Industry Perspective on Application of Physiologically based Absorption Modeling in Generic Drug Research

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Disclaimer

This presentation and the information herein are the opinions of the presenter, and not of the presenter's current and past employers

Use of PBPK Modeling in Drug Development

Compound & Formulation properties –
- Molecular weight
- Log P/Log D
- pKa
- Solubility (SGF, FaSSIF, FeSSIF, buffer)
- PSD
- Permeability (P_{eff})
- Dose
- Dissolution

+

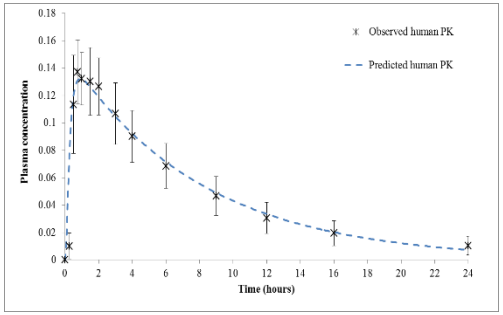
Pharmacokinetics –
- Compartmental PBPK

+

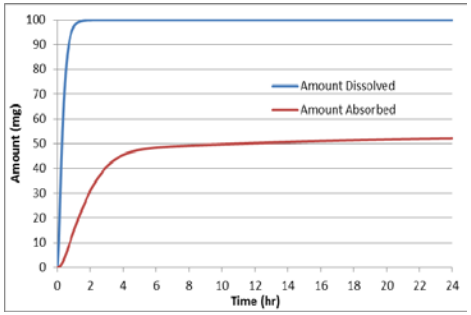
GI Physiology –
- Human, preclinical species
- Fasted vs. fed
- Stomach & intestinal transit times
- Stomach & intestinal pH
- GI volumes
- Length & radius of each segment
- Bile salt concentration

Individual simulation
Population simulation
Parameter sensitivity analysis

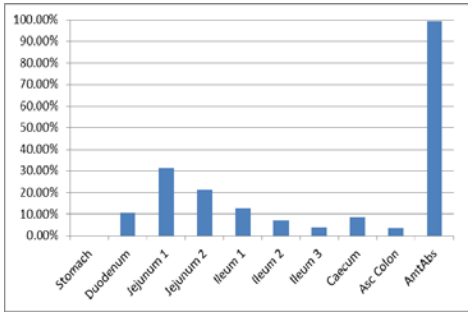
Plasma concentration vs. time profile



Fraction absorbed & fraction dissolved



Regional absorption



- Integration of all available *in vitro* and *in vivo* data to provide a more holistic view of formulation bioperformance
- Provides a more mechanistic understanding of *in vitro* formulation performance and bioperformance
- Allows exploration of multiple options in a much shorter timeframe and with fewer experiments

“Prediction is very difficult,

especially if it’s about the future”

Niels Bohr

“All models are wrong,

but some are useful”

George Box

Application of Absorption Modeling in Development

Application of Absorption Modeling to Predict Bioequivalence Outcome of Two Batches of Etoricoxib Tablets

BE Prediction

Amitava Mitra,[1,3] Filippos Kesisoglou,[1] and Peter Dogterom[2]

Mitra et al. AAPS PharmSci Tech. 16:76-84 (2015)

Application of Physiologically Based Absorption Modeling to Formulation Development of a Low Solubility, Low Permeability Weak Base: Mechanistic Investigation of Food Effect

Food Effect Prediction

Hefei Zhang,[1,2] Binfeng Xia,[1] Jennifer Sheng,[1] Tycho Heimbach,[1] Tsu-Han Lin,[1] Handan He,[1] Yanfeng Wang,[1] Steven Novick,[1] and Ann Comfort[1]

Zhang et al. AAPS PharmSciTech. 15:400-406 (2014)

Physiologically Based Absorption Modelling to Predict the Properties on Pharmacokinetics of Bitopertin

API Particle Size & Formulation Effect

Neil Parrott,[1,4] Dominik Hainzl,[1] Emmanuel Scheubel,[2] Siegfried Krimmer,[2] Christophe Boetsch,[3] Elena Guerini,[3] and Meret Martin-Facklam[3]

Parrott et al. AAPS J. 16:1077-1084 (2014)

Utilizing Physiologically Based Pharmacokinetic Modeling to Inform Formulation and Clinical Development for a Compound with pH-Dependent Solubility

DDI with Stomach Acid Reducing Agents

JOHN CHUNG,[1] MAURICE EMERY, ZHIGANG YU,[3] JAN WAHLSTROM[2]

Chung et al. J Pharm Sci. 104:1522-1532 (2015)

Application of Absorption Modeling in Rational Design of Dru Quality-by-Design Paradigm

Qbd Application

Filippos Kesisoglou[1,2] and Amitava Mitra[1,2]

Kesisoglou & Mitra. AAPS J. 17:1224-1236 (2015)

Physiologically Based Absorption Modeling for Amorphous Solid Dispersion Formulations

Amorphous Solid Dispersion

Amitava Mitra,* Wei Zhu, and Filippos K

Mitra et al. Mol. Pharm. 13:3206-3215 (2016)

SIMULATION OF THE *IN VIVO* EX IBUPROFEN BASED ON *IN VITRO* PROFILES FROM SOLID DOSAGE FORMS

Dissolution Changes

DANIELA ELEN DREEA
STĂNESCU[2*], M NDRU
BURCEA DRAG VIAN
ȘTEFAN RĂDULESCU[4]

Popa et al. Farmacia. 62:483-493 (2014)

PBPK Models in Regulatory Submissions

The Utility of Modeling and Simulation in Drug Development and Regulatory Review

SHIEW-MEI HUANG, DARRELL R. ABERNETHY, YANING WANG, PING ZHAO, ISSAM ZINEH

Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland

Huang et al. J. Pharm Sci. 102(9):2912-23 (2013)

Best Practice in the Use of Physiologically Based Pharmacokinetic Modeling and Simulation to Address Clinical Pharmacology Regulatory Questions

P Zhao[1], M Rowland[2,3] and S-M Huang[1]

Zhao et al. Clin Pharm & Ther. 92:17-20 (2012)

Application of Physiologically Based Absorption Modeling for Amphetamine Salts Drug Products in Generic Drug Evaluation

ANDREW H. BABISKIN, XINYUAN ZHANG

Babiskin & Zhang. J Pharm Sci. 104:3170-3182 (2015)

Virtual Bioequivalence

- Use of physiological absorption model to predict the outcome of a BE study comparing test and reference formulations
  - Conduct “x” number of virtual trials in a model generated population in crossover manner to assess the outcome of a BE study
- Applications -
  - Predict outcome of formulation changes on BE outcome
  - Minimize the number of “pilot” PK studies
  - Provide more confidence in the outcome of a “pivotal” BE study

Possible Improvements in Current Absorption Models (*not an exhaustive list…)*

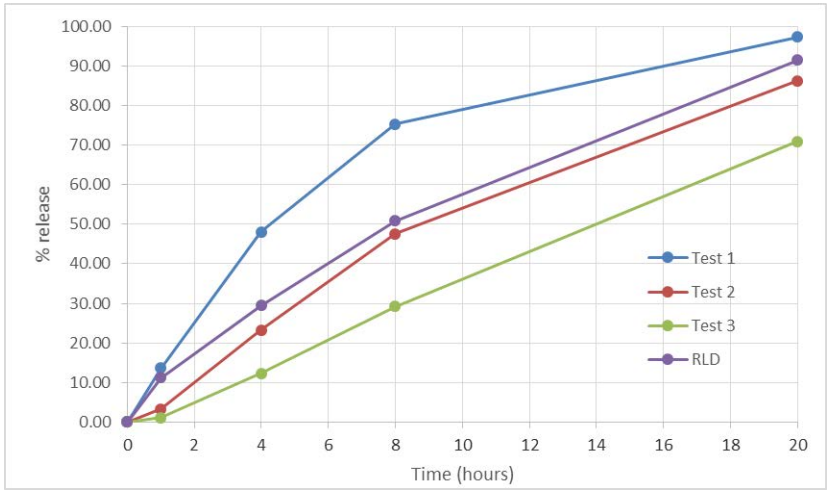
- Intra-individual variability in physiological parameters for accurate prediction of bioequivalence
- Better colonic absorption model (water volume & permeability) for accurate prediction of controlled release formulations
- Food effect - ability to assess impact of high, medium, low fat/calorie meals
- Simultaneous input of 2 solubilities e.g. crystalline/amorphous, salt/free form, 2 polymorphs
- Apriori prediction of precipitation for weak bases and amorphous formulations
- Addition of UWL/mucus layer and impact on permeability
- Availability of models for specific populations (e.g. oncology)
- Etc…

A. Mitra, B. Abrahamsson, T. Heimbach, S. Beilles, *An Assessment of Potential Areas of Improvement in the Application of Current Oral Absorption Modeling tools*, Presented at 2015 AAPS Annual Meeting

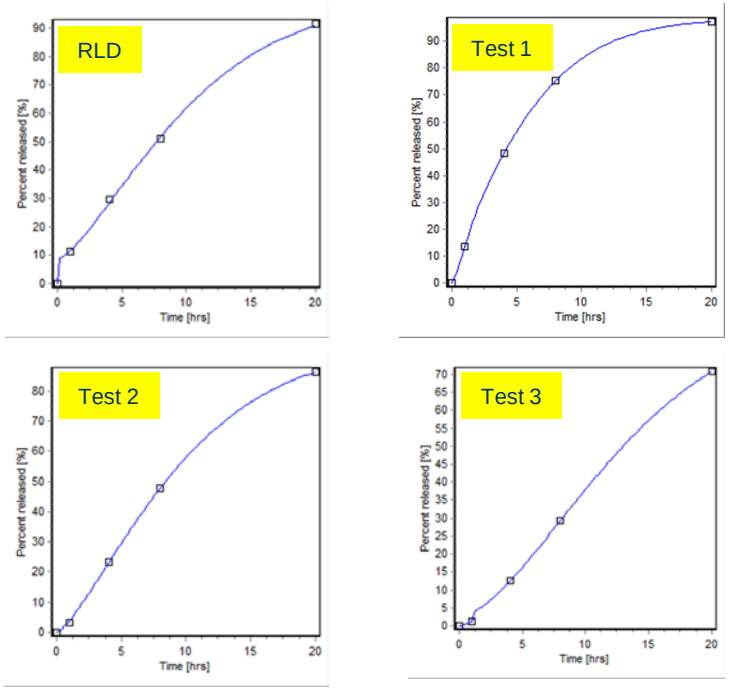
Case Study 1: Virtual BE for Controlled Release Formulation

- BCS 1 compound
- Controlled Release formulation

USP-2, pH 6.8

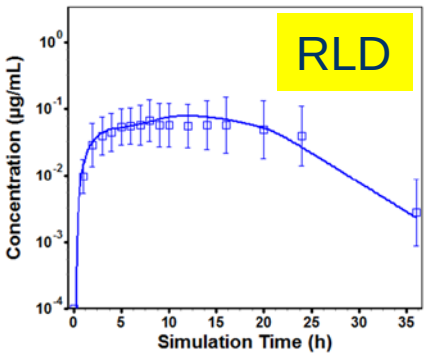


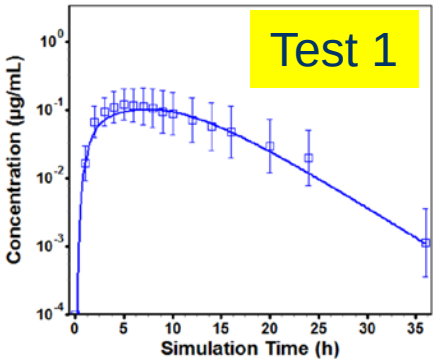
Dissolution data fitted to double Weibull function

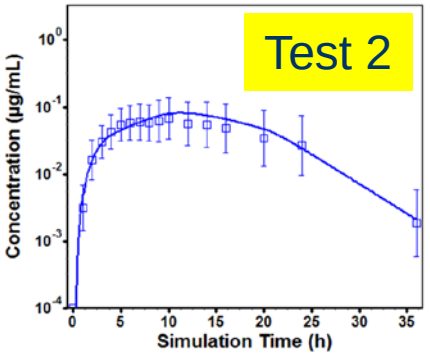


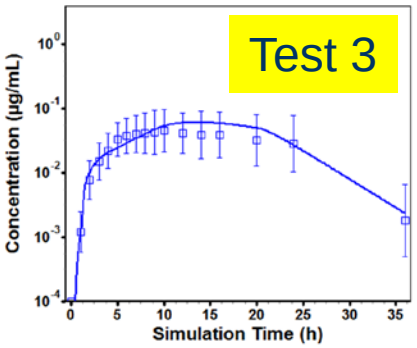
Single Simulations to Assess Formulation Performance

Fasted State

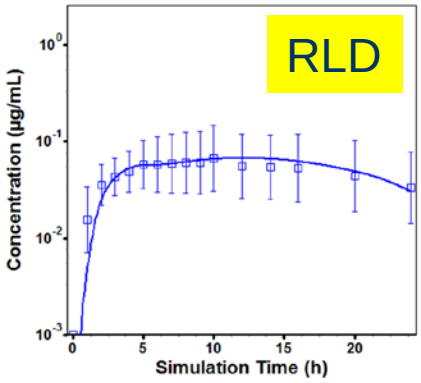


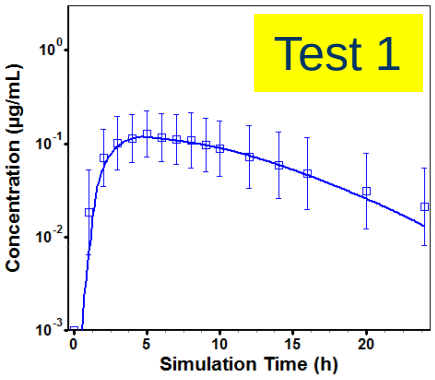


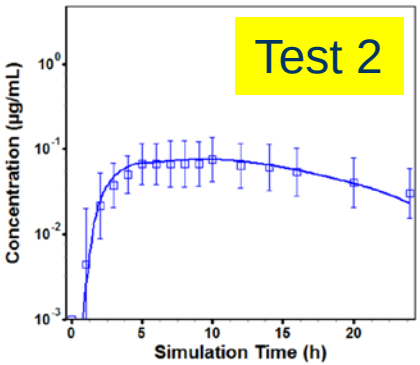


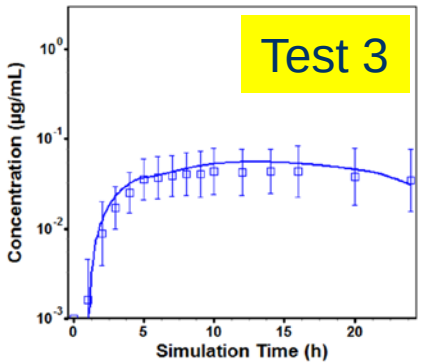


Fed State



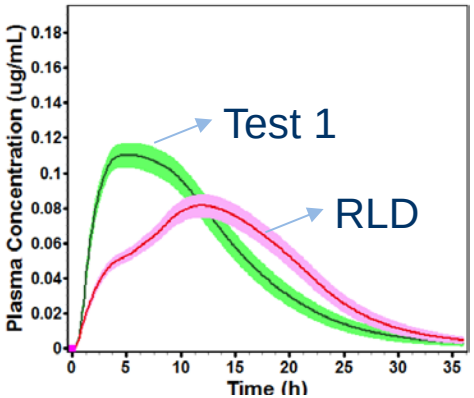


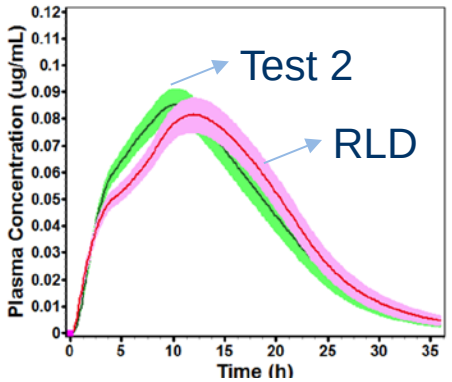


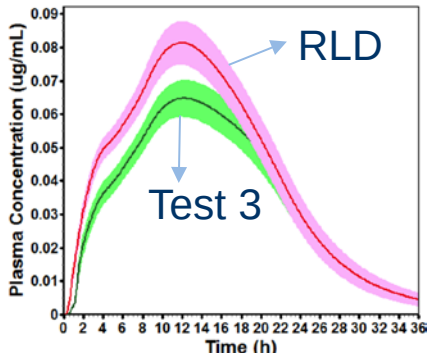


Population Simulations to Assess Fasted BE Study between RLD and Test Tablets

- 10 population simulations were conducted in a cross-over manner with 25 subjects in each study
- The GMR & 90%CI were calculated separately

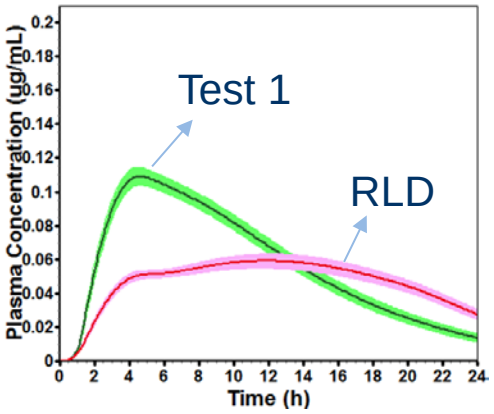


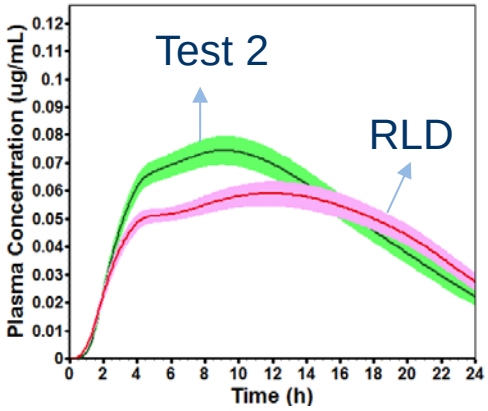


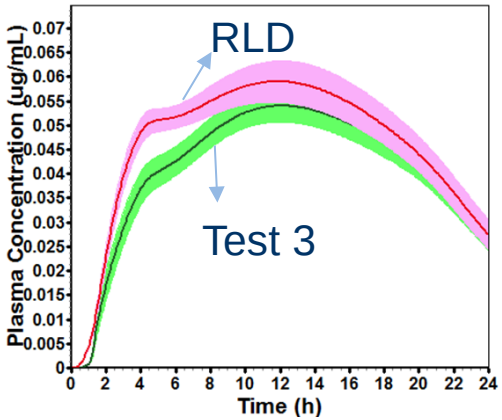


	AUC_{0-t} GMR (90% CI)	C_{max} GMR (90% CI)	AUC_{0-t} GMR (90% CI)	C_{max} GMR (90% CI)
	Observed		Predicted	
Test 1 vs. RLD	1.11 (0.99-1.23)	1.83 (1.67-1.98)	1.09 (0.91-1.18)	1.54 (1.23-1.77)
Test 2 vs. RLD	0.86 (0.74-0.98)	1.02 (0.87-1.17)	0.95 (0.89-1.01)	1.10 (0.88-1.02)
Test 3 vs. RLD	0.75 (0.63-0.87)	0.75 (0.59-0.91)	0.84 (0.77-0.99)	0.84 (0.70-0.95)

Population Simulations to Assess Fed BE between RLD and the Test Tablets



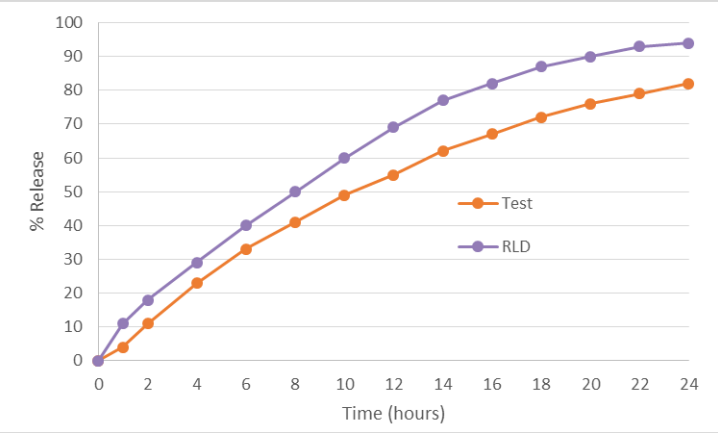




	AUC_{0-t} GMR (90% CI)	C_{max} GMR (90% CI)	AUC_{0-t} GMR (90% CI)	C_{max} GMR (90% CI)
	Observed		Predicted	
Test 1 vs. RLD	1.29 (1.18-1.39)	2.07 (1.88-2.27)	1.20 (1.01-1.27)	1.85 (1.71-2.01)
Test 2 vs. RLD	1.06 (0.95-1.17)	1.15 (0.96-1.35)	0.95 (0.89-1.19)	1.21 (1.05-1.41)
Test 3 vs. RLD	0.82 (0.70-0.92)	0.72 (0.52-0.91)	0.88 (0.71-1.01)	0.92 (0.81-1.05)

Projection of Pivotal BE Study in Fasted and Fed States

USP-2, pH 6.8



Outcome of 10 Virtual Trials for Each Formulation in Fasted State

		Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7	Trial 8	Trial 9	Trial 10	Average
RLD	AUC											
	C_{max}											
Test	AUC											
	C_{max}											

Projection of Pivotal BE Study in Fasted and Fed States

M&S Projections

	AUC_{0-t} GMR (90% CI)	Cmax GMR (90% CI)
Test vs. RLD (*fasted*)	0.86 (0.82-0.92)	0.88 (0.83-0.95)
Test vs. RLD (*fed*)	0.99 (0.95-1.04)	1.01 (0.97-1.06)

Observed BE Data

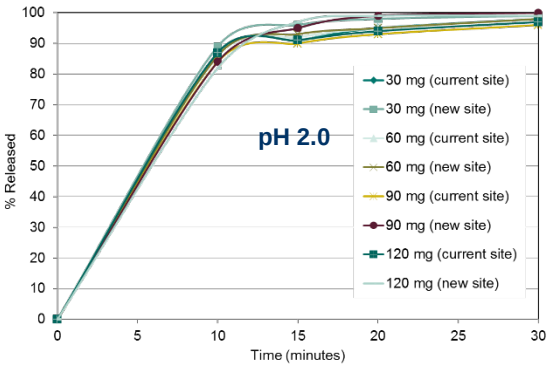
	AUC_{0-t} GMR (90% CI)	Cmax GMR (90% CI)
Test vs. RLD (*fasted*)	0.89 (0.85-0.99)	0.90 (0.86-0.95)
Test vs. RLD (*fed*)	1.00 (0.94-1.07)	0.99 (0.93-1.08)

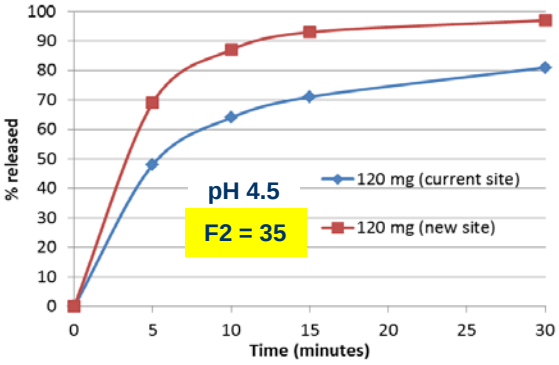
Case Study 2: Dissolution Input for Prediction of BE for IR Product

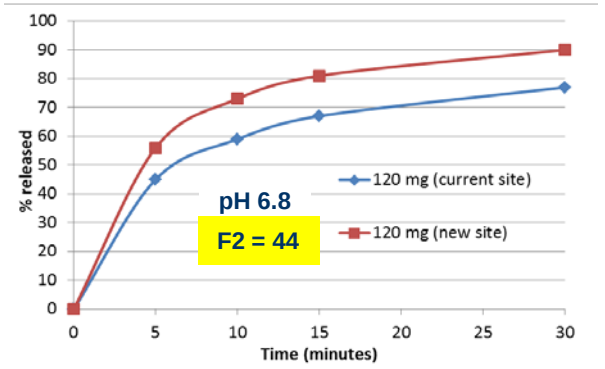
Etoricoxib
BCS II compound

pH 2.0 =25.1 mg/mL
pH 3.07 = 2.01 mg/mL
pH 4.01 = 0.3 mg/mL
pH 5.03 = 0.09 mg/mL
pH 6.9 = 0.05 mg/mL

Dissolution of etoricoxib tablets at three pH conditions

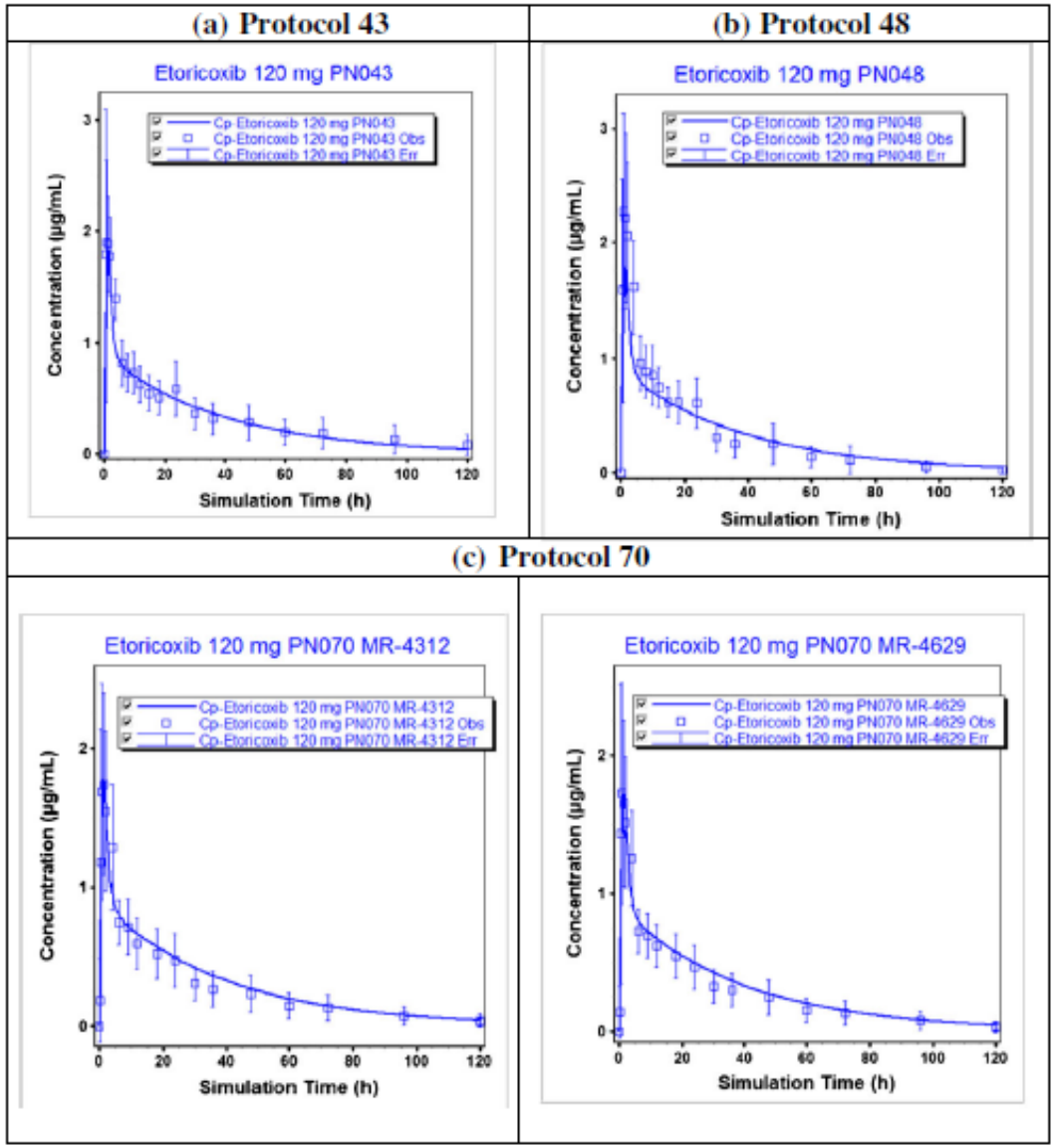






Mitra, A., et al., AAPS PharmSci Tech, 16:76-84 (2015)

Assessment of the Model Performance against the Observed Clinical Data



Predicted Human PK & BE Study Outcome

M&S Projections

	$AUC_{0\text{-}120\ hr}$ (%CV)	C_{max} (%CV)	Relative $AUC_{0\text{-}120\ hr}$	Relative C_{max}
pH 2.0 dissolution				
120 mg (current site)	35.9 (15.8%)	1.81 (14.8%)	--	--
120 mg (new site)	37.1 (15.3%)	1.85 (14.4%)	1.03	1.02
pH 4.5 dissolution				
120 mg (current site)	34.4 (16.3%)	1.65 (18.6%)	--	--
120 mg (new site)	35.8 (15.3%)	1.82 (14.4%)	1.04	1.10
pH 6.8 dissolution				
120 mg (current site)	30.8 (17.2%)	1.50 (18.6%)	--	--
120 mg (new site)	34.1 (15.1%)	1.71 (19.1%)	1.11	1.14

Observed BE Results

PK Parameters	Treatment		Geometric Mean Ratio (A vs. B)	90% Confidence Internal (A vs. B)
	New Site	Current Site		
$AUC_{0\text{-}\infty}$ (µg*hr/mL)	32.3 ± 13.1	32.1 ± 14.6	1.01	0.97, 1.06
C_{max} (µg/mL)	1.94 ± 0.47	1.98 ± 0.41	0.97	0.89, 1.06
T_{max} (hr)	1.25 (0.5-2.0)	1.00 (0.5-4.0)	–	–

Dissolution at pH 2.0 is the most clinically relevant in this specific case

17

Conclusion

- Current industry experiences highlight the increasing value of PBPK modeling applications in drug development
- Use of PBPK modeling and simulation has been recommended and accepted by regulatory agencies
- There is tremendous potential for application of modeling tools in generic drug development
  - More publications are needed with examples of where it works & where it doesn’t
  - An area to explore bioperformance of formulations that are not Q1/Q2 to RLD or get around formulations
  - Develop knowledge base of models that may be suitable for virtual BE trials
  - Complex dosage forms such as long acting injectables (suspension, implant)

Future Use of Virtual BE

- Expand BCS class waivers
- Do we do too many fed BE studies?
- Describe what happens in steady state BE study
- Describe what would happen in a steady state BE study in patients
- Conclude risk in patient population that are not studied

21

Slide courtesy of Rob Lionberger (FDA/CDER/OGD)

Presented at 2016 AAPS Annual Meeting *(Role of PBPK based virtual trials modeling in generic product development and regulation)*