products

- Specific aims: risk assessment
  - Evaluate BE in special population.
  - Evaluate potential risks associated with wide dissolution specification.
  - Evaluate the sensitivity of PK metrics to the change of critical formulation factors.

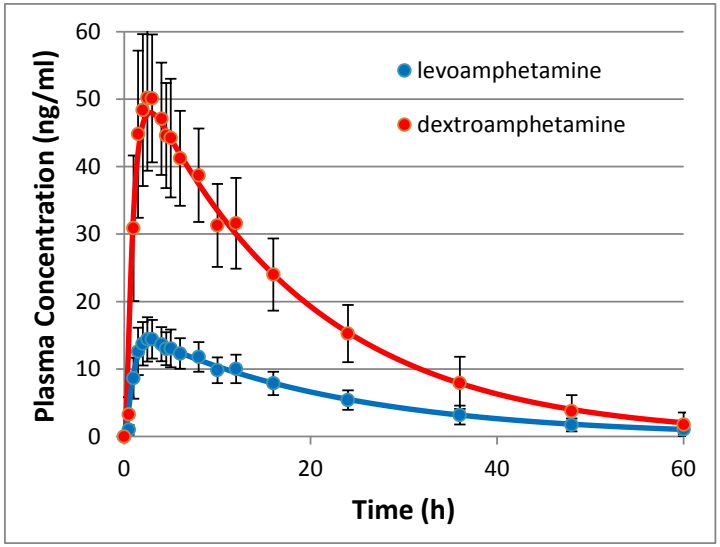
Amphetamine salts parameters

Adderall XR capsules	Mixed amphetamine salts (MAS) ER capsules: amphetamine aspartate; amphetamine sulfate; dextroamphetamine saccharate; dextroamphetamine sulfate (1:1:1:1) IR:DR (enteric-coated) (1:1)[1] pellets			
Dexedrine ER capsules	dextroamphetamine sulfate			
pKa	9.9			
Solubility	High across physiological pH			
logP	1.8			
Permeability	High (ADMET predictor)			
Elimination half-life (hr) [2]	Isomer	adults	adolescents	children
	D-amphetamine	10	11	9
	L-amphetamine	13	13-14	11

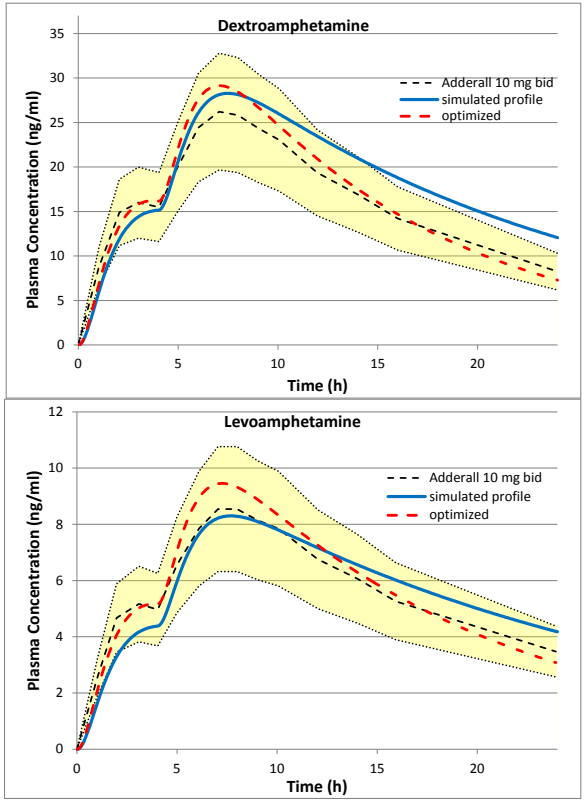
[1] Drugs@FDA. Clinical Pharmacology Biopharmaceutics Review(s)
[2] Adderall XR label

ACAT model predicts PK after administration of MAS IR tablets

SD, fasting

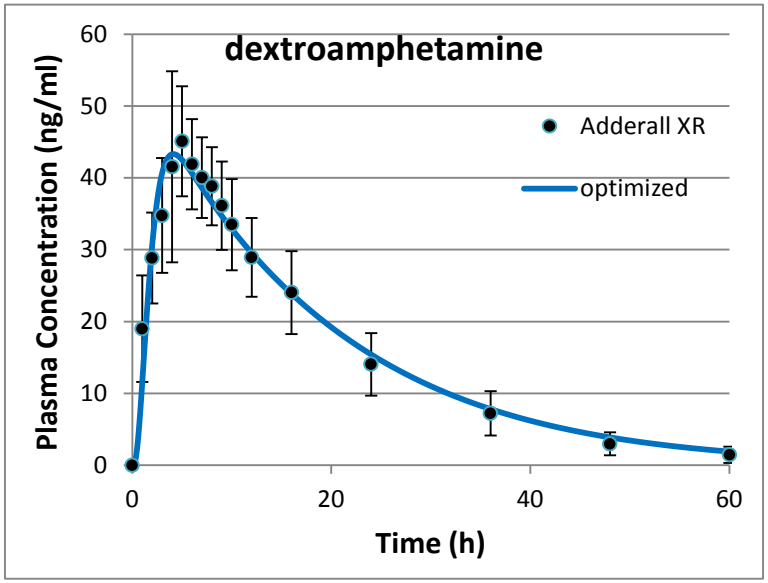


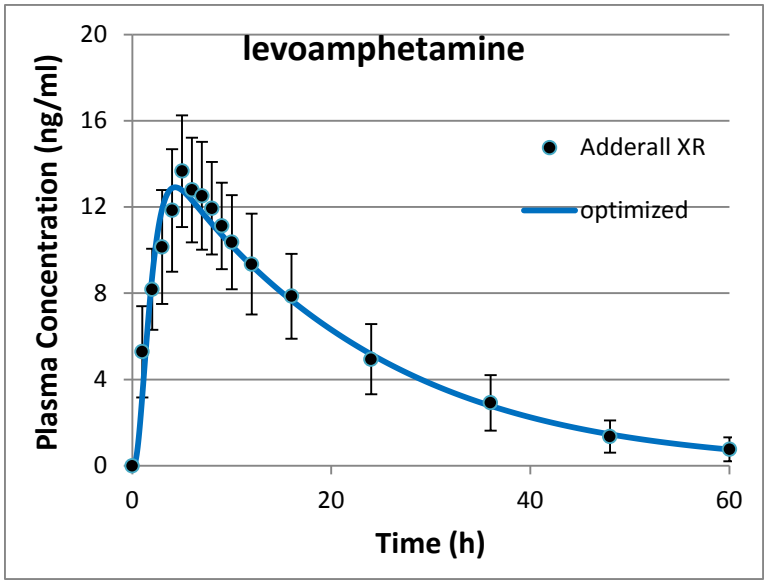
bid four hours apart, fed



- One compartment PK model.
- PK (Cmax, AUCt, and Tmax) parameters are sensitive to the change of permeability.
- PK parameters (CL and Vc) were optimized for the bid study.

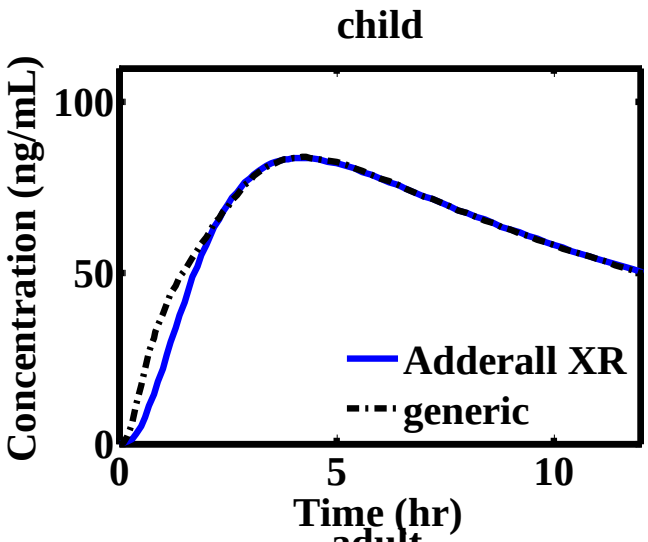
ACAT model predicts PK after administration of MAS ER capsules

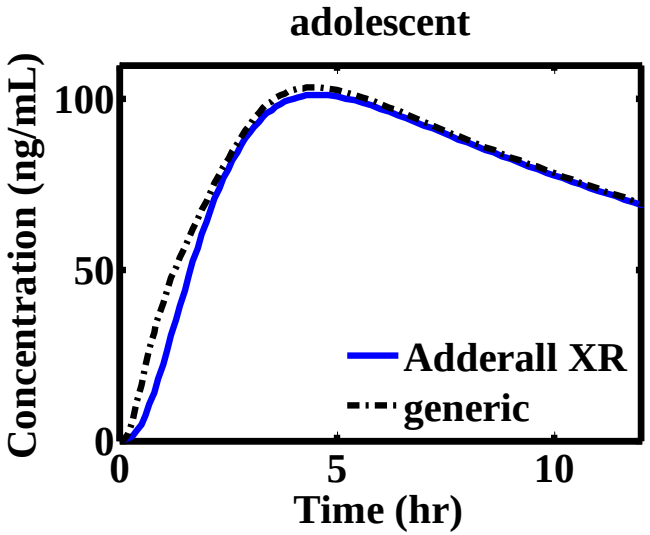


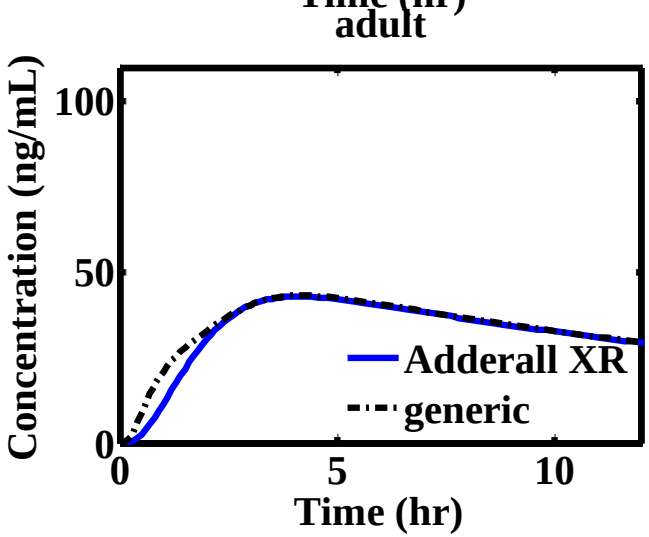


- 'Mixed Multiple Doses' with equal doses of IR: Capsule and DR: MultiPart EntCoat at the same start time (0 hours).
- Z-factor model for dissolution.
- CR: dispersed dosage form for a generic

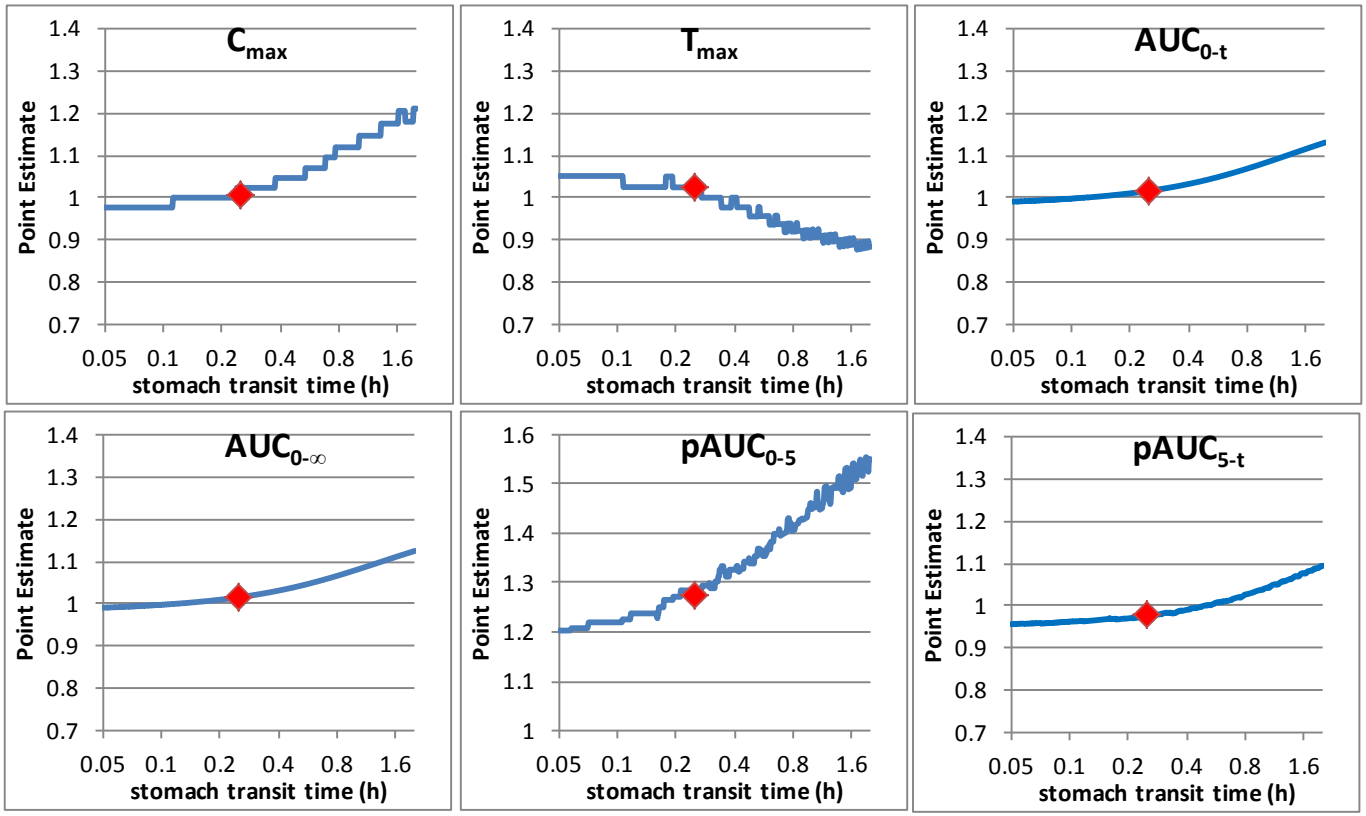
BE extrapolated to other populations



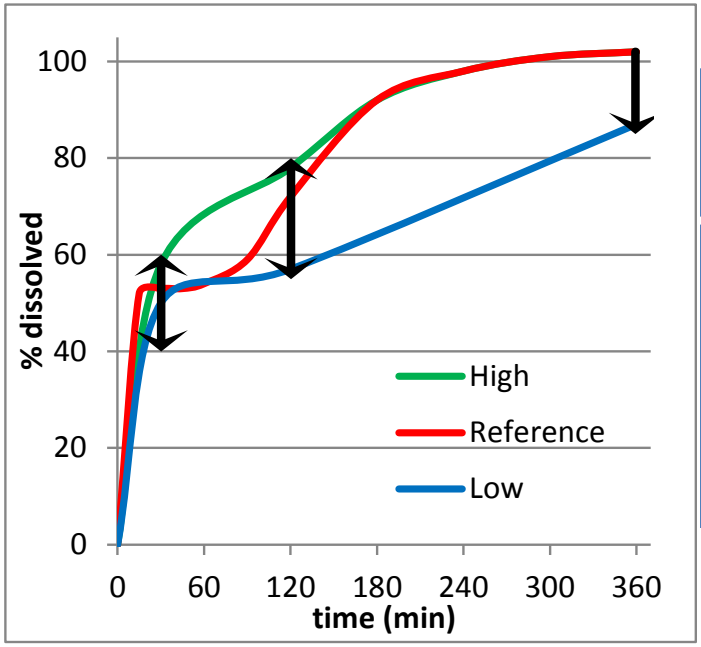




Early partial AUC T/R ratio is sensitive to prolonged stomach transit time

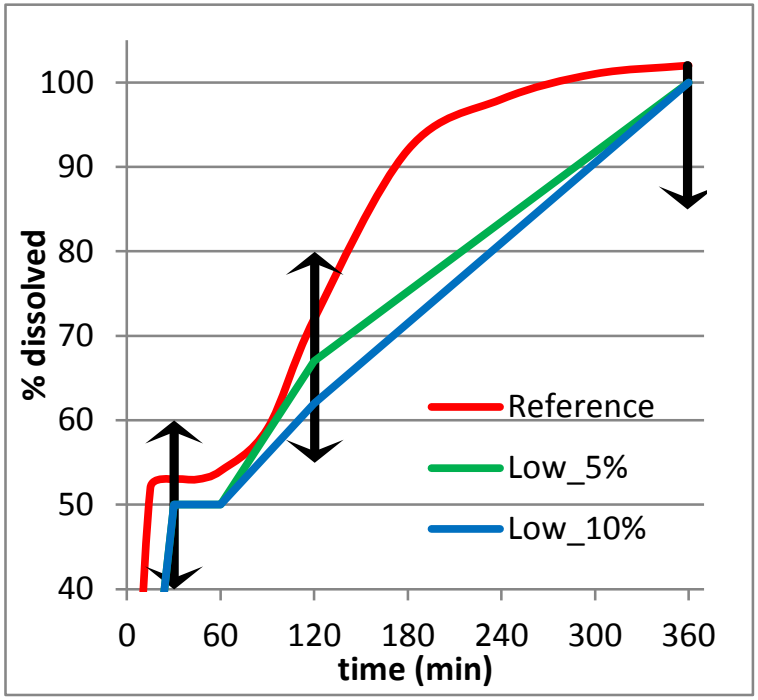


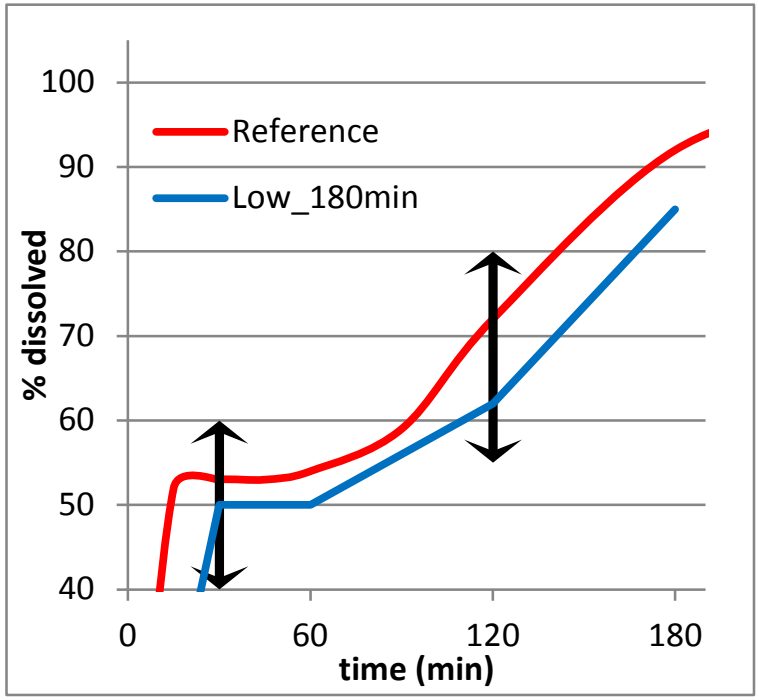
Wide dissolution specification maybe problematic



Condition	No. of subjects	Reference vs. Reference	Reference vs. Low	Reference vs. High
Fasting	12	88.9	0.6	83.5
	24	100	0.6	99.4
	36	100	0.2	100
	48	100	0.2	100
	72	100	0.1	100

Virtual batches meet specification, pass BE?





Risks of BIE are associated with wide specification

Condition	No. of subjects	Reference vs. Low_10%	Reference vs. Low_5%	Reference vs. Low_180min
Fasting	12	10.6	29.6	40.9
	24	14.6	55.0	72.5
	36	16.3	72.7	89.8
	48	22.7	84.6	94.8
	72	31.8	95.7	99.2

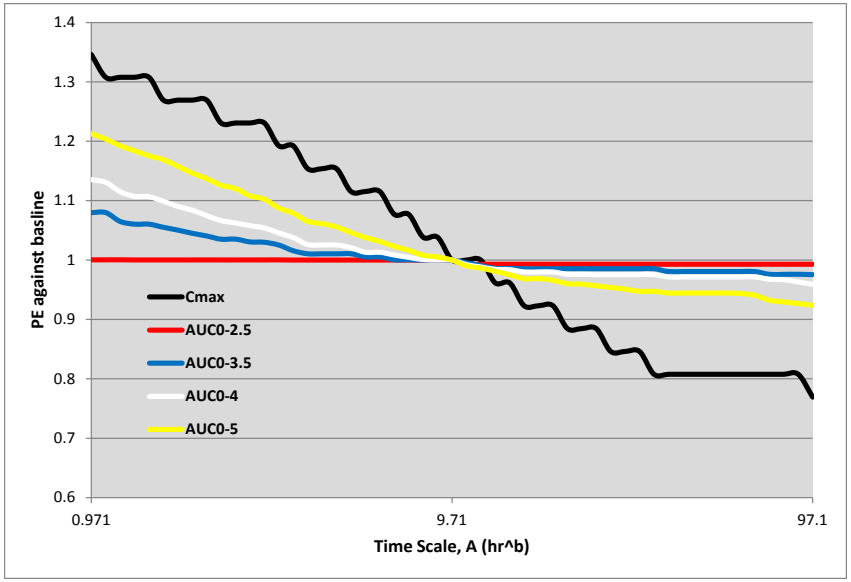
Early partial AUC is sensitive to the change of IR:SR ratio

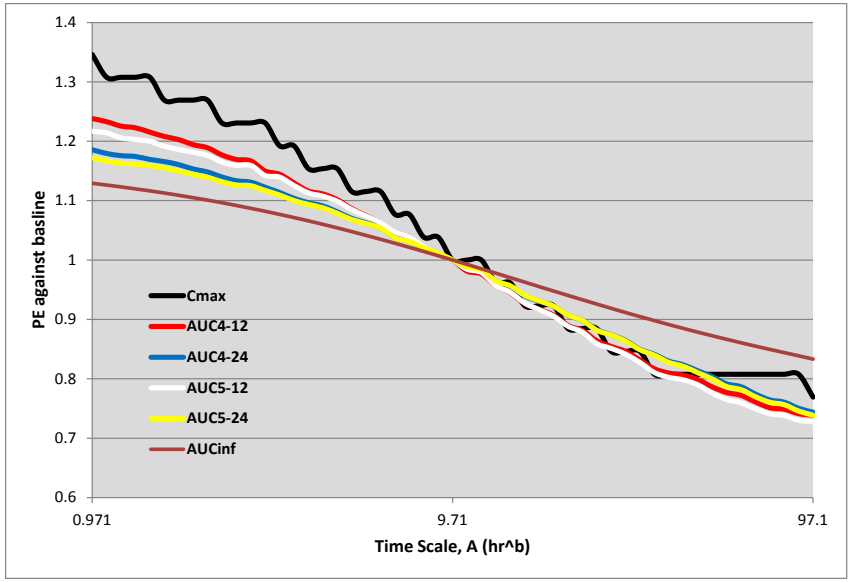
Dextroamphetamine sulfate ER capsules

Trial	No. of Subjects	C_{max}	AUC_{0-4}	AUC_{4-12}	AUC_{4-24}	AUC_{5-12}	AUC_{5-24}
IR:SR vs. IR:SR	12	62.0	71.9	65.7	69.6	63.7	67.2
	24	96.3	97.9	96.5	97.5	96.3	97.0
	36	99.7	99.9	100	99.9	99.9	99.7
	48	100	100	100	100	100	99.9
	72	100	100	100	100	100	100
IR:SR vs. IR+10:SR-10	12	54.9	7.4	56.5	65.4	59.6	64.5
	24	82.5	7.5	84.6	90.6	86.8	91.7
	36	94.3	8.0	95.8	98.7	96.9	98.8
	48	98.7	10.0	99.1	99.8	99.2	99.8
	72	99.8	9.3	99.9	100	99.9	100
IR:SR vs. IR+20:SR-20	12	23.2	0	25.2	43.4	32.3	47.2
	24	39.6	0	44.7	69.0	55.5	74.5
	36	50.7	0	58.3	85.2	71.4	89.7
	48	61.0	0	67.0	90.6	79.7	93.7
	72	78.3	0	83.9	97.8	92.8	98.7

IR, CR:dispersed

Late pAUC does not add additional values to ensure BE





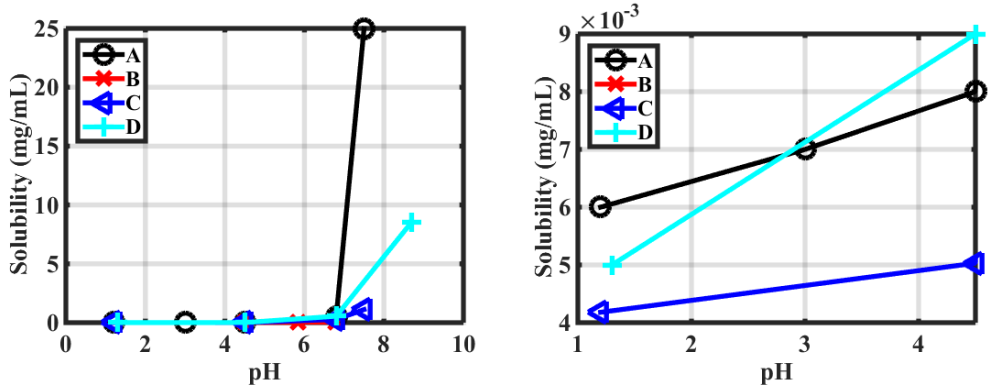
Conclusions (Case Study #1)

- BE most likely can be extrapolated from healthy subjects to other populations.
- Risks of BIE may be associated with batches that meet dissolution specification. Simulations could be conducted to identify the appropriate specification.
- Early pAUC is sensitive to the change in IR:ER ratio.
- Late pAUC does not add additional values to ensure BE.

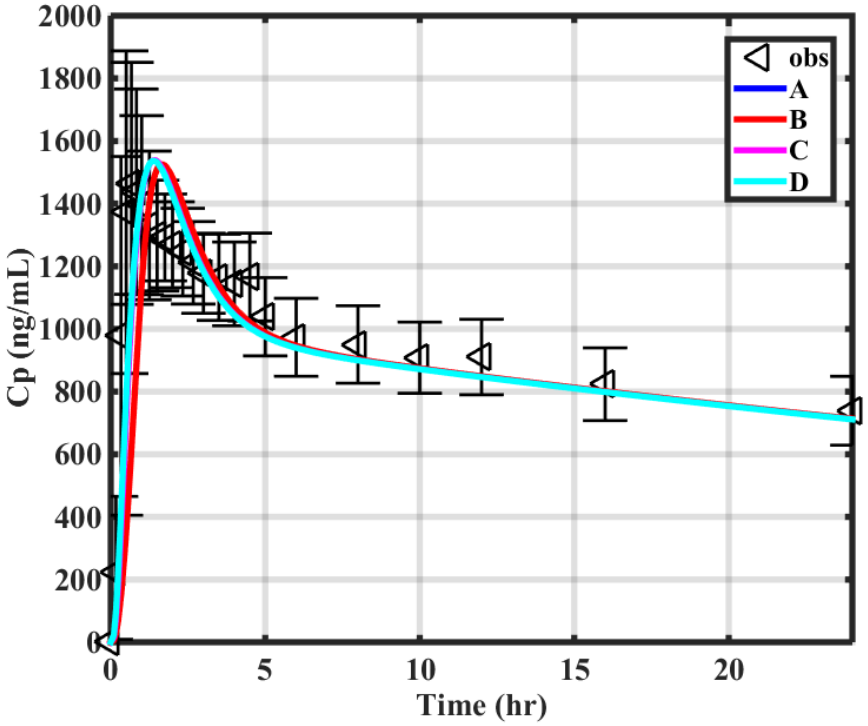
Case Study #3: Warfarin Sodium Tablets

- Specific aims:
  - Explore the impact of critical drug substance properties and formulation factors on in vivo performance
  - Investigate the impact of slower dissolution in acidic pH media on BA/BE
  - Explore in vitro in vivo correlation, if exists

Warfarin Sodium Parameters

API	Warfarin sodium
pKa	5.28
Solubility vs. pH: Various solubility values were reported	
logP	2.6
Permeability	High
Elimination half life (hr)	Average 40 hrs, range 20-60 hrs

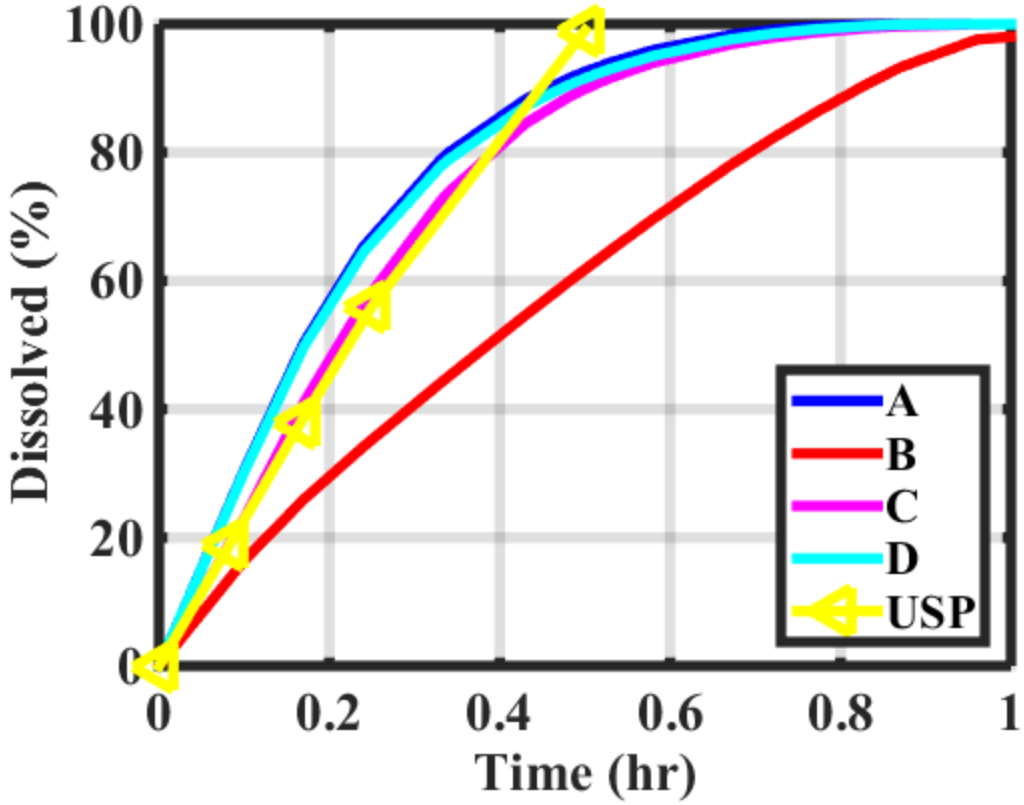
Solubility profile does not impact PK significantly



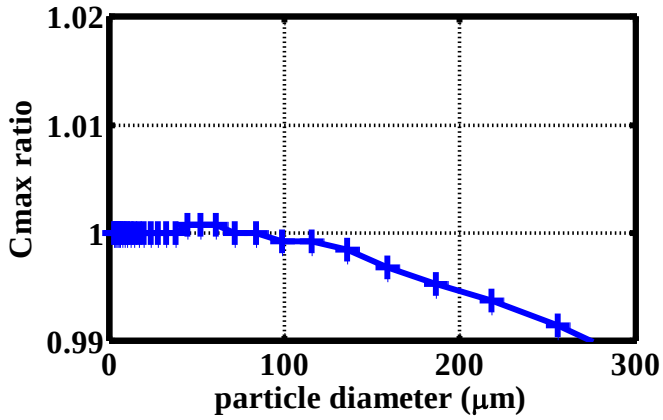
Ratios	Cmax	AUCt
B/A	0.9929	0.9978
C/A	1.0015	0.9998
C/A	0.9999	1.0000

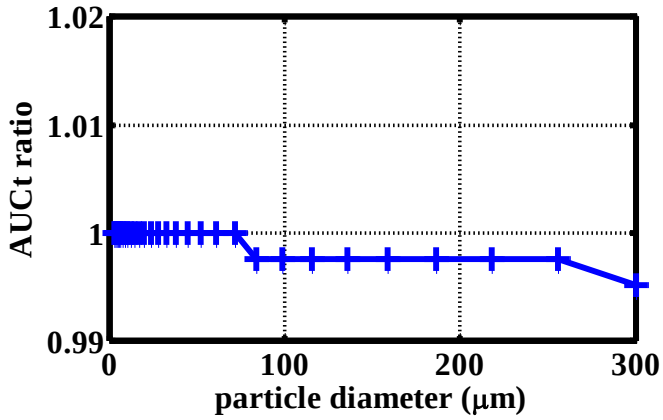
The Johnson model for dissolution: $\frac{dM_D}{dt} = \frac{D_w}{\rho h r_t}\frac{(1+2s)}{s}(C_s - C_l)M_{u,t}$

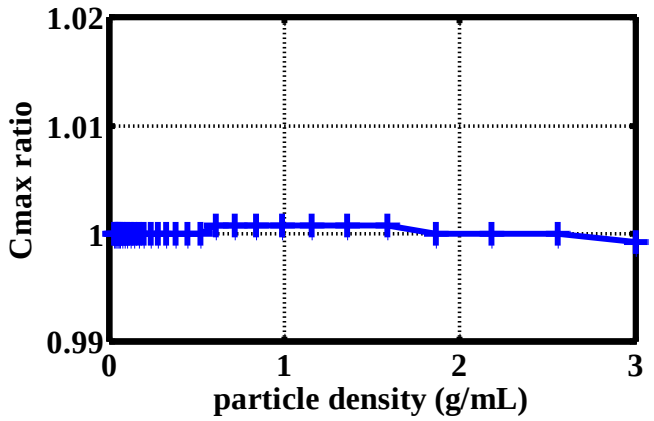
Rapid in vitro and in vivo dissolution

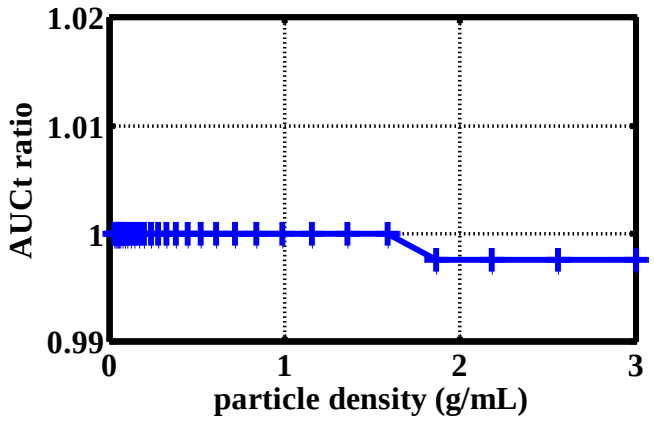


Particle size and density do not impact PK significantly

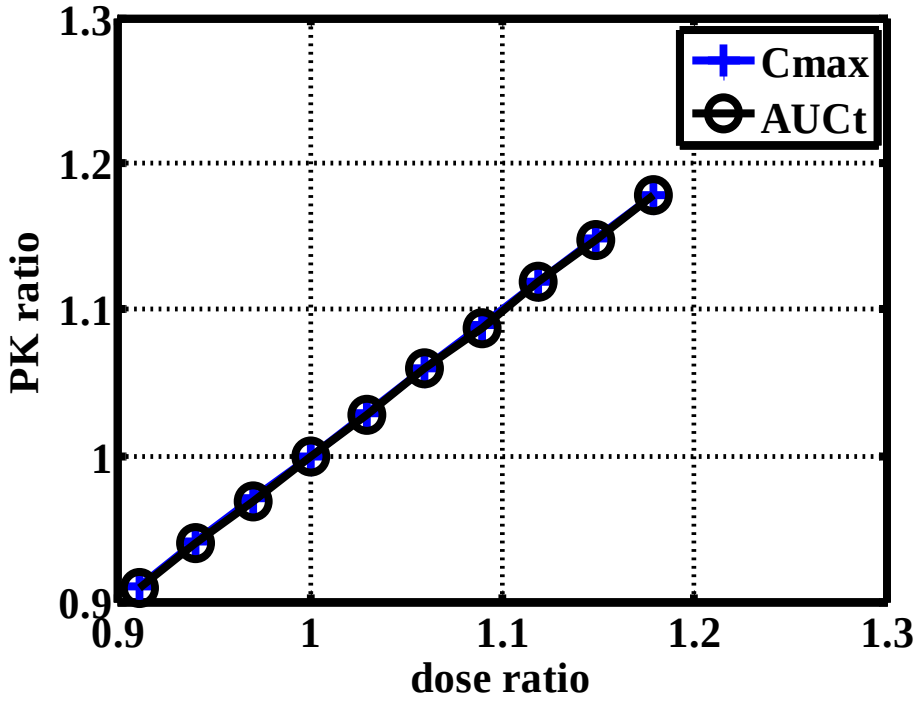








Effect of Dose on PK (under single dose condition)



Exploring the effect of dissolution rate in different pH media

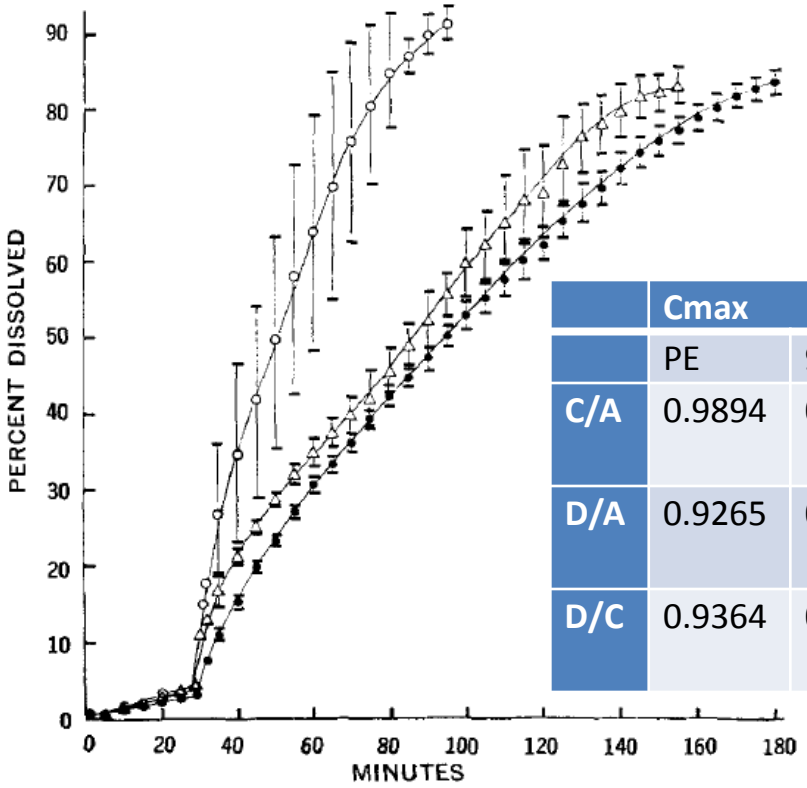
Z factor (mL/mg/s)	pH		
	1.2	4.5	6.8
L	0	0	0
M	0.0063	0.0063	1.49E-04
H (reference)	0.063	0.063	1.49E-03

Slow dissolution in pH 6.8 may affect BE

1.2	4.5	6.8	Cmax Ratio	AUCt Ratio
0	0	0	0.000	0.000
0.0063	0	0	0.031	0.031
0.063	0	0	0.195	0.196
0	0	1.49E-04	0.821	0.970
0.0063	0	1.49E-04	0.822	0.971
0.063	0	1.49E-04	0.823	0.977

$$\frac{dM_D}{dt} = zM_{u,0}\left(\frac{M_{u,t}}{M_{u,0}}\right)^{2/3}(C_s - C_l)$$

Model needs improvement for IVIVC



	Cmax				AUCt			
	PE	90% CI	CV%	Pred.	PE	90% CI	CV%	Pred.
C/A	0.9894	0.8954, 1.0934	13.5616	1.00	1.0206	0.9449, 1.1023	10.4427	1.00
D/A	0.9265	0.8472, 1.0131	12.1280	1.00	1.0592	1.0107, 1.1100	6.3451	1.00
D/C	0.9364	0.8387, 1.0454	14.9682	1.00	1.0592	0.9500, 1.1337	11.9887	1.00

Figure 3—*Dissolution results obtained with Tablets A, C, and I used in Study No. 2. Key: ○, Tablet A; △, Tablet C; and ●, Tablet D Points are averages for five tablets. Bars mark off 1* **SD** *on either sid of the average.*

Wagner et al. (1971) In vivo and in vitro availability of commercial warfarin tablets.

Conclusions (Case Study #3)

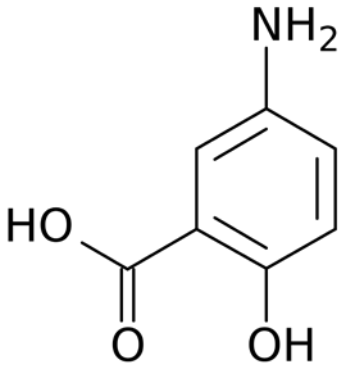
- Model does not capture the early Tmax.
- Solubility in low pH, particle size, and particle density do not have significant impact on BA.
- Dissolution rate at pH6.8 is the most relevant to BA.
- Dose (potency) impacts PK.
- Model needs improvement for IVIVC.

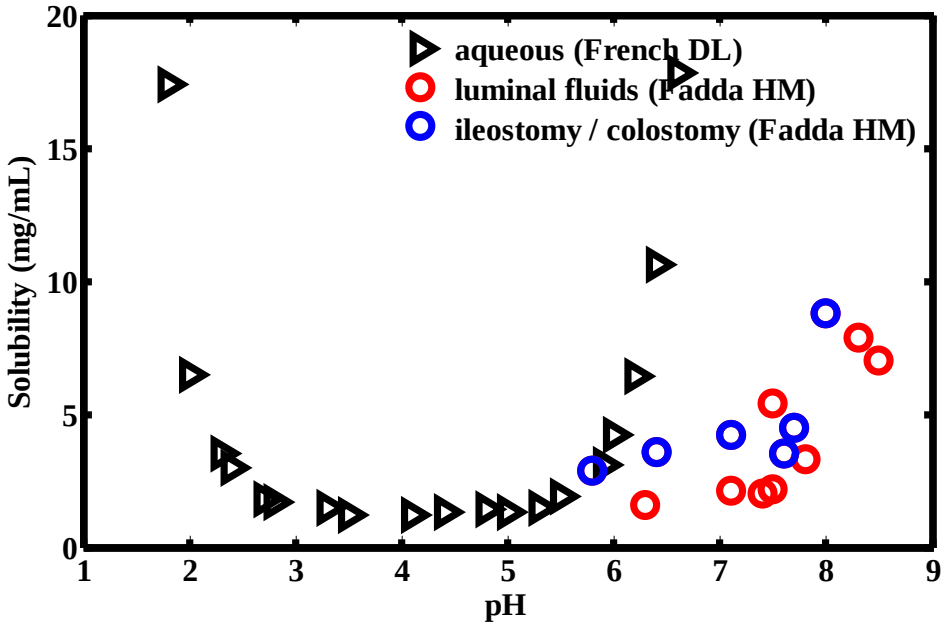
Case Study #4: Mesalamine ER capsules

- Specific aims
  - Assess relationship between GI luminal concentration and plasma concentration for mesalamine extended release capsules.

Mesalamine ER capsules

- pKa: 2.7, 5.8, and 12
- pH dependent solubility
- Half life: 42 mins after iv
- Metabolized by N-Acetyltransferases
- Targets lower GIT and acts topically for ulcerative colitis (UC)
- Modified release dosage form





Approaches

Model was developed based on i.v., suspension, and suppository PK data.

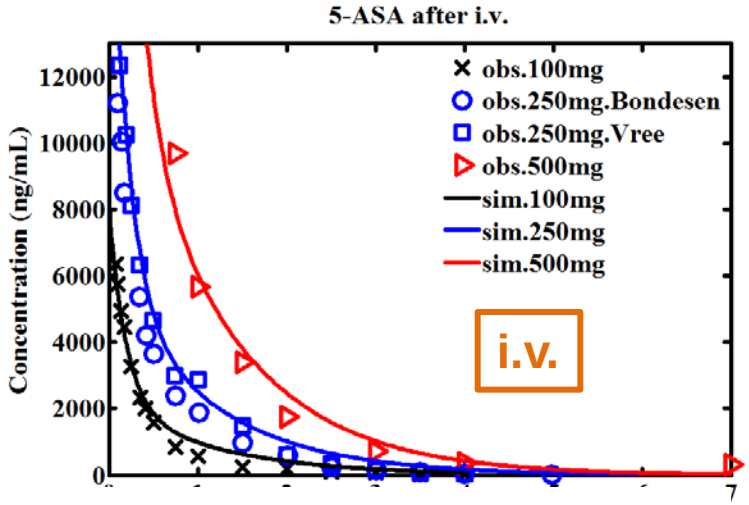
Fit pH dependent dissolution profiles as model input for in vitro dissolution.

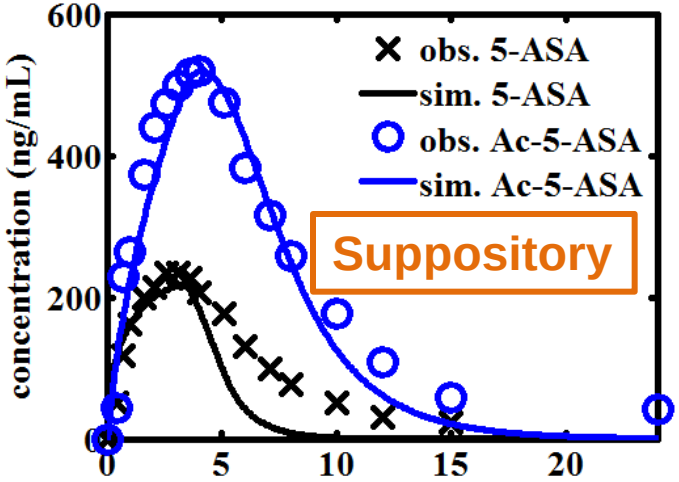
$$\frac{dM}{dt} = zM_{u,0}\left(\frac{M_{u,t}}{M_{u,0}}\right)^{\frac{2}{3}}(C_s - C)$$

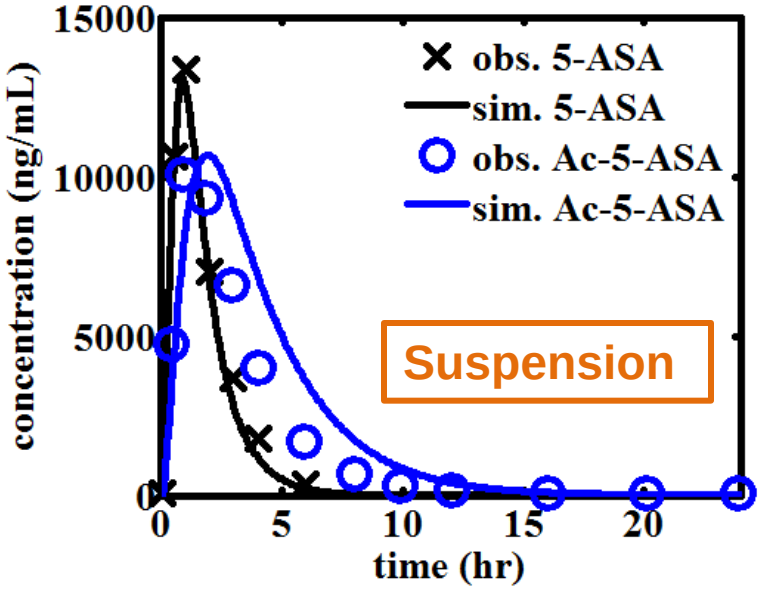
Adjust pH in the GI lumen against observed PK profiles for each subject.

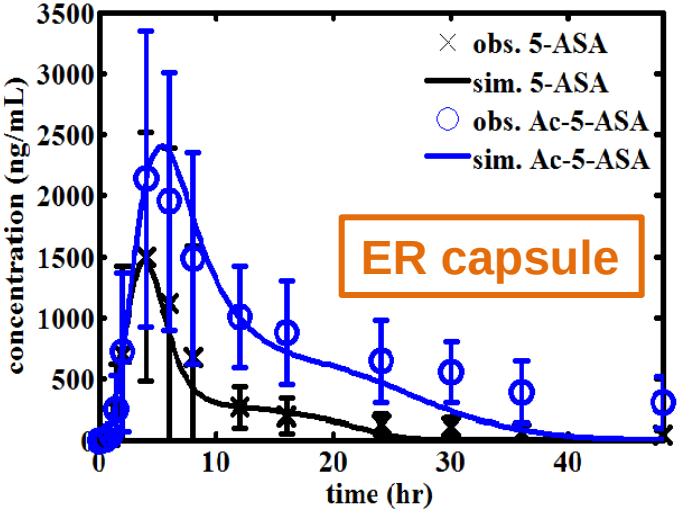
Perform simulation to answer specific questions.

Model Development and Validation

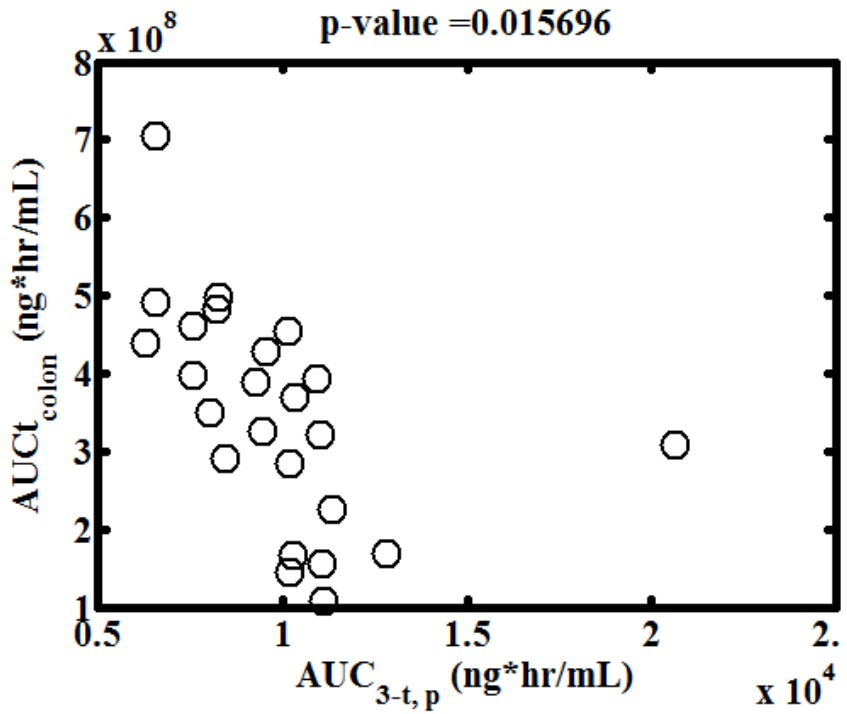


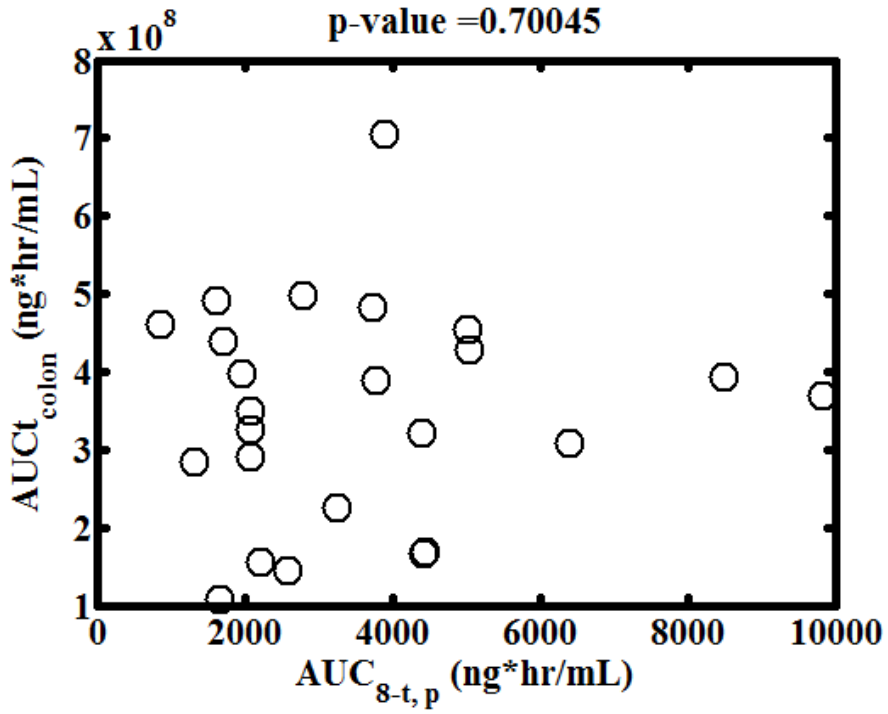






Colon and plasma exposure correlation





Conclusions (Case Study #4)

- Physiologically based absorption model has the potential to predict GI local exposure.

- However, models need to be further validated against observed local concentration which could be very difficult.

Challenges and Opportunities

- Oral administration
  - Colon absorption
  - Impact of hydrodynamics
  - Food effect prediction
- Non-oral administration
  - Model validation
  - Unknown

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Job Opportunities with DQMM (Division of Quantitative Methods and Modeling)

www.fda.gov/GDUFARegScience

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Thank you and questions.