The Utility of in silico PBPK Absorption Modeling and Simulation as a Tool to Develop Bio-Predictive Dissolution Methods

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Outline

- Introduction
- Impacts made by Physiologically based PK modeling at OGD/FDA
- Case Presentation
  - Oxybutynin HCl ER Tablets
- Summary
- Relevant GDUFA funded research/contracts

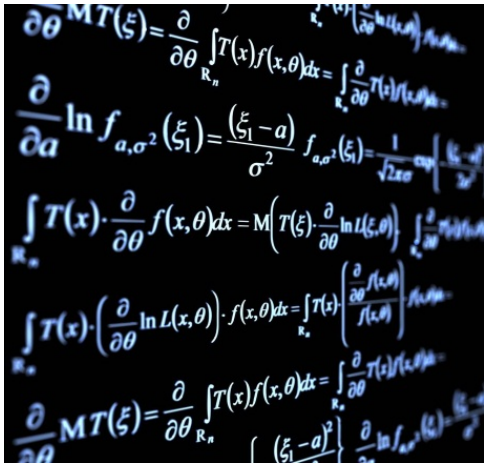
Quantitative Tool Sets

Non-Oral Drug

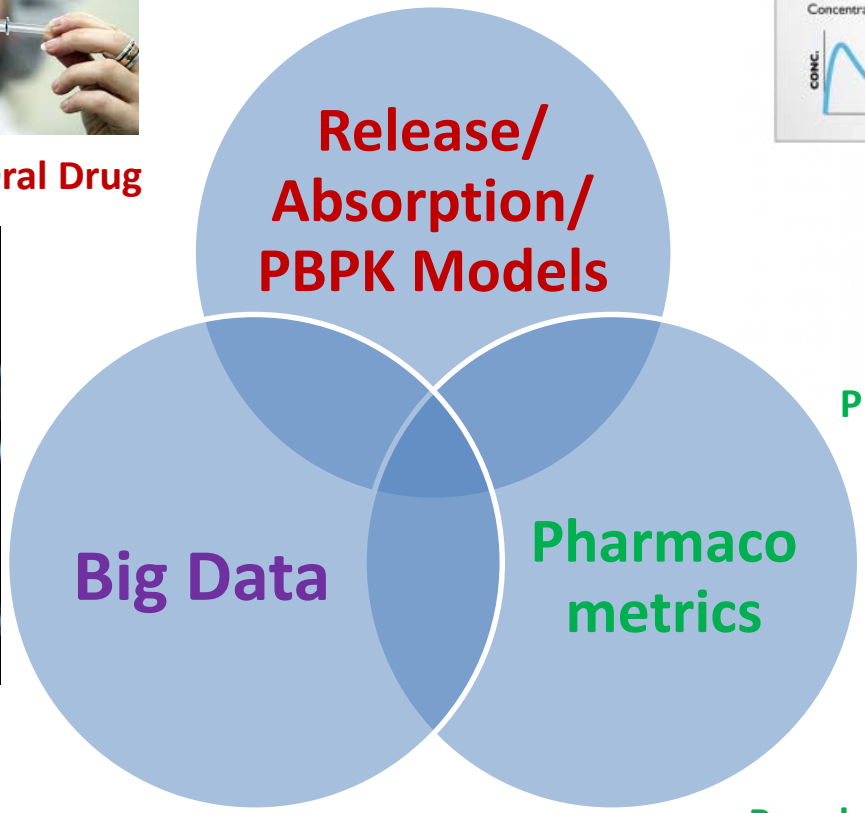
Oral Drug

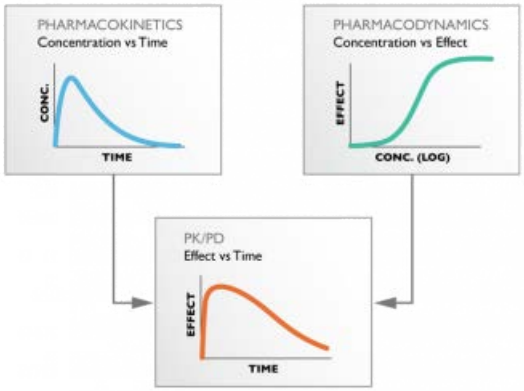
Our Goal is to support

- Generic drug research
- Policy development
- Regulatory decisions

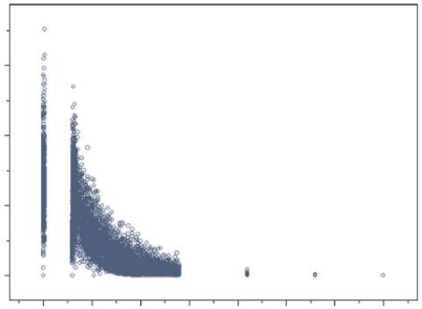


Analytics for complex products
Systems pharmacology
Risk models
Business process models





PK-PD model



Population model

Modeling and Simulation Impact Various Regulatory Activities in the Office of Generic Drugs (Calendar Year 2016)

Type	No.	Examples
ANDA Reviews & Citizen petitions	22	❖ Implement clinical relevant PK metrics for BE assessment
Pre-ANDA interactions (including CC)	26	❖ Development of BE criteria for analgesics ❖ Assessment of BE standards for GI locally acting products ❖ Simulation of in vivo alcohol dose dumping studies
BE Guidances	31	❖ Simulations for the development of BE criteria for HVDs and NTI drugs
Regulatory Research Studies	30	❖ Pharmacokinetic(PK)/Pharmacodynamic (PD) modeling and simulation to determine the appropriate study design and evaluate clinical endpoint sensitivity for BE assessment

ANDA: abbreviated new drug application; BE: bioequivalence: CP: citizen petition; CC: controlled correspondence; GI: gastrointestinal; HVD: highly variable drugs; NTI: narrow therapeutic index.

Modeling and Simulation for Generic Drug Development

- OGD uses modeling and simulation for guidance development and for regulatory decisions regarding novel approaches for BE assessment

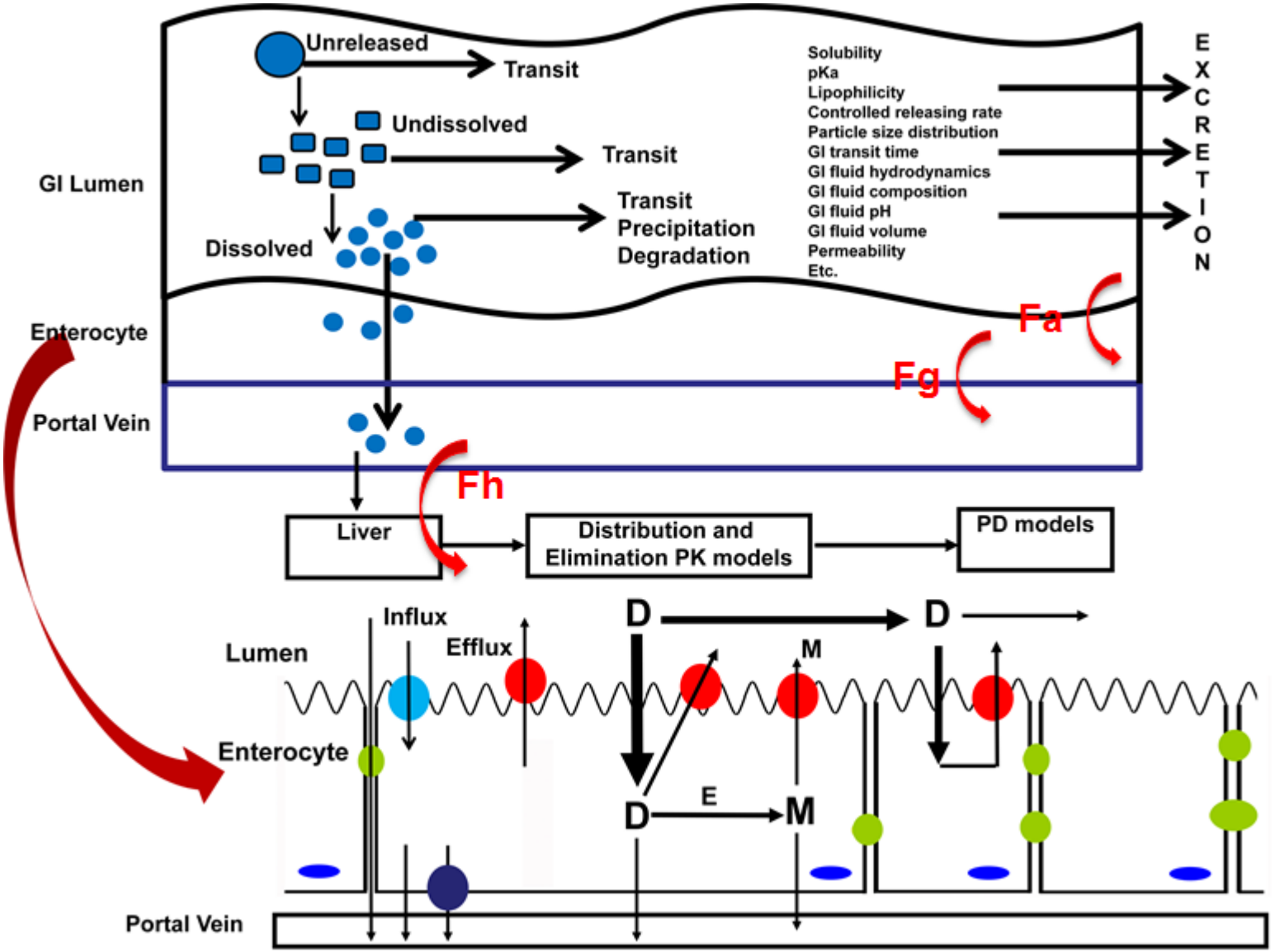
- The generic industry is encouraged use Model-Informed Drug Development (MIDD) before they propose novel methods in an ANDA to support new BE approaches

- Vision: Accelerate development and review of complex and locally acting products by modeling and simulation

PBPK Models

- Oral absorption models are established and commercially available and are useful to FDA and the generic drug industry
- Non-oral absorption models are at an earlier stage of development but are critical to FDA and the generic drug industry in introducing new approaches for bioequivalence assessment of locally acting drugs

Factors Affecting Oral Absorption



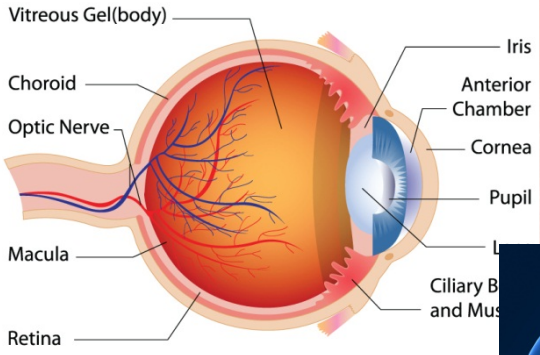
Source: Xinyuan (Susie) Zhang

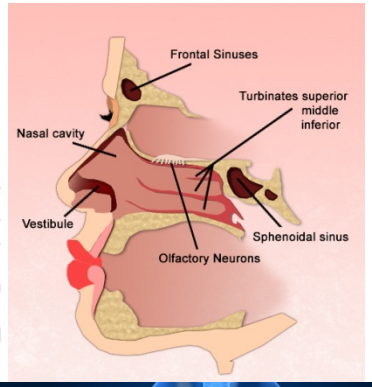
Physiologically Based Models

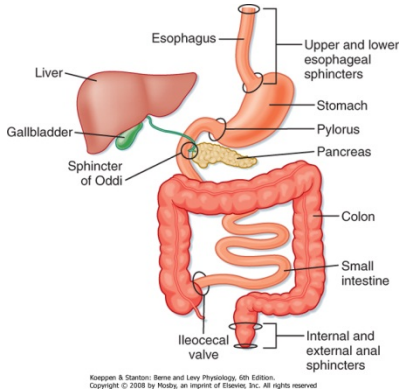
Drug Substance
Formulations
Physiological System

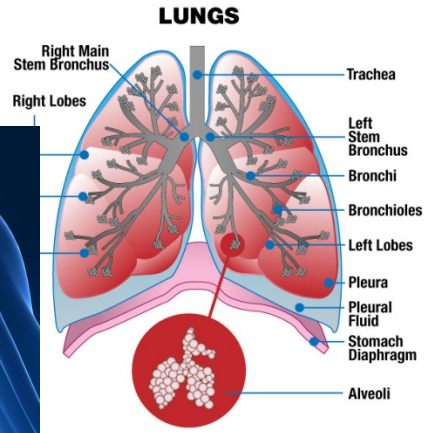
→ **In vitro testing** →

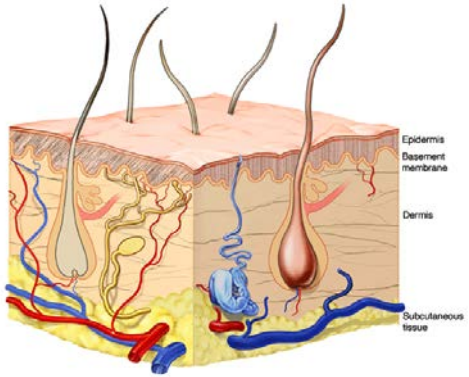
In vivo Performance





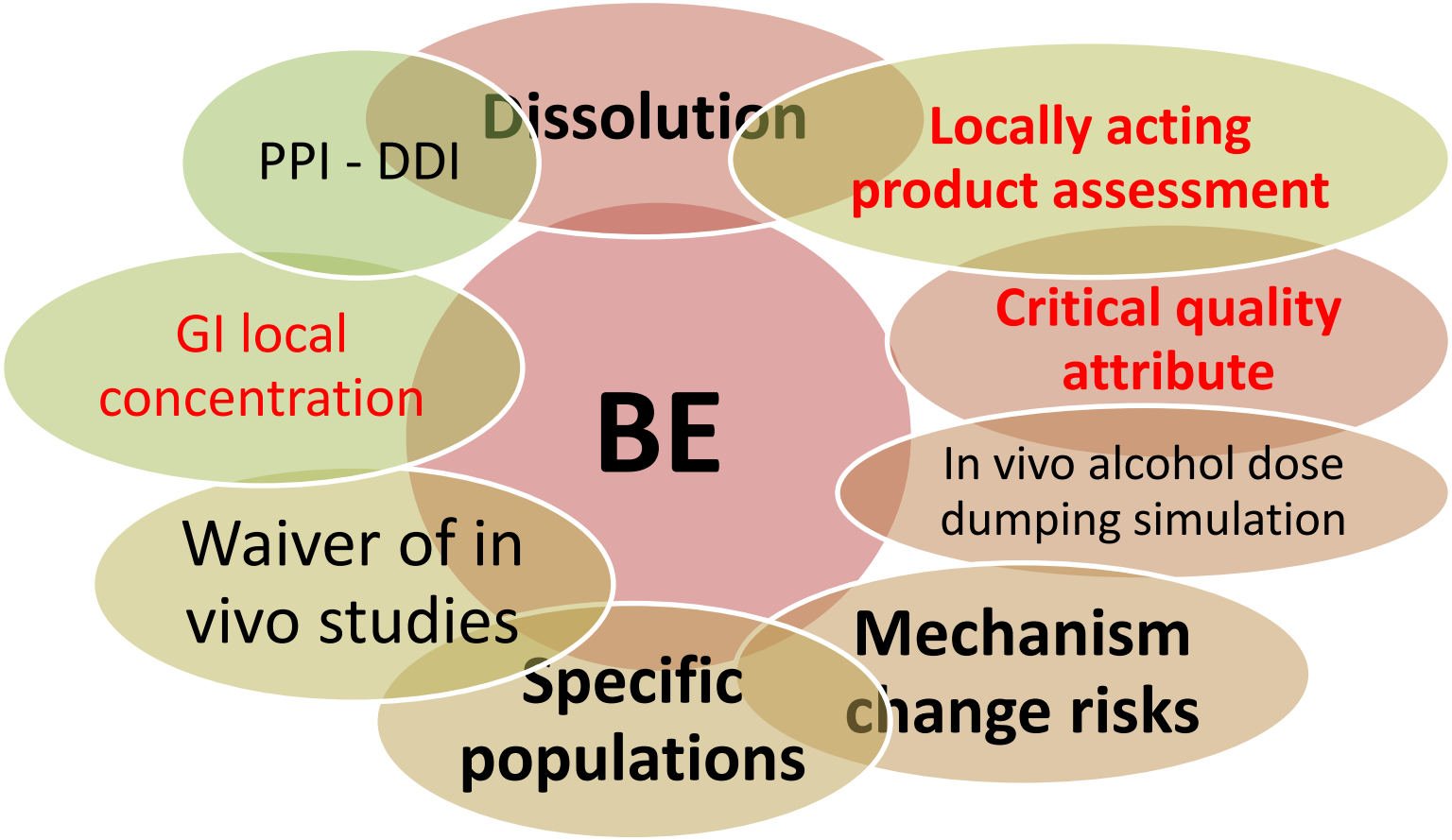






Based on the publication by Jiang W, Kim S, Zhang X, Lionberger RA, Davit BM, Conner DP, Yu LX. Int J Pharm. 2011 Oct 14;418(2):151-60.

General PBPK Model Applications for Generic Products



Increasing trends in using PBPK models to support regulatory decision making in the realm of generic drug development

BE: bioequivalence; PPI : proton pump inhibitor; GI: gastrointestinal ; DDI: drug-drug interaction

Highlights of PBPK Impacts (Year 2016)

Category	Example Drug	Impact on regulatory decision making
Dissolution	Fingolimod, Oxybutynin	Risk assessment for not conducting in vivo studies for lower strength generic products when bioequivalence has been established at higher strengths
Product quality	Prasugrel	Conclusion that less than 20% free base in prasugrel HCl product ensures in vivo BE of the generic product including subjects on PPI
Mechanism change risks	Venlafaxine	Model predicted that a delayed onset of venlafaxine release up to 4 h predicted to demonstrate BE for the openable matrix release mechanism against the osmotic pump based release mechanism
PPI effect	Several ER products	Risk assessment of changing drug release to a PH dependent mechanism
PK metrics determination	Mesalamine Suppositories	Determination of PK metrics for BE evaluation
Alcohol dose dumping	Metformin Hydrochloride ER Tablet	Assessment of alcohol dose dumping potential
Virtual simulation	Methylphenidate	Assessment of using PBPK model in combination with a two way crossover study to meet the guidance recommendation of a four way crossover study for BE assessment

PPI: proton pump inhibitor; ER : extended release

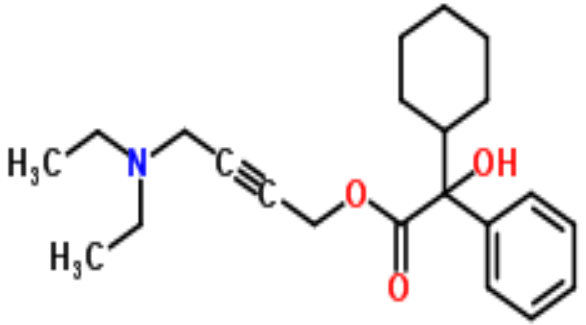
Case: Oxybutynin HCl ER Tablets

- **Intended Purpose of the Model**
  - To quantitatively describe the delay in oxybutynin absorption when oxybutynin is formulated as an enteric-coated matrix tablet compared to an OROS® tablet
  - To assess the risk of not conducting BE study for the lower strengths of oxybutynin extended release products
- **Model Development and Parameter Estimation**
  - In vivo dissolution

Source: Eleftheria Tsakalozou & Xinyuan (Susie) Zhang

Oxybutynin Properties

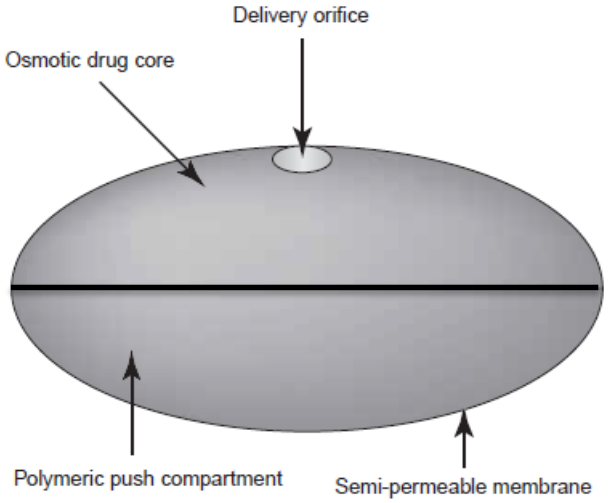
- Relief from urinary and bladder difficulties (frequent urination, inability to control urination)
- High solubility, High permeability (BCS I)
- pKa: 7.88 (base)
- logP: 4.87
- Solubility= 0.29 mg/mL (pH=9.39)
- Peff= 2.67 x 10^{-4} cm/sec (human)
- Half-life: 2-3 h
- Metabolized by CYP3A4 (gut, liver)
- No reported food effect

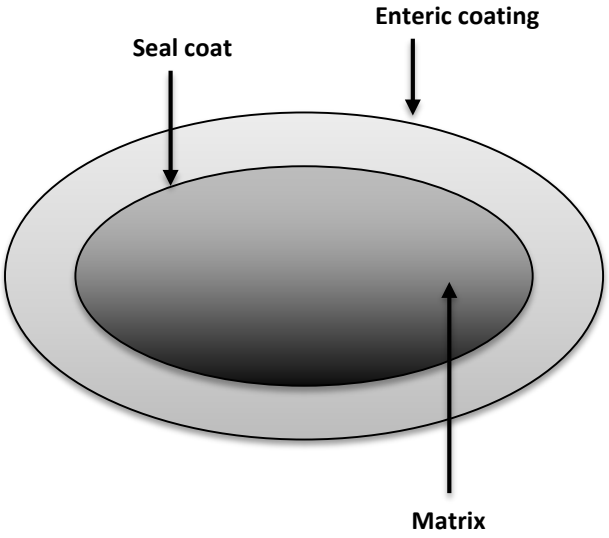


Certain properties are predictions from GastroPlus, ADMET Predictor v7.2.0.0, Prescribing Information Ditropan XL, Drugs@FDA

Kennelly et al. Rev Urol 12, 12-19 (2010), Guay et al. Clin Pharmacokinet 42, 1243-1285 (2003), Yaich et al. Pharmacogenetics 1998, 8:449-451, Benet et al. *AAPS J* **13**, 519-547 (2011)

Formulation Attributes





Ditropan XL®
Osmotic pump/OROS: controlled rate drug delivery system
pH or gastrointestinal motility-independent

Hydrophilic Matrix Tablet with enteric coating

Abramov et al, Expert Opin Pharmacother. 2004 Nov;5(11):2351-9

PBPK Absorption Modeling Approaches

Model was developed based on in vitro data (drug physicochemical properties and metabolism) and i.v. and oral PK data.

Fit in vitro dissolution profiles as model input- Weibull function and establish in vitro-in vivo correlations (IVIVC) or relationships (IVIVR).

Leverage human observed data obtained from bioequivalence studies evaluating osmotic pump and enteric-coated matrix delivery systems.

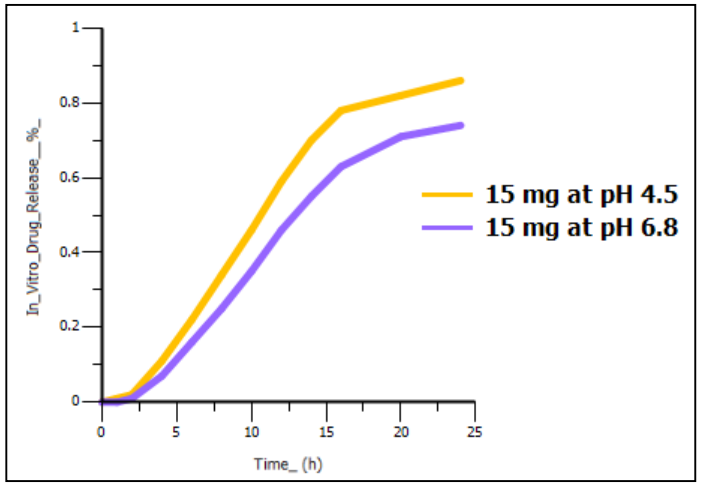
$$\%DrugRelease = Max\ x\left(1 - f1\ x\ \exp[\frac{-(t-Tlag)^{b1}}{a1}] - f2\ x\ \exp[\frac{-(t-Tlag)^{b2}}{a2}]\right)$$

Perform simulations to answer specific questions utilizing the developed IVIVC/IVIVRs.

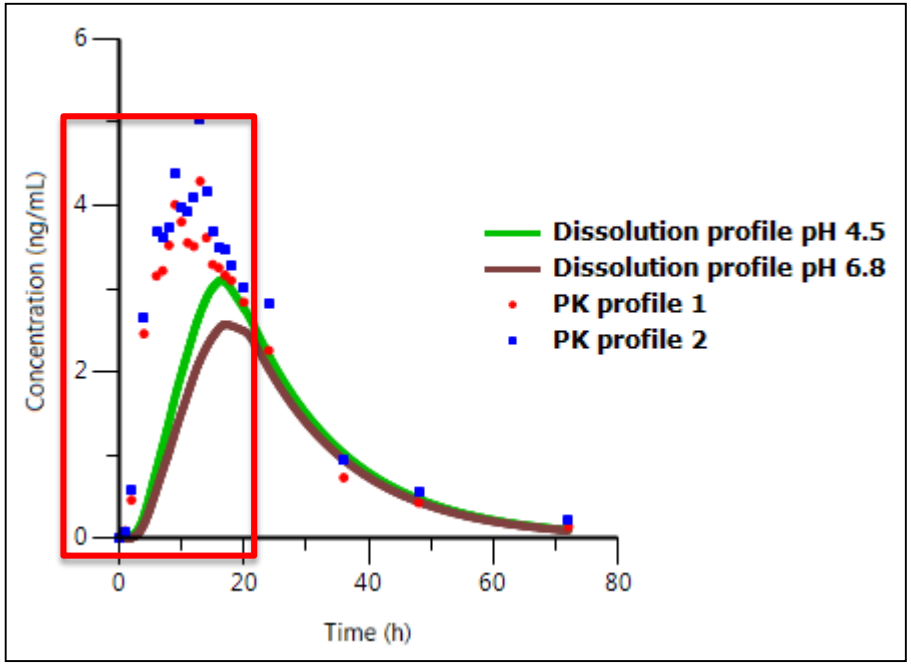
Model Development and Sensitivity Analysis

GastroPlus:
Osmotic pump, RLD
ACAT coupled with one-compartment model
IV and PO data from IR formulations

Model input:
quality control dissolution

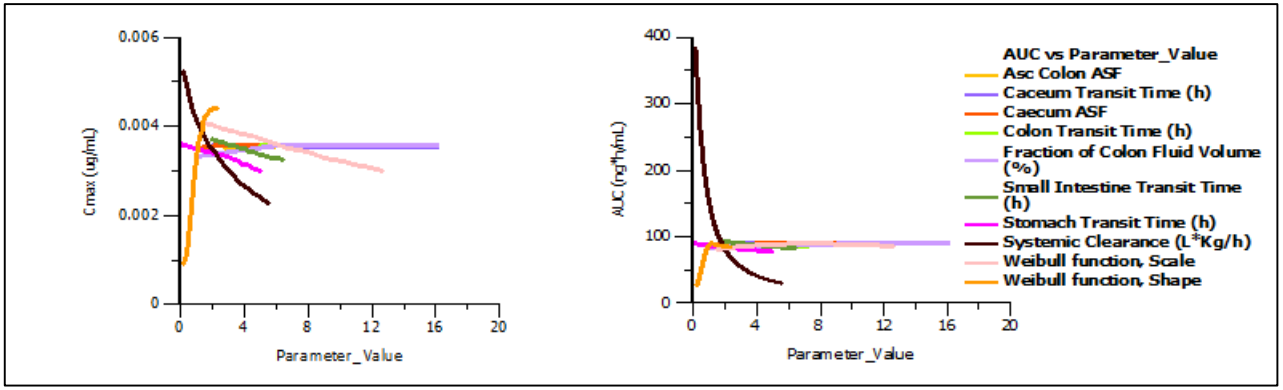


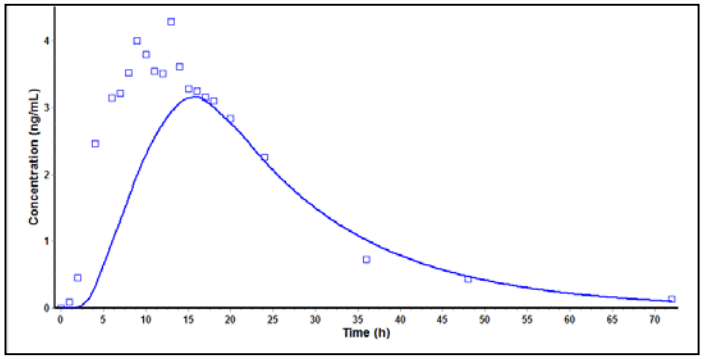
Model output:
predicted mean concentration profile



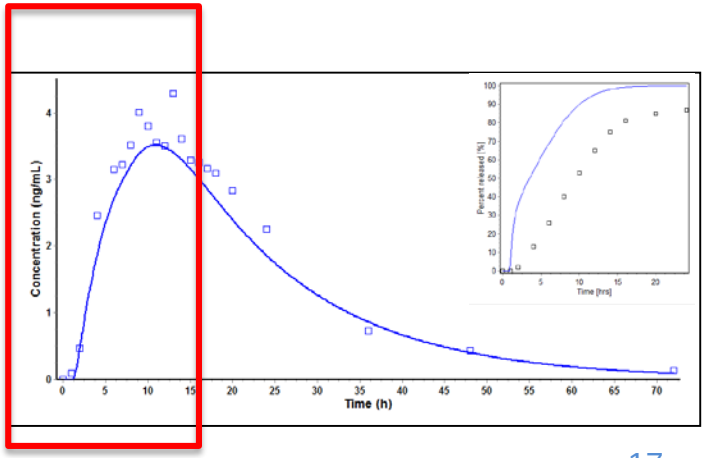
Model Development and Sensitivity Analysis

Sensitivity Analysis



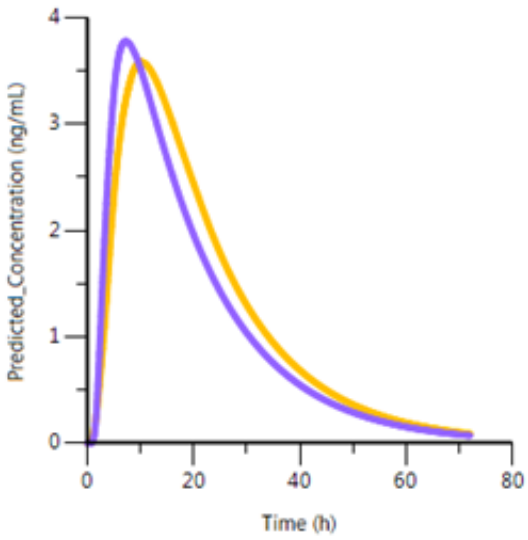


Weibull function Optimization

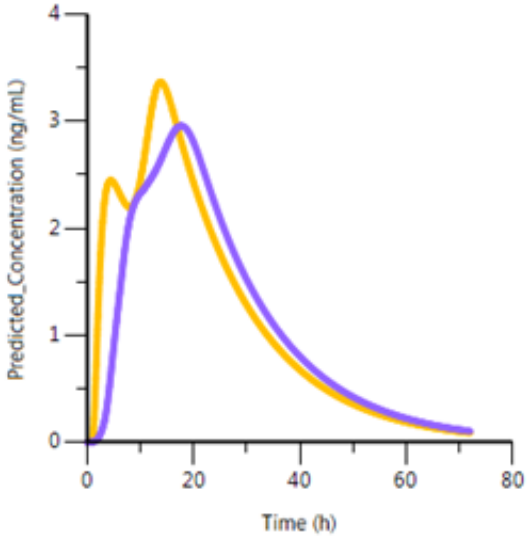


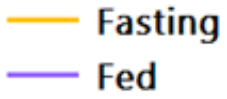
Model Predictions Under Fasted and Fed State

Osmotic pump



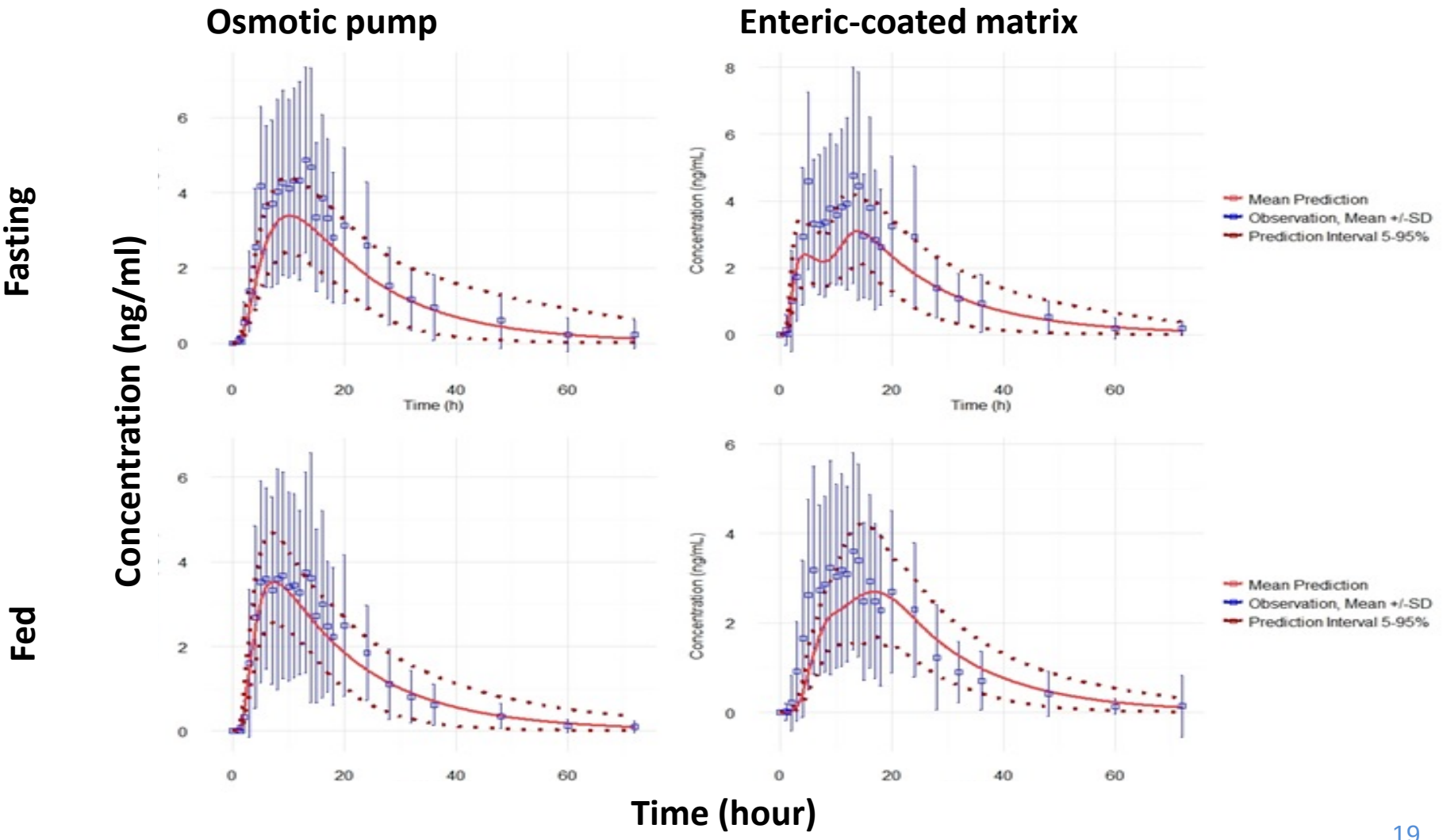
Enteric-coated matrix





- Absence of food effect with the osmotic pump formulation
- Delay is absorption in the presence of food with the enteric-coated matrix formulation
- Double peaks observed with the enteric-coated matrix formulation

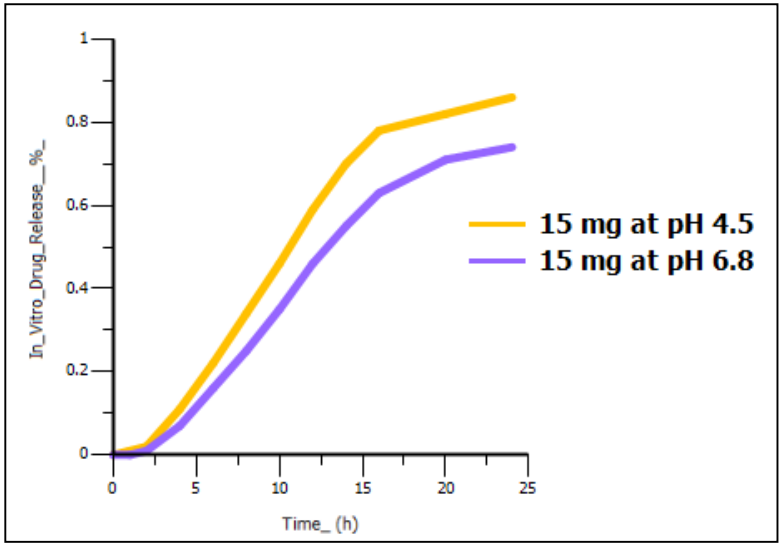
Models Described Observed Data Reasonably Well

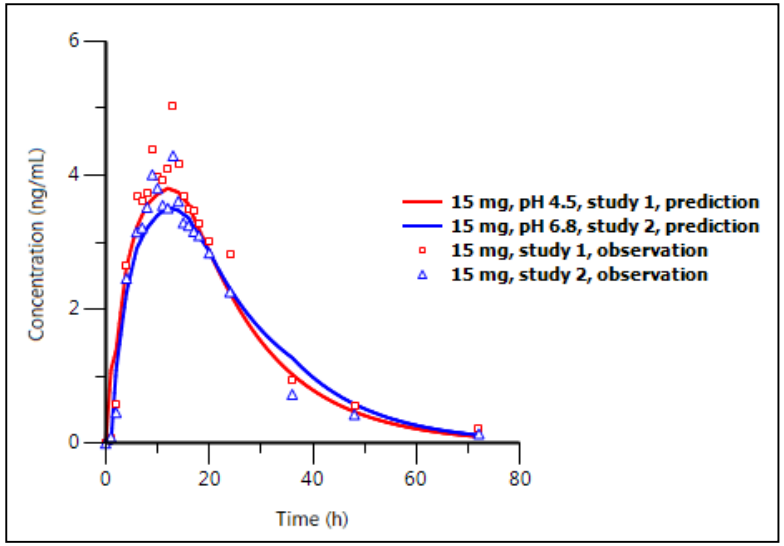


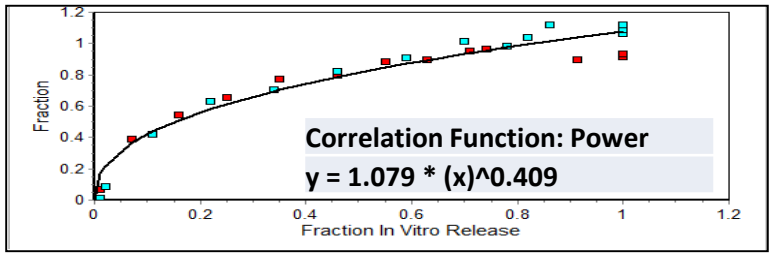
Dose level: 15 mg oxybutynin, PK data extracted from 5 ANDAs submitted to USFDA

IVIVR Development

GastroPlus: IVIVCPlus®



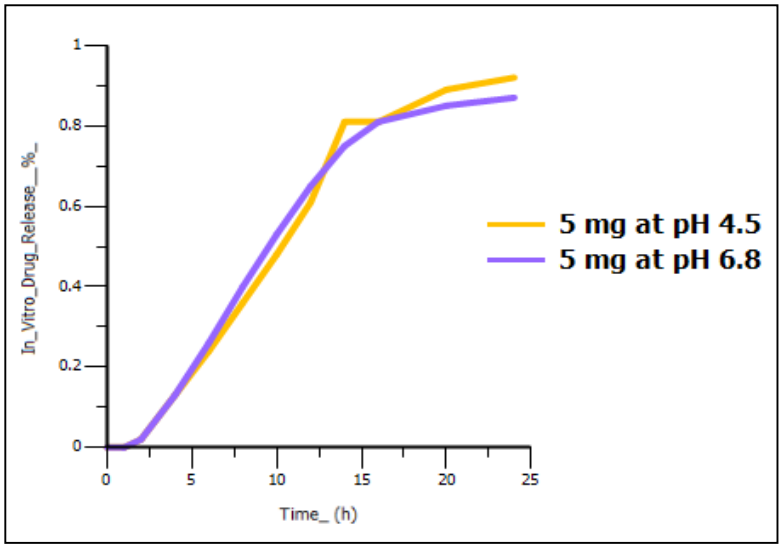




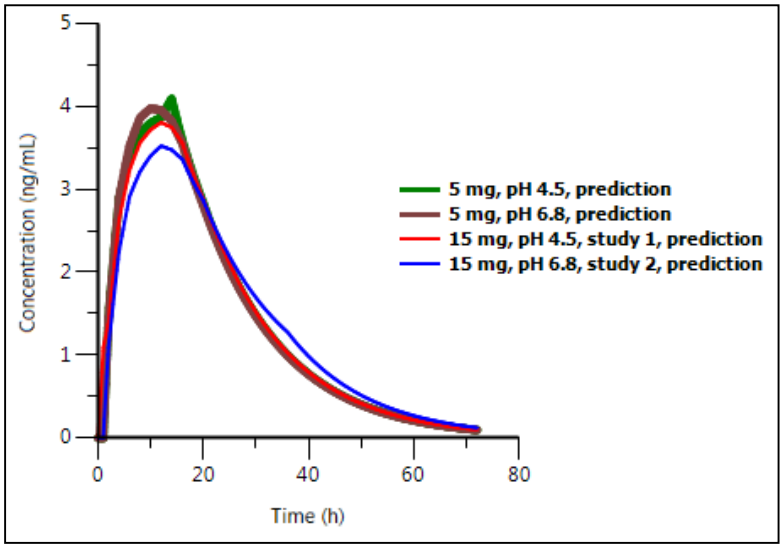
Prediction Errors (%)				
	Cmax (ng/mL)		AUC (ng/mL*h)	
Study	1	2	1	2
Wagner-Nelson	24.1	17.8	9.6	-7.2
MAM	34.6	25.9	25.1	9.8

Predictions Leveraging the Developed IVIVR

GastroPlus: IVIVCPlus®



Leverage IVIVR



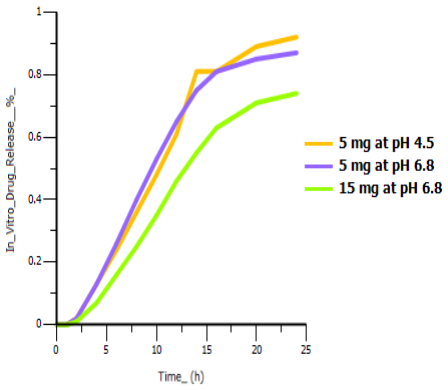
Limitations:

- QC dissolution
- Formulations of different release rates
- Internal and external validation

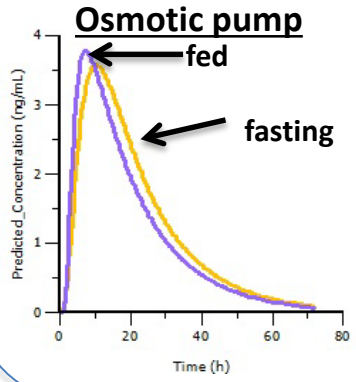
Risk Assessment for Not Conducting In Vivo Studies in Lower Strength Oxybutynin Generic Products

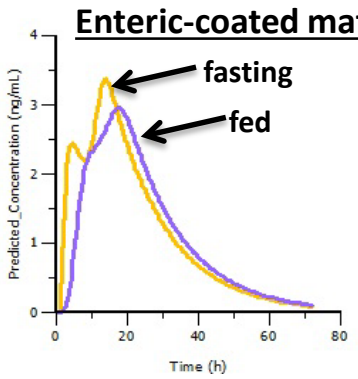
IVIVR development

In vitro dissolution

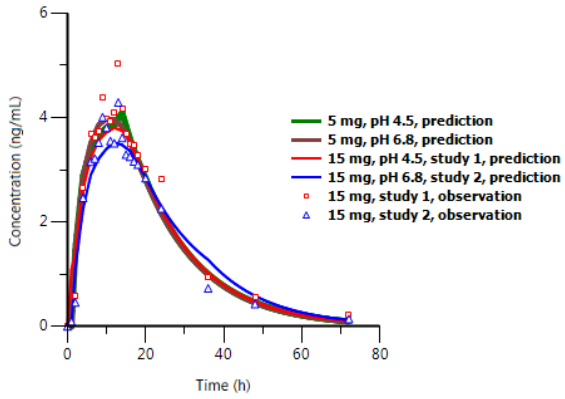


Simulated PK profiles for different formulations under fasting and fed conditions





IVIVR application



Bioequivalence evaluation of lower strengths osmotic pump oxybutynin drug products leveraging developed IVIVR.

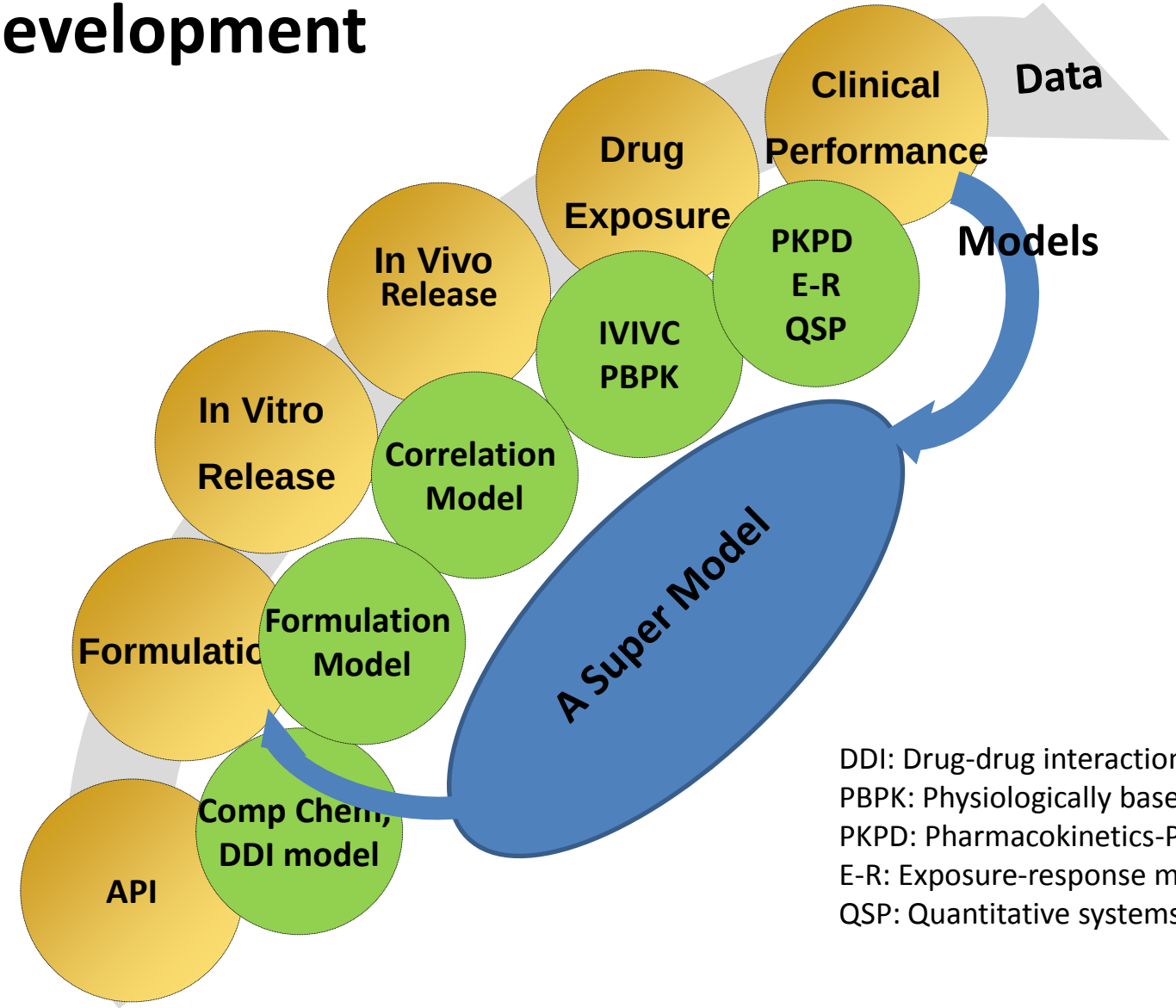
Case Conclusions

- In vitro dissolution does not appear to be predictive of in vivo drug release
  - Additional step for conversion to bio-relevant dissolution profile
  - Additional work is needed to identify bio-predictive dissolution profile condition

- Developed mechanistic absorption pharmacokinetic models
  - described well oxybutynin disposition following administration of oxybutynin formulated as an OROS or enteric-coated matrix extended release formulations under fasting and fed conditions.
  - captured the multiple peak PK profile observed with enteric-coated matrix formulations.

- Established IVIVR
  - can be utilized for risk assessment of not conducting in vivo studies for lower strength generic products when bioequivalence has been established at higher strengths.

An Integrated Modeling System for Drug Development



DDI: Drug-drug interaction
PBPK: Physiologically based PK model
PKPD: Pharmacokinetics-Pharmacodynamics
E-R: Exposure-response model
QSP: Quantitative systems pharmacology

Summary

- At ANDA stage, quality control dissolution profiles and PK profiles for both IV and oral routes of administration are usually available
- In vivo dissolution profile can be predicted via PBPK based deconvolution
- Comparison of in vitro vs in vivo drug release is the first step towards identifying bio-predictive dissolution conditions
- When bio-predictive dissolution conditions cannot be established, a function can be used to convert a discriminatory in vitro dissolution profile to its corresponding in vivo dissolution profile when developing an IVIVC or IVIVR in order to predict in vivo PK

Acknowledgement

- Office of Research and Standards, OGD
  - Rob Lionberger, PhD
  - Susie Zhang, PhD
  - Hong Wen, PhD
  - Dajun Sun, PhD
  - Zhanglin Ni, PhD
  - Jianghong Fan, PhD
  - DQMM Colleagues
- Office of Bioequivalence, OGD
- Office of Clinical Pharmacology, OTS
- Office of Pharmaceutical Quality
- Office of New Drugs


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Relevant GDUFA Funded Grants/Contracts (1)

	Grants/Contracts	Institute	Start	End	Status
BE investigations	Evaluation of Clinical and Safety Outcomes Associated with Conversion from Brand-Name to Generic Tacrolimus products in high risk Transplant Recipients	University of Cincinnati	9/2013	3/2017	Ongoing
	Bioequivalence and Clinical Implications of Generic Bupropion	Washington University	9/2013	8/2017	Ongoing
	Assessing Clinical Equivalence for Generic Drugs Approved By Innovative Methods	Brigham & Women's Hospital	9/2013	9/2015	Ongoing
	Development of an in vitro dissolution technique to understand the clinical based outcomes of orally inhaled drug particles	University of Bath	9/2013	10/2016	Ongoing
New BE metrics (pAUC)	Pharmacometric modeling and simulation for evaluation of bioequivalence for leuprolide acetate injection	University of Utah	9/2015	8/2018	Ongoing
	Pharmacokinetic pharmacodynamic studies of methylphenidate extended release products in pediatric attention deficit hyperactivity disorder	Massachusetts General Hospital	9/2014	8/2017	Ongoing
	Pharmacometric modeling and simulation for evaluation of bioequivalence for leuprolide acetate injection	University of Maryland	9/2014	8/2017	Ongoing
	Pharmacokinetics study of opioid drug product following insufflation of milled drug products	Vince & Associates Clinical Research	9/2015	9/2017	Ongoing
Physiologically based models for systemic and locally acting products	Structural nested models for assessing the safety and effectiveness of generic drugs	Johns Hopkins University	9/2015	8/2018	Ongoing
	Enhancing the reliability, efficiency, and usability of Bayesian population PBPK modeling	University of Colorado	9/2016	8/2018	Ongoing
	Novel Method to Evaluate Bioequivalence of Nanomedicines	Nanotechnology Characterization Lab	5/2016	4/2018	Ongoing
	An integrated multiscale-multiphysics modeling and simulation of ocular drug delivery with whole-body pharmacokinetic response	CFD Corporation	9/2014	8/2017	Ongoing
	Investigate the sensitivity of pharmacokinetics in detecting differences in physicochemical properties of the active in suspension nasal products for local action	University of Florida	9/2013	11/2017	Ongoing

Relevant GDUFA Funded Grants/Contracts (2)

	Grants/Contracts	Institute	Start	End	Status
Model based BE assessment for PK and performance	Correlation of Mesalamine Pharmacokinetics with Local Availability	University of Michigan	9/2013	9/2015	Completed
	Evaluation of model-based bioequivalence statistical approaches for sparse design PK studies	University of Paris	9/2016	9/2017	Ongoing
	A model and system based approach to efficacy and safety questions related to generic substitution	University of Florida	9/2014	8/2018	Ongoing
	Data-fusion based platform development of population PKPD modeling and statistical analysis for bioequivalence assessment of long-acting injectable products	University of Massachusetts	9/2015	8/2018	Ongoing
	Pharmacokinetic and pharmacodynamic (PK-PD) studies of cardiovascular drugs	University of Florida	9/2014	8/2017	Ongoing
	Computational drug delivery; leveraging predictive models to develop bioequivalent generic long-acting injections	Qrono, Inc.	9/2015	9/2018	Ongoing
	Prediction of In Vivo Performance for Oral Solid Dosage Forms	University of Michigan	9/2013	11/2017	Ongoing
Post market evaluation	Postmarketing Surveillance of Generic Drug Usage and Substitution Patterns	UMD	9/2013	10/2015	Completed
	Base IDIQ for Postmarket Bioequivalence Study	Biopharma Services USA	5/2016	5/2017	Ongoing
	Comparative Surveillance of Generic Drugs by Machine Learning	Marshfield Clinic, Inc.	9/2015	11/2016	Ongoing
	Characterization of epilepsy patients at-risk for adverse outcomes related to switching antiepileptic drug products	University of Maryland	9/2014	9/2017	Ongoing
	A model and system based approach to efficacy and safety questions related to generic substitution	University of Florida	9/2014	8/2018	Ongoing
	Novel approaches for confounding control in observational studies of generic drugs	Brigham & Women's Hospital	9/2015	8/2018	Ongoing
NTI classification	Clinical practice data to aid narrow therapeutic index drug classification	Duke University	9/2013	9/2016	Completed
	Therapeutic index evaluation for tacrolimus and levetiracetam	Johns Hopkins University	9/2013	3/2015	Completed
	Population pharmacokinetic and pharmacodynamic, dose-toxicity modeling and simulation for narrow therapeutic index (NTI) drugs	University of Maryland	9/2014	8/2017	Ongoing
	Effect of Therapeutic Class on Generic Drug Substitutions	Johns Hopkins University	9/2014	4/2017	Ongoing