Pioneering Modeling Methodologies in Generic Drug Development

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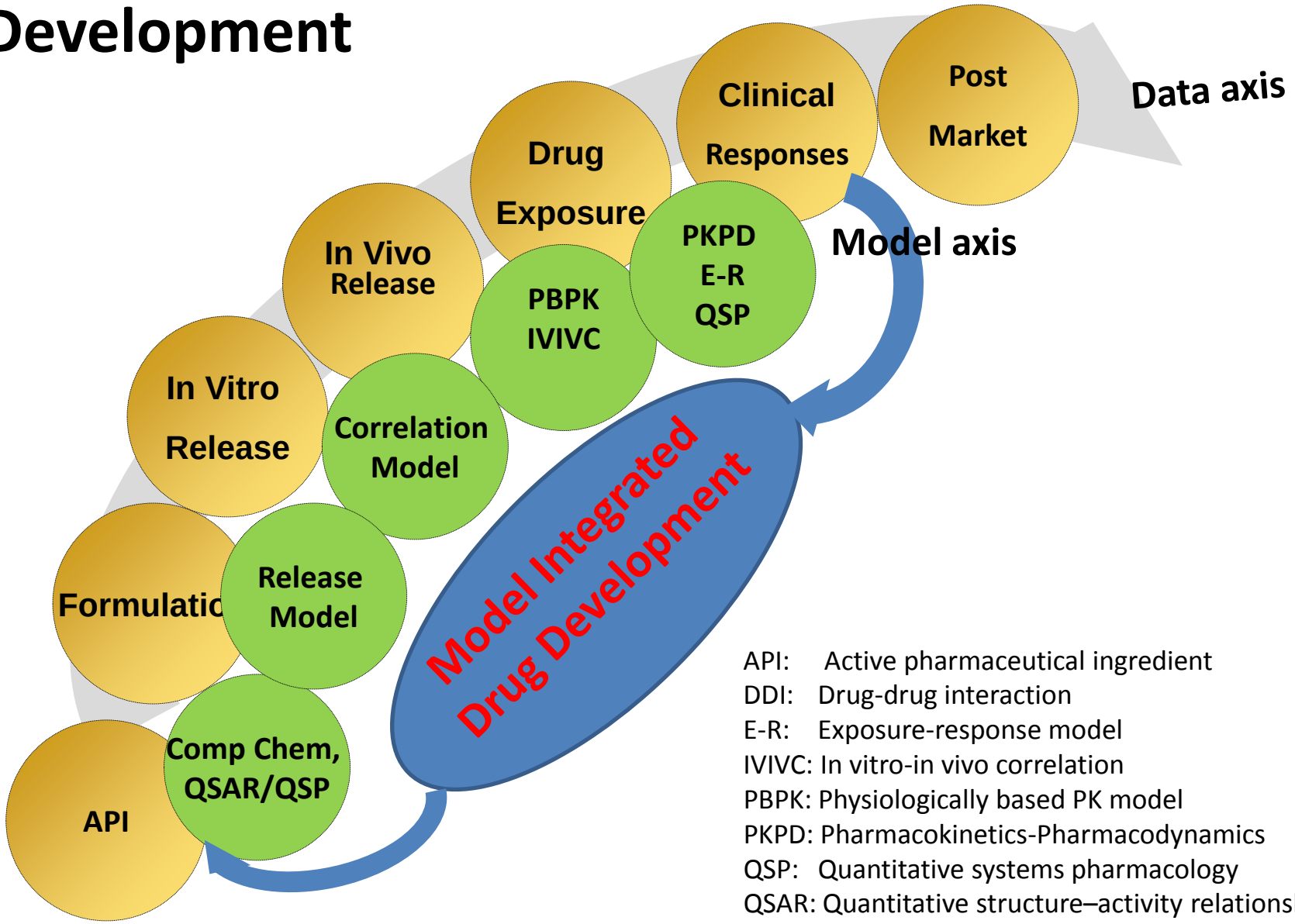
DIA Webinar
5/17/2018

Modernize ANDA Program to Make High Quality Generic Products Quickly Accessible

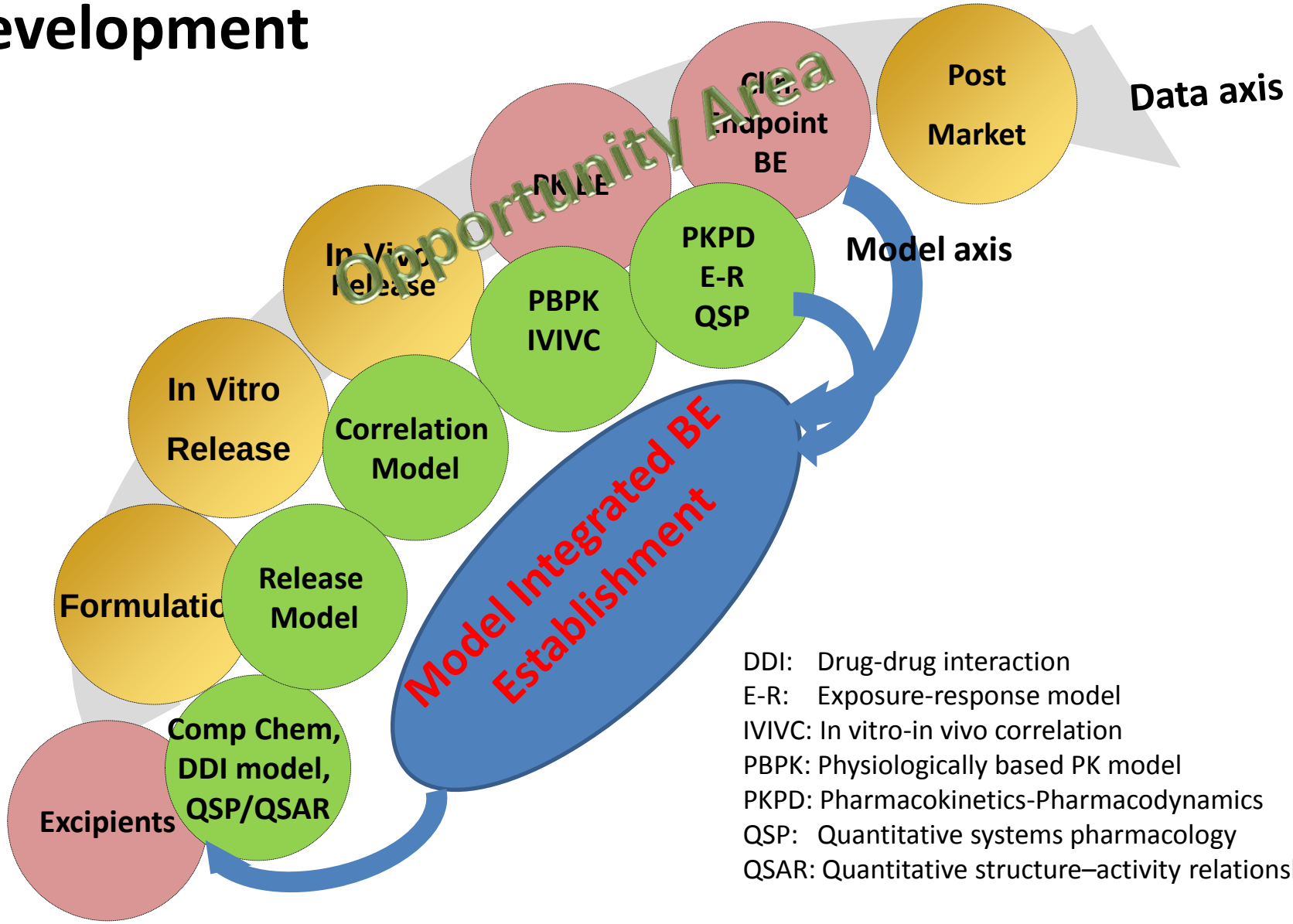
- Increase first cycle approval rate; decrease number of review cycles
- Shorten drug development timeline
- Reduce costly but insensitive in vitro/in vivo studies
- Reduce chance of exposing human subjects to otherwise unnecessary studies
- Ensure timely availability of high quality and affordable generics for patients
- ***All of the above are especially important for locally acting, complex, and modified release products.***

An Integrated Modeling System for New Drug Development



API: Active pharmaceutical ingredient
DDI: Drug-drug interaction
E-R: Exposure-response model
IVIVC: In vitro-in vivo correlation
PBPK: Physiologically based PK model
PKPD: Pharmacokinetics-Pharmacodynamics
QSP: Quantitative systems pharmacology
QSAR: Quantitative structure–activity relationship

Integrated Modeling System for Generic Drug Development



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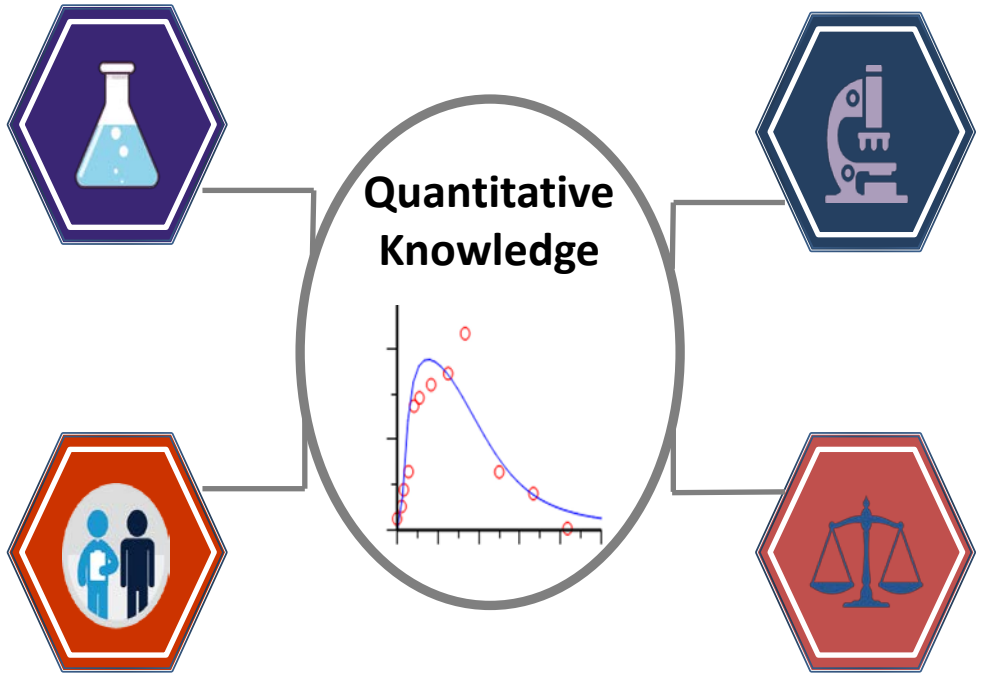
Role of Quantitative Methods and Modeling in Generic Drug Development and Review

Generic Industry

Formulation Design and Process

BE Study Design and Implementation



FDA

In Vitro BE Assessment and Q3 Determination; Critical Quality Attributes Identification

BE metric Standardization

Modeling and Simulation Impact Various Regulatory Activities in OGD (FY2017)

Type	No.	Examples
ANDA Assessments & Citizen Petitions	37	❖ Assessment of clinically relevant pharmacokinetics metrics for BE evaluation (e.g., pAUCs) ❖ EMD profile analysis of particle size distribution ❖ Impact of dissolution profile deviations
Pre-ANDA Interactions (including CC)	15	❖ Trial simulations for alternative BE study designs ❖ Evaluate drug deposition and absorption for solution-based metered dose inhalers
BE Guidances	15	❖Q3 parameters for in vitro only BE assessment ❖NTI assessment for NMEs
Regulatory Research Studies	32	❖ Evaluation of post-marketing switching patterns ❖ Model-based BE assessment; Meta-analysis for opioid products with abuse deterrence properties ❖ Physiologically based pharmacokinetics platform development for non-oral routes

ANDA: abbreviated new drug application; BE: bioequivalence; CC: controlled correspondence; HVD: highly variable drugs; NTI: narrow therapeutic index; EMD: earth mover's distance; pAUC: partial area-under-curve; NME: new molecular entity

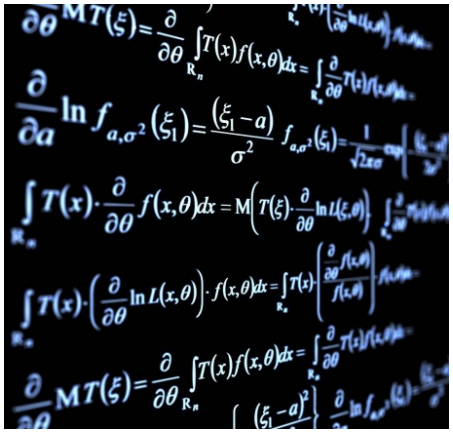
Core Tool Sets

Non-Oral Drug

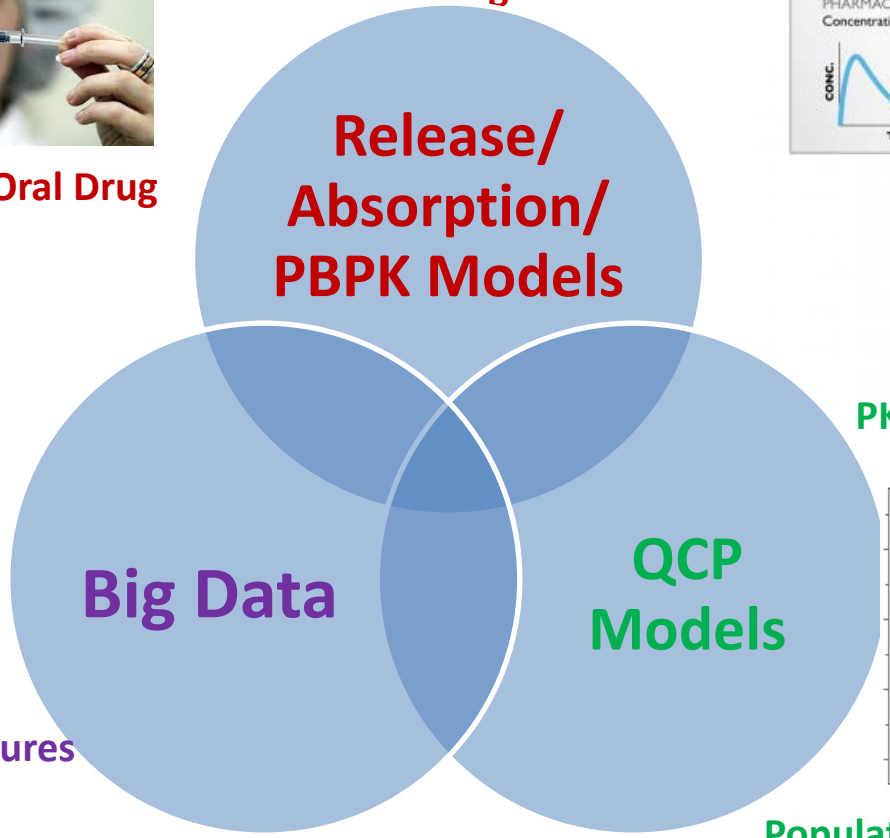
Oral Drug

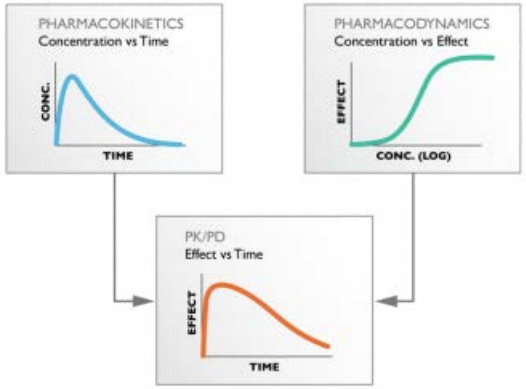
Our Goal is to Facilitate

- Generic drug development/review
- Policy development
- Regulatory decisions

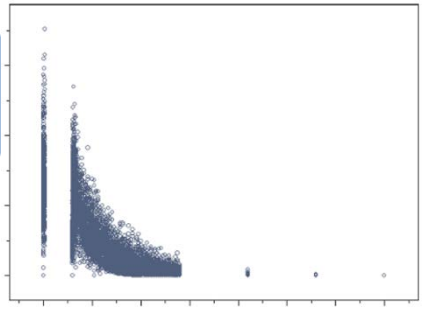


-Machine learning toolsets
-Analytics for complex mixtures
-Systems pharmacology
-Risk-based models
-Business process models-





PK-PD model



Population based model

PBPK: Physiologically based PK; QCP: Quantitative clinical pharmacology

Physiologically Based Pharmacokinetic (PBPK) TOOLKIT for Generics

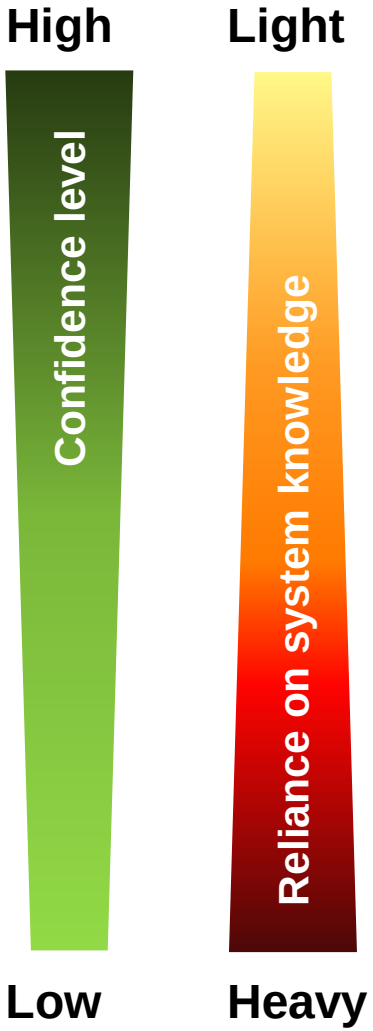
- Oral absorption models are established and commercially available and are useful to FDA and the generic drug industry.
- Non-oral absorption models are at an earlier stage of development yet are critical to FDA and the generic drug industry, especially for equivalence assessment of locally acting drugs.
  - Lung, ocular, dermal, intranasal, long-acting injectable, nanoparticle, etc.

What is PBPK Modeling?

- **Definition**
  - A mathematical modeling technique for predicting the absorption, distribution, metabolism and excretion (ADME) of synthetic or natural chemical substances in humans and other animal species (Wikipedia)
- **Systemic drug concentration profile prediction in human blood/serum**
  - Based on product information (i.e., API, excipient, and formulation)
  - Based on co-medications: drug-drug interaction
- **Local drug concentration profile prediction in interested tissue/organ/site of action**
  - Based on local physiological environment and product information
- **A modeling system for virtual simulations**

PBPK Applications in NDA: Current Status

	Applications	Status
Drug-drug Interactions	*Drug as enzyme substrate*	• *Substrate/inhibitor models verified with key clinical data can be used to simulate untested scenarios and support labeling*
	Drug as enzyme perpetrator	• *Use to confirm the lack of enzyme inhibition* • *Additional evidence needed to confirm predictive performance for positive interactions*
	Transporter-based	• *In vitro-in vivo extrapolation not mature* • *Complicated by transporter-enzyme interplay* • *Predictive performance yet to be demonstrated*
Specific populations	*Organ impairments (hepatic and renal)*	• *Predictive performance yet to be improved* • *System component needs an update*
	Pediatrics	• *Allometry is reasonable for PK down to 2 years old* • *Less than 2 years old ontogeny and maturation need to be considered*
Others with limited experiences	*Pregnancy, ethnicity, geriatrics, obesity, disease states* *Food effect, formulation change, PH effect (including DDIs on gastric PH)* *Tissue concentration*	



Wagner, CPT-PSP, 2015

Slide from Ping Zhao, 2016 ASCPT

Modeling Absorption for Generics

Drug substance and product information:

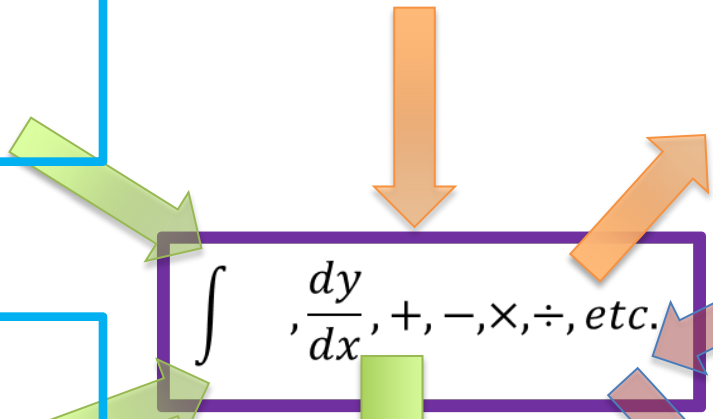
- Dose and dose volume
- Solubility vs. pH profiles
- logP, pKa
- Dissolution: MR: dissolution profiles; IR: particle size and density
- Diffusion coefficient
- Permeability
- Metabolic kinetics

PK parameters

- Clearance, Vd
- Tissue/organ parameters for physiologically based distribution and elimination models

Physiological parameters

- GI transit time
- GI geometry
- GI fluid properties
- Enzymes/transporters distribution
- Blood flow



- Fh, BA
- PK profiles

Metabolite info

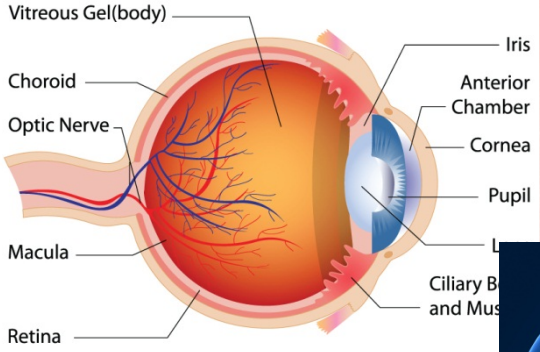
Parent and metabolite PK

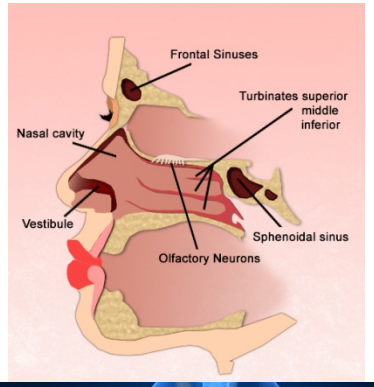
- Fa, Fg
- In vivo dissolution
- Drug in each cmpt

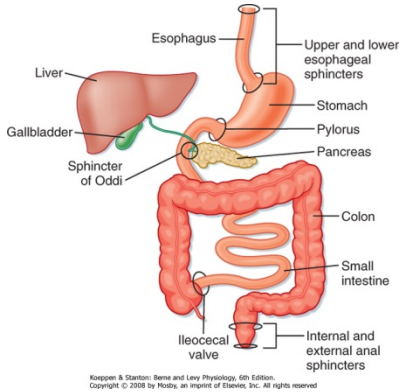
Adopted from Dr. X Zhang

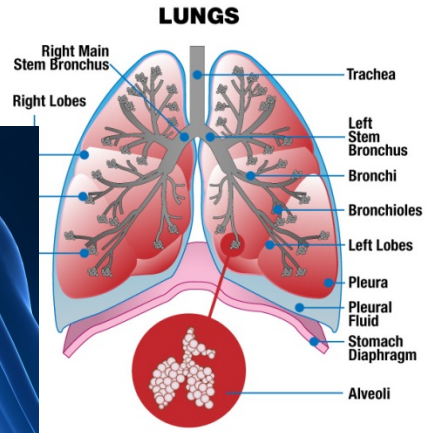
Modeling Local Drug Exposure

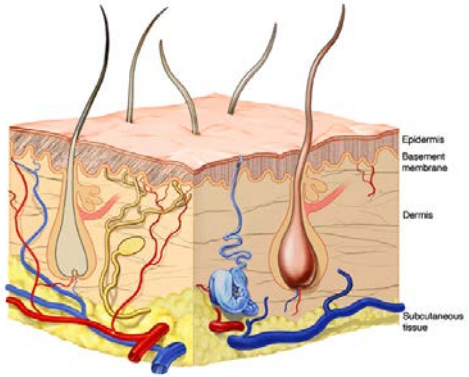
Drug Substance Formulations In Vitro Testing → **Physiological System** → **In Vivo Performance**





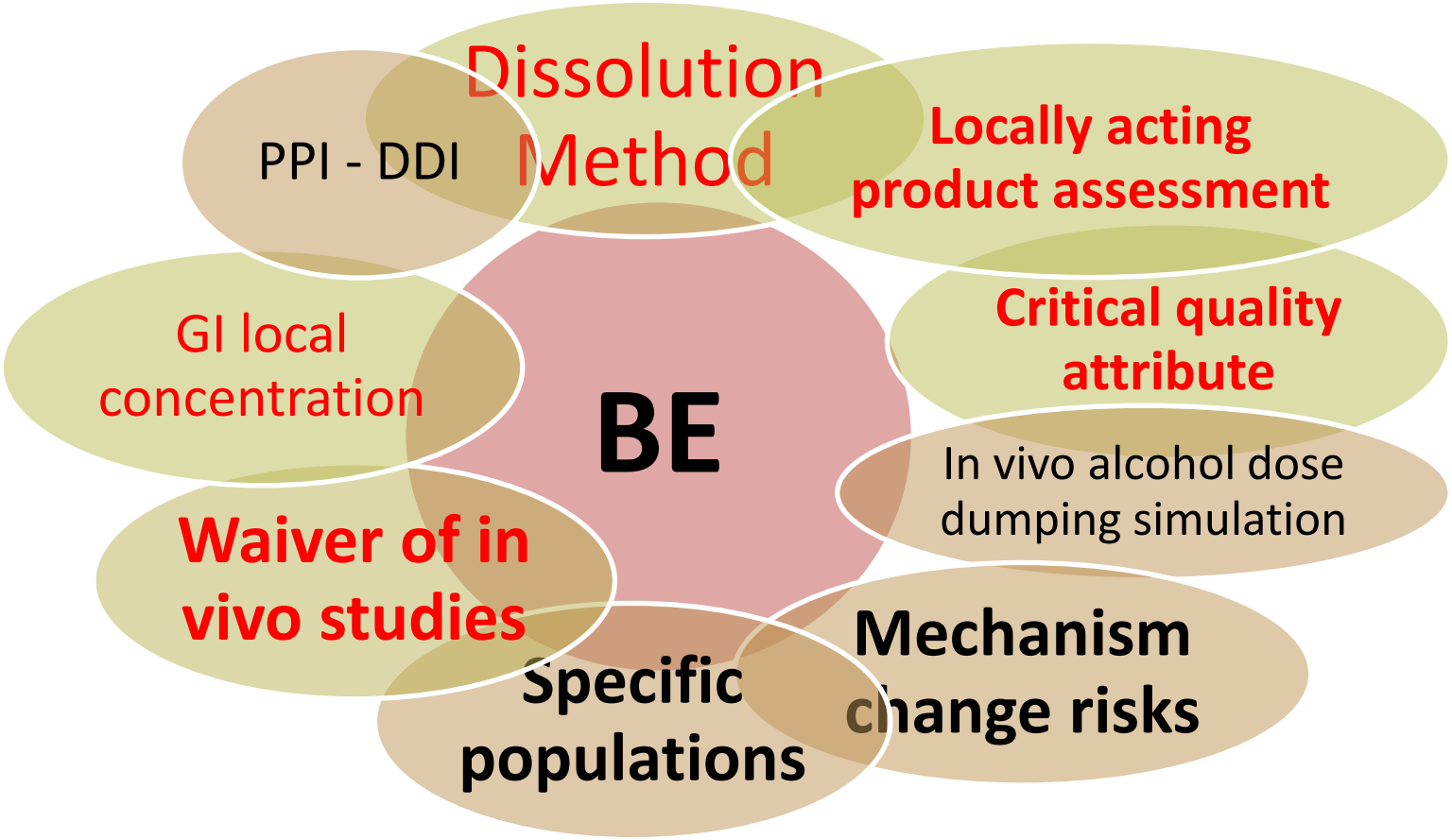






Based on the publication by Jiang W, Kim S, Zhang X, Lionberger RA, Davit BM, Conner DP, Yu LX. Int J Pharm. 2011 Oct 14;418(2):151-60.

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

Red color: opportunity areas for industry

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

Highlights of PBPK Impacts

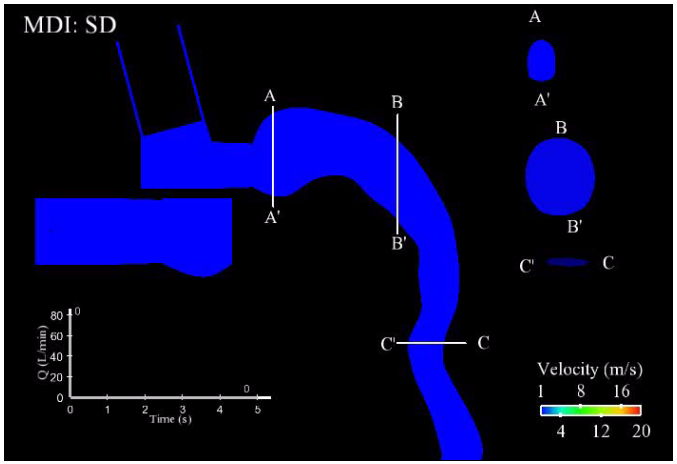
Category	Example Drug	Impact on regulatory decision making
Product quality/dissolution	Celecoxib, Theophylline ER, Metoprolol ER	Impact of dissolution failure on BE
	Ophthalmic emulsions and suspensions	Impact of quality attributes on ocular bioavailability and tear film breakup time
	Warfarin	Impact of tablet aging and dissolution on BE
Mechanism change risks	Venlafaxine ER	Based on dissolution profile and modeling predictions, FDA requested applicant to reformulate the product
Risk assessment for BE extrapolation	Oxybutynin ER	Risk assessment for not conducting lower strength in vivo study when BE is established with higher strength
PPI effect	Nifedipine ER, Paliperidone ER, Prasugrel	Risk assessment of changing drug release to a pH-dependent mechanism
Abuse deterrence	Hydrocodone ER	IVIVC development for chewing deterrence route using artificial chewing apparatus
	Oxycodone ER	Impact of particle size on nasal insufflation utilizing CFD modeling
Clinical endpoint/PD waiver	Diclofenac (topical)	Assessment of dermal PBPK model in place of a comparative clinical endpoint study
	Beclomethasone (inhalation)	Assessment of inhalation PBPK and CFD models (droplet composition and deposition pattern) for purpose of waiving PD study
BCS waivers	BCSIII oral dosage forms	Research into excipients that can affect drug intestinal uptake
PK metrics determination	Mesalamine solid oral dosage forms	Determination of PK metrics for BE evaluation

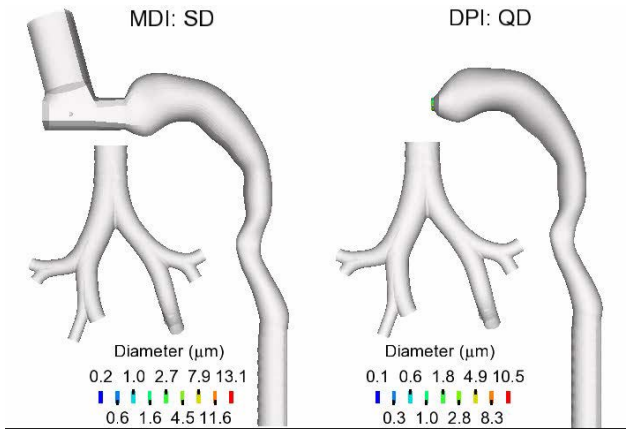
PPI: proton pump inhibitor; ER : extended release

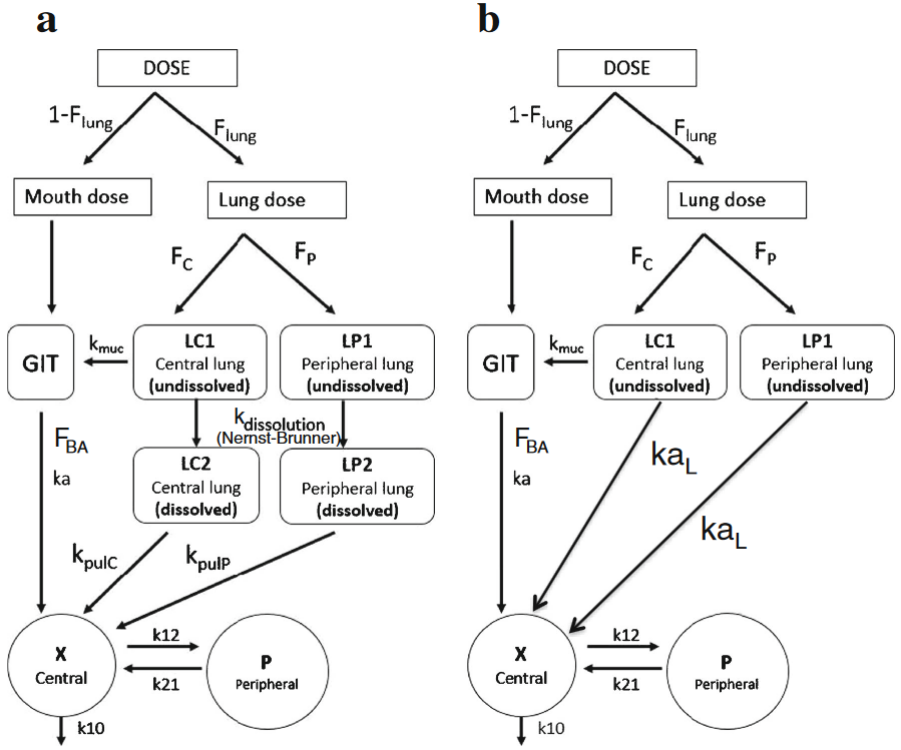
Case: Computational Modeling in Orally Inhaled Product Development

- Bioequivalence assessment of orally inhaled product presents a challenge since systemic (blood) drug exposure may not reflect local drug concentration at site of action.
- Computational modeling provides a connection between in vitro parameters (e.g., spray angle and plume geometry) and lung regional deposition and absorption of orally inhaled aerosols.
- Quantitative methods and modeling can inform regulatory decision-making otherwise difficult to make with available in vitro or in vivo data, by predicting:
  - Regional deposition of aerosolized drug within individual branches/lobes of the airway
  - Local bioavailability and its relationship with systemic pharmacokinetics
- Computational fluid dynamics (CFD) and physiologically based pharmacokinetic (PBPK), in combination, present the next generation modeling toolset that can offer an opportunity to preclude conducting PD endpoint BE studies.

PBPK Predictions of Orally Inhaled Drug Absorption







Compartmental model schemes for dry powder inhaler drug delivery from Bhagwat et al. (2017)

Right: Bhagwat S, Schilling U, Chen MJ, Wei X, Delvadia R, Absar M, Saluja B, Hochhaus G. Predicting Pulmonary Pharmacokinetics from In Vitro Properties of Dry Powder Inhalers. Pharmaceutical research. 2017 (in press).
Left: Longest, P. W., Tian, G., Walenga, R. L., and Hindle, M. (2012) Comparing MDI and DPI Aerosol Deposition Using in Vitro Experiments and a New Stochastic Individual Path (SIP) Model of the Conducting Airways. Pharmaceutial Research, 29(6), 1670-1688

PBPK Predictions of Orally Inhaled Drug Absorption

- Compartmental modeling approach used to predict dissolution and absorption of deposited drug particles
- Combination of CFD and PBPK can predict local and systemic absorption
- Useful for determining the extent that in vitro testing is indicative of local and systemic delivery, and for identifying appropriate bioequivalence limits on in vitro parameters

What is Quantitative Clinical Pharmacology?

- **Clinical pharmacology** aims to investigate various observable human drug responses and elucidate mechanisms of drug actions and sources of their variability.
- **Quantitative clinical pharmacology** adds measureable, numerical meaning to the mass, volume, concentration and time dimensions of drug disposition, as well as quantifiable metrics for pharmacodynamic (PD) effects:
  - Patterns/time profiles of PK and PD/clinical responses
  - PK-PD/clinical response relationships
  - Dose optimization for desired clinical responses

Quantitative Clinical Pharmacology TOOLKIT for Generics

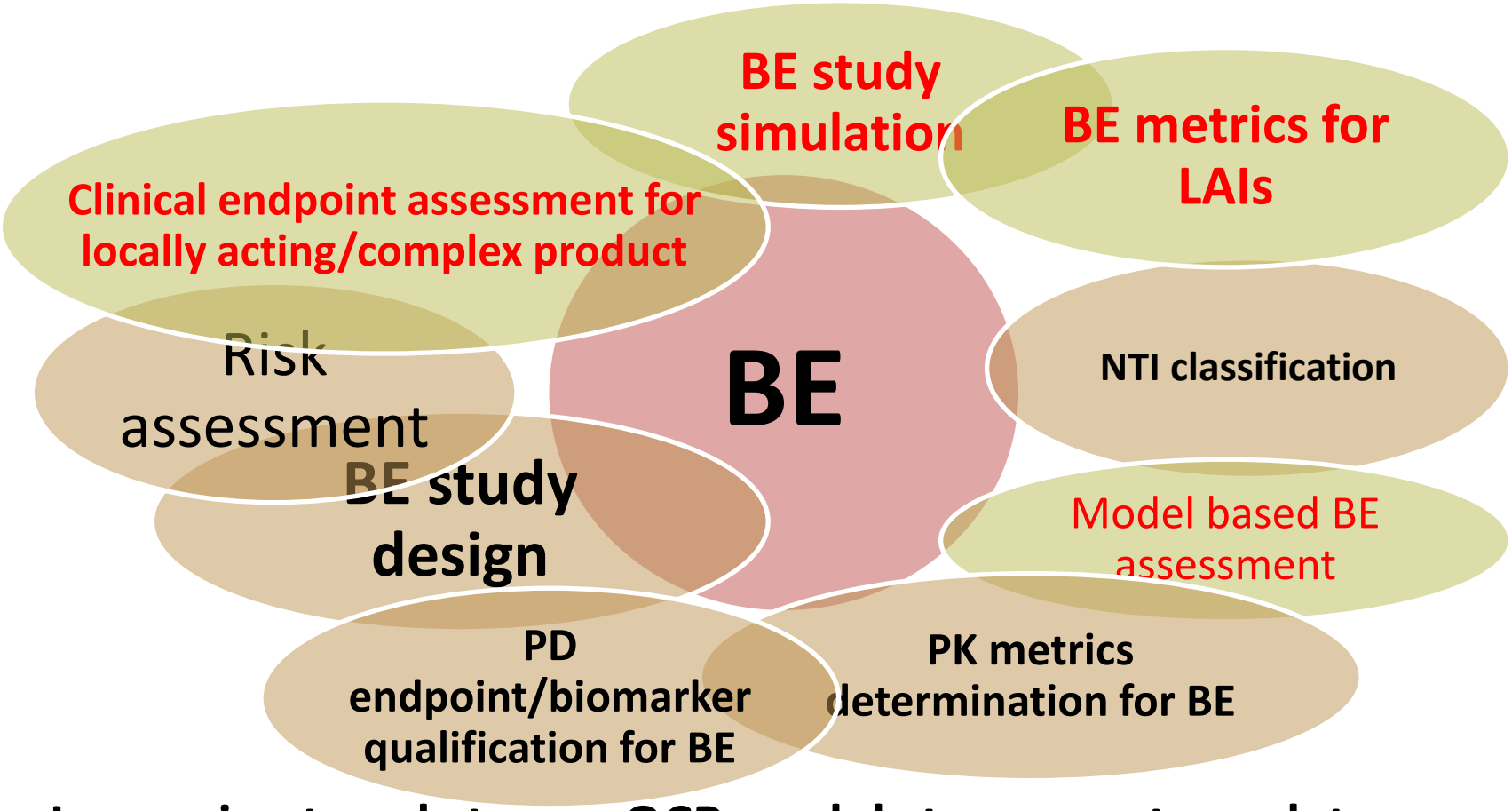
NEW DRUGS	GENERIC DRUGS
• PK-PD modeling	→ • Same – core of BE assessment
• Exposure-response analysis	→ • Narrow Therapeutic Index
• Clinical trial simulation	→ • **Virtual BE study/alternative design**
• Population PK	→ • Model-based BE assessment for drugs with sparse PK

What is a Virtual BE Study?

- Use of model to compare test and reference formulations
- Model must have a formulation variable that can be adjusted to represent the difference between T and R
- Model generates a population for BE study, compares T and R in that population
  - Simulate many studies to estimate probability of success or failure

BE: bioequivalence; T: test product; R: reference product

General QCP Model Applications for Generic Products



Increasing trends to use QCP models to support regulatory decision makings in the realm of generic drug development

Red color: opportunity areas for industry

QCP: quantitative clinical pharmacology

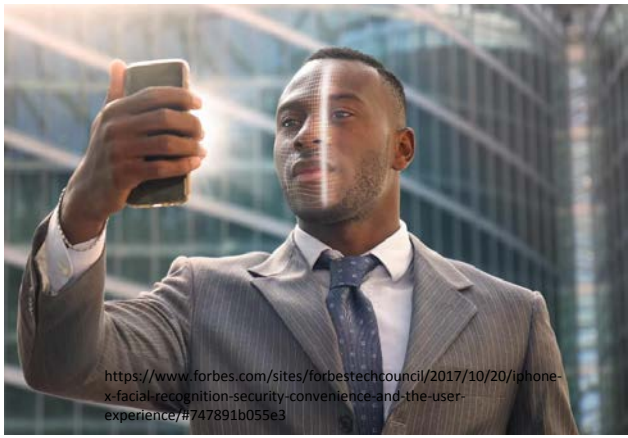
Highlights of QCP Impact

Category	Example Drug	Impact on regulatory decision making
PK metrics determination	Methylphenidate transdermal systems	Recommendation of pAUC for BE assessment to ensure comparable drug concentrations during clinically relevant time windows
BE Study design and BE methodology development via modeling and virtual simulations	Levonorgestrel-releasing intrauterine device	Recommendation of one-year in vivo BE study (90% CI of the residual drug amount within 95.00 - 105.26%) to ensure that residual drug amount at five year is within 80.00 - 125.00%
	Paliperidone extended- release products	Assessment on alternative BE study designs (single dose versus multiple dose studies) and associated BE metrics/limit
BE on clinical endpoint	Brimonidine topical gel	Pharmacodynamic (PD) simulations were used to predict PD and/or therapeutic equivalence at unstudied time points
In vitro BE	Cyclosporine ophthalmic emulsion	Evaluation on particle size distribution to establish BE
BE methodology enhancement	Albuterol inhalation products	Dose-scale methodology on in vivo PD data processing and statistical algorithms
New BE options	Ivermectin topical cream	Recommend two BE options: in vitro/PK or comparative clinical endpoint studies

QCP: quantitative clinical pharmacology;

What is Big Data Analytics?

- Big data analytics examines large amounts of data to uncover hidden patterns, correlations and other insights (SAS.com).
- iPhone face recognition: It does not use a PBPK or QCP model of your face but directly processes data into a prediction.



https://www.forbes.com/sites/forbestechcouncil/2017/10/20/iphone-x-facial-recognition-security-convenience-and-the-user-experience/#747891b055e3

Big Data
TOOLKIT for Generics

- Big data methods to reform conventional Pharmacometrics toolsets
  - Machine learning for survival analysis
- Post market product performance evaluation
  - Sentinel database and analytics
- Review efficiency and quality enhancement
  - AI tools to automate data construction, analysis, and reporting
- Scientific research optimization and workload management
  - ANDA submission prediction
  - Pharmacoeconomics: opportunity areas for healthcare cost reduction

GDUFA Research

- GDUFA I supported the build out of the modeling and simulation tool chain for generic drugs.
- GDUFA II will continue to build on the toolset and capitalize on the GDUFA regulatory science program.

QMM Related GDUFA Funded Grants/Contracts (1)

	Grants/Contracts	Institute	Start	End	Status
BE investigations	Wireless Sampling Pill to Measure in Vivo Drug Dissolution in GI Tract and Computational Model To Distinguish Meaningful Product Quality Differences and Ensure Bioequivalence (BE) in Patients	University of Michigan	9/2015	9/2018	Ongoing
	Characterization of epilepsy patients at-risk for adverse outcomes related to switching antiepileptic drug products	University of Maryland	9/2015	9/2018	Ongoing
	Base IDIQ for Postmarket Bioequivalence Study	Biopharma Services USA	5/2016	5/2018	Ongoing
	Bioequivalence Study of Lamotrigine Extended Tablets in Healthy Subjects	Vince & Associates Clinical Research	9/2015	9/2017	Completed
	Bioequivalence and Clinical Implications of Generic Bupropion	Washington University	9/2013	8/2017	Completed
	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	Completed
	Evaluation of in vitro release methods for liposomal amphotericin B	ZoneOne Pharma	9/2014	9/2016	Completed
	Assessing Clinical Equivalence for Generic Drugs Approved By Innovative Methods	Brigham & Women's Hospital	9/2013	9/2015	Completed
	Pharmacokinetic Study of Bupropion Hydrochloride Products with Different Release Patterns	University of Michigan	9/2013	11/2015	Completed
	Investigation of inequivalence of bupropion hydrochloride extended release tablets: in vitro metabolism quantification	University of Michigan	9/2013	9/2015	Completed
New BE metrics	Pharmacometric modeling and simulation for evaluation of bioequivalence for leuprolide acetate injection	University of Utah	9/2015	8/2018	Ongoing
	Pharmacokinetics study of opioid drug product following insufflation of milled drug products	Vince & Associates Clinical Research	9/2015	9/2017	Completed
	Pharmacokinetic pharmacodynamic studies of methylphenidate extended release products in pediatric attention deficit hyperactivity disorder	Massachusetts General Hospital	9/2014	8/2017	Completed
	Pharmacometric modeling of immunosuppressant for evaluation of bioequivalence criteria	University of Utah	9/2014	2019	Ongoing
	BE and Characterization of Generic Drugs: Methylphenidate and Warfarin	Vince & Associates Clinical Research	9/2014	12/2016	Completed
Physiologically based models for systemic and locally acting products	Design, Development, Implementation and Validation of a Mechanistic Physiologically-based Pharmacokinetic (PBPK) Framework for the Prediction of the In Vivo Behavior of Supersaturating Drug Products	Simcyp, Ltd.	9/2016	8/2018	Ongoing
	Development and validation of dermal PBPK modeling platform toward virtual bioequivalence assessment considering population variability	Simcyp, Ltd	9/2014	8/2018	Ongoing
	Physiologically based biopharmaceutics and pharmacokinetics of drug products for dermal absorption in humans	University of South Australia	9/2014	8/2018	Ongoing
	Enhancing the reliability, efficiency, and usability of Bayesian population PBPK modeling	Colorado State University	9/2016	8/2018	Ongoing
	A cluster-based assessment of drug delivery in asthmatic small airways	University of Iowa	9/2016	9/2018	Ongoing
	Novel Method to Evaluate Bioequivalence of Nanomedicines	Nanotechnology Characterization Lab	5/2016	4/2018	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
	An integrated multiscale-multiphysics modeling and simulation of ocular drug delivery with whole-body pharmacokinetic response	CFD Corporation	9/2014	8/2017	Completed
	PBPK modeling and simulation for ocular dosage forms	Simulations Plus	9/2015	8/2017	Completed

QMM Related GDUFA Funded Grants/Contracts (2)

	Grants/Contracts	Institute	Start	End	Status
Model based BE assessment	Evaluation and development of model-based bioequivalence analysis strategies	Uppsala University	6/2017	6/2019	Ongoing
	Evaluation of model-based bioequivalence statistical approaches for sparse design PK studies	University of Paris	9/2016	9/2018	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	8/2018	Ongoing
	Computational drug delivery: leveraging predictive models to develop bioequivalent generic long-acting injections	Qrono, Inc.	9/2015	9/2018	Ongoing
	In Vivo Predictive Dissolution (IPD) to Advance Oral Product Bioequivalence (BE) Regulation	University of Michigan	9/2015	9/2018	Ongoing
	Prediction of In Vivo Performance for Oral Solid Dosage Forms	University of Michigan	9/2013	11/2017	Ongoing
	Correlation of Mesalamine Pharmacokinetics with Local Availability	University of Michigan	9/2013	9/2015	Completed
Post marketing evaluation	Generic drug substitution in special populations	Auburn University/ IMPAQ International	9/2016	8/2018	Ongoing
	Comparative Surveillance of Generic Drugs by Machine Learning	Marshfield Clinic, Inc.	9/2015	9/2018	Ongoing
	Novel approaches for confounding control in observational studies of generic drugs	Brigham & Women's Hospital	9/2015	8/2018	Ongoing
	Structural nested models for assessing the safety and effectiveness of generic drugs	Johns Hopkins University	9/2015	8/2018	Ongoing
	Base IDIQ for Postmarket Bioequivalence Study	Biopharma Services USA	5/2016	5/2018	Ongoing
	Pharmacometic modeling and simulation for generic drug substitutability evaluation and post marketing risk assessment	University of Maryland	9/2014	2/2018	Ongoing
	A model and system based approach to efficacy and safety questions related to generic substitution	University of Florida	9/2014	8/2018	Ongoing
	Transplant outcomes using generic and brand name immunosuppressants: studying medications used by people who have received kidney and liver transplants	Arbor Research Collaborative for Health	9/2014	8/2017	Completed
	Post-market authorized generic evaluation (PAGE)	Auburn University	9/2014	8/2017	Completed
	Effect of Therapeutic Class on Generic Drug Substitutions	Johns Hopkins University	9/2014	4/2017	Completed
	Assessing the post-marketing safety of authorized generic drug products	Brigham & Women's Hospital	9/2014	6/2017	Completed
	Postmarketing Surveillance of Generic Drug Usage and Substitution Patterns	University of Maryland	9/2013	10/2015	Completed
NTI classification	Population pharmacokinetic and pharmacodynamic, dose-toxicity modeling and simulation for narrow therapeutic index (NTI) drugs	University of Maryland	9/2014	8/2018	Ongoing
	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

Recent Modeling Activities at OGD

- BE evaluations for locally acting , complex, and modified release products:
  - Efficacy extrapolation in the generic drug review
- Support for in vitro only BE assessment:
  - BCSII-IV drugs– past FDA/CERSI workshops
- Big data analytics:
  - Informing generic research prioritization
  - Introduce new toolsets to the community of pharmacometrics
- Post marketing signal evaluation tools
  - Method exploration for noise elimination
  - Signal detection in Sentinel
  - Translating concept of real world study to post market performance evaluation
- Risk based BE standards:
  - Product specific guidance for dabigatran
- In vitro BE methodologies:
  - EMD metric for particle size distribution evaluation

Take Home Messages

- Quantitative Methods and Modeling (QMM) is modernizing generic drug assessment especially for locally acting, complex, and/or modified release products:
  - Office of Research and Standards/Office of Generic Drugs uses QMM to modernize guidance development and product assessments to reduce regulatory burden
  - Generic drug applicants identify opportunities of leveraging QMM in pre-ANDA interactions and ANDAs to shorten development timeline and cut cost
- Emerging tools like big data analysis aid product development, post-marketing evaluation, and workload management.
- Global stakeholder engagement with QMM can greatly benefit the global generic enterprise as a whole.

Thank You!