Quantitative Methods and Modeling to Support GDUFA Regulatory Science Research Program

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CDER, FDA

Generic Drug Research Public Workshop

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Outline

- Introduction
- Impacts made by quantitative methods and modeling
  - Physiologically based PK model
  - Pharmacometrics/Quantitative clinical pharmacology
  - Health outcomes and big data
- Relevant GDUFA funded research/contracts
- Your input!

NDA vs. ANDA Review Process

New Drug NDA Requirements	Generic Drug ANDA Requirements
1. Drug Substance	1. Drug Substance
2. Manufacturing	2. Manufacturing
3. Drug Product	3. Drug Product
4. Microbiology	4. Microbiology
5. Biopharmaceutics	5. Biopharmaceutics
6. Preclinical Studies	
7. Clin. Pharm.	6. Bioequivalence (BE)
8. Clinical Studies	

BE: Is the drug delivered to the action site in the same way for different formulations?

If yes, brand product can be substituted by generics upon their approval

ANDA: abbreviated new drug application; NDA: new drug application

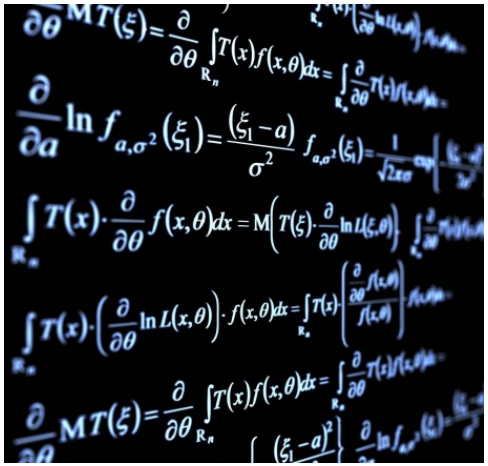
Quantitative Tool Sets

Non-Oral Drug

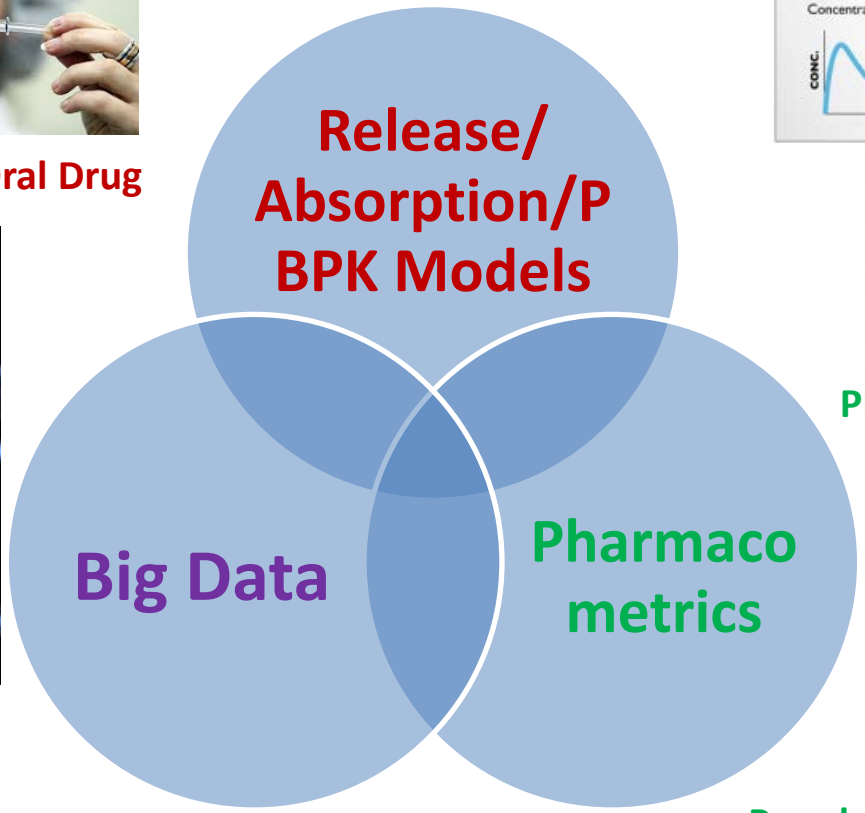
Oral Drug

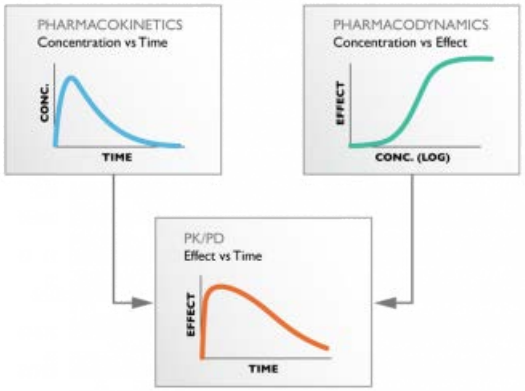
Our Goal is to support

- Generic drug research
- Policy development
- Regulatory decisions

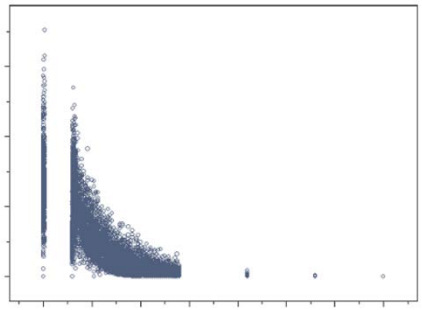


Analytics for complex products
Systems pharmacology
Risk models
Business process models





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 to evaluate deviations from guidance or unusual review situations
- The generic industry could 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

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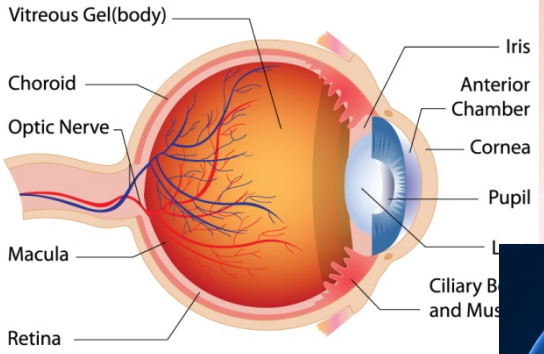
Physiologically based PK (PBPK) model

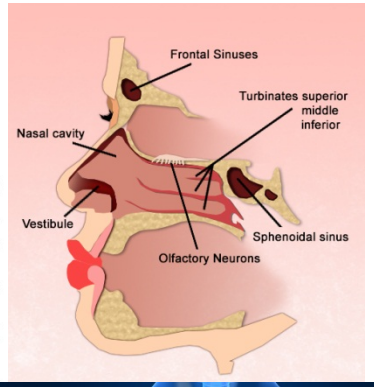
PBPK Models

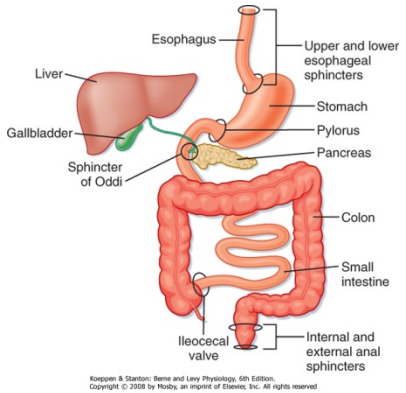
- Oral absorption models are established and commercially available and are useful to FDA and the generic drug industry
- Non-oral absorption models are at an earlier stage of development but are critical to FDA and the generic drug industry if we want new approaches to equivalence of locally acting drugs

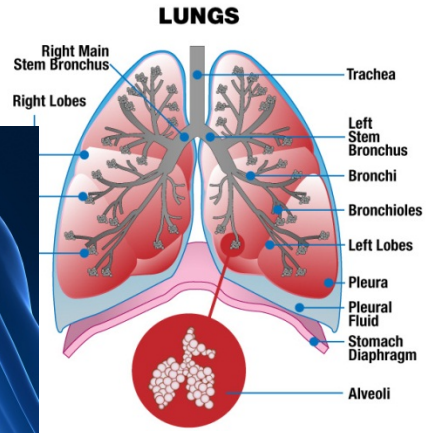
Physiologically Based Models

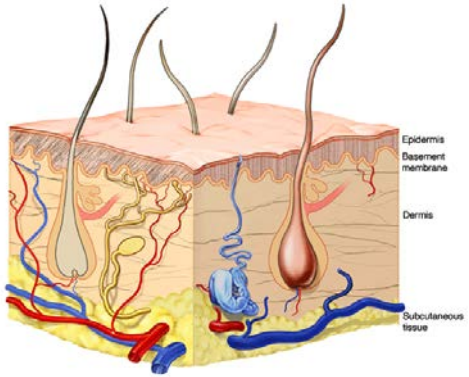
Drug Substance Formulations In Vitro Testing → **Physiological System** → **In vivo Performance**





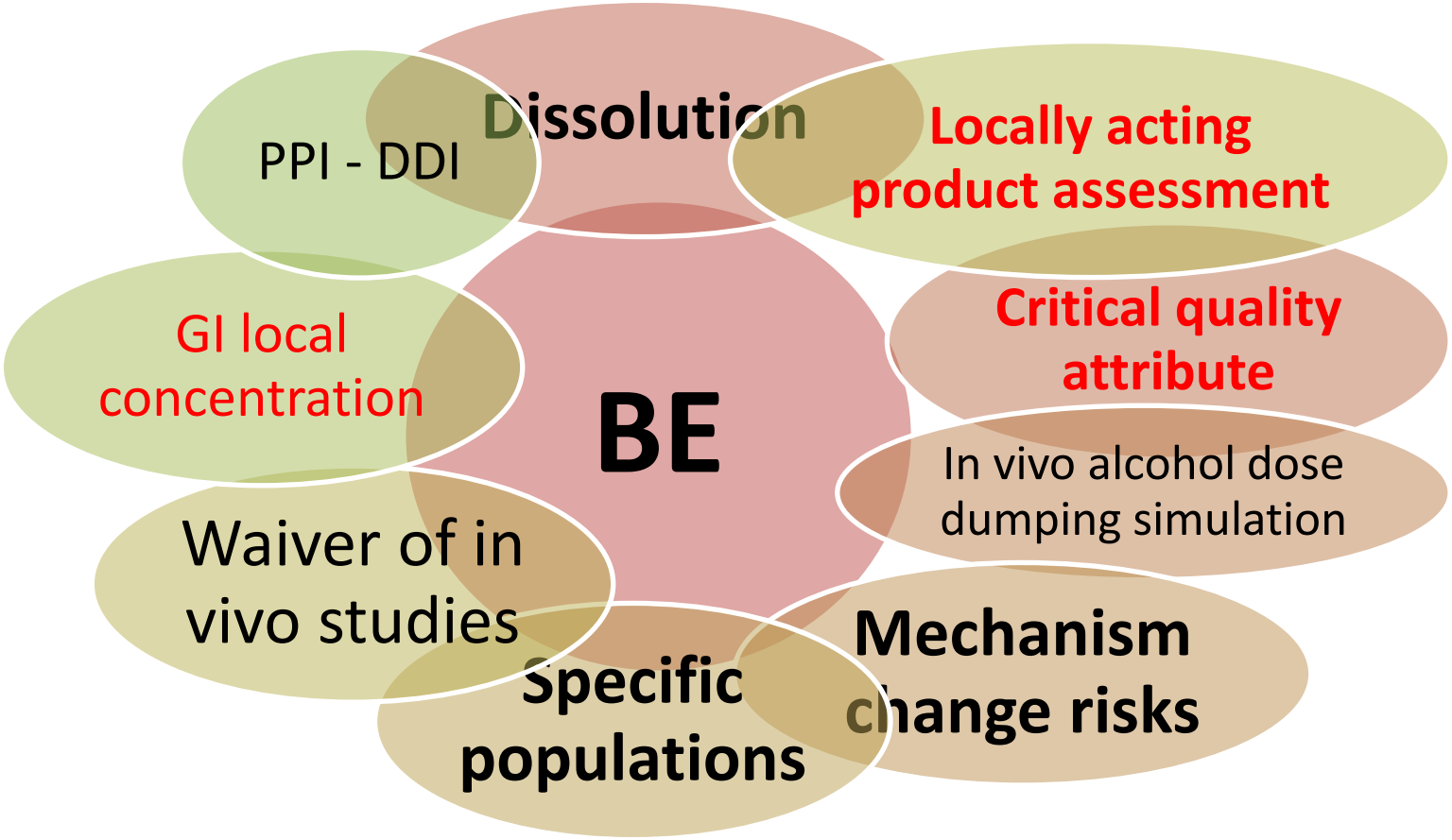






Based on the publication by Jiang W, Kim S, Zhang X, Lionberger RA, Davit BM, Conner DP, Yu LX. Int J Pharm. 2011 Oct 14;418(2):151-60.

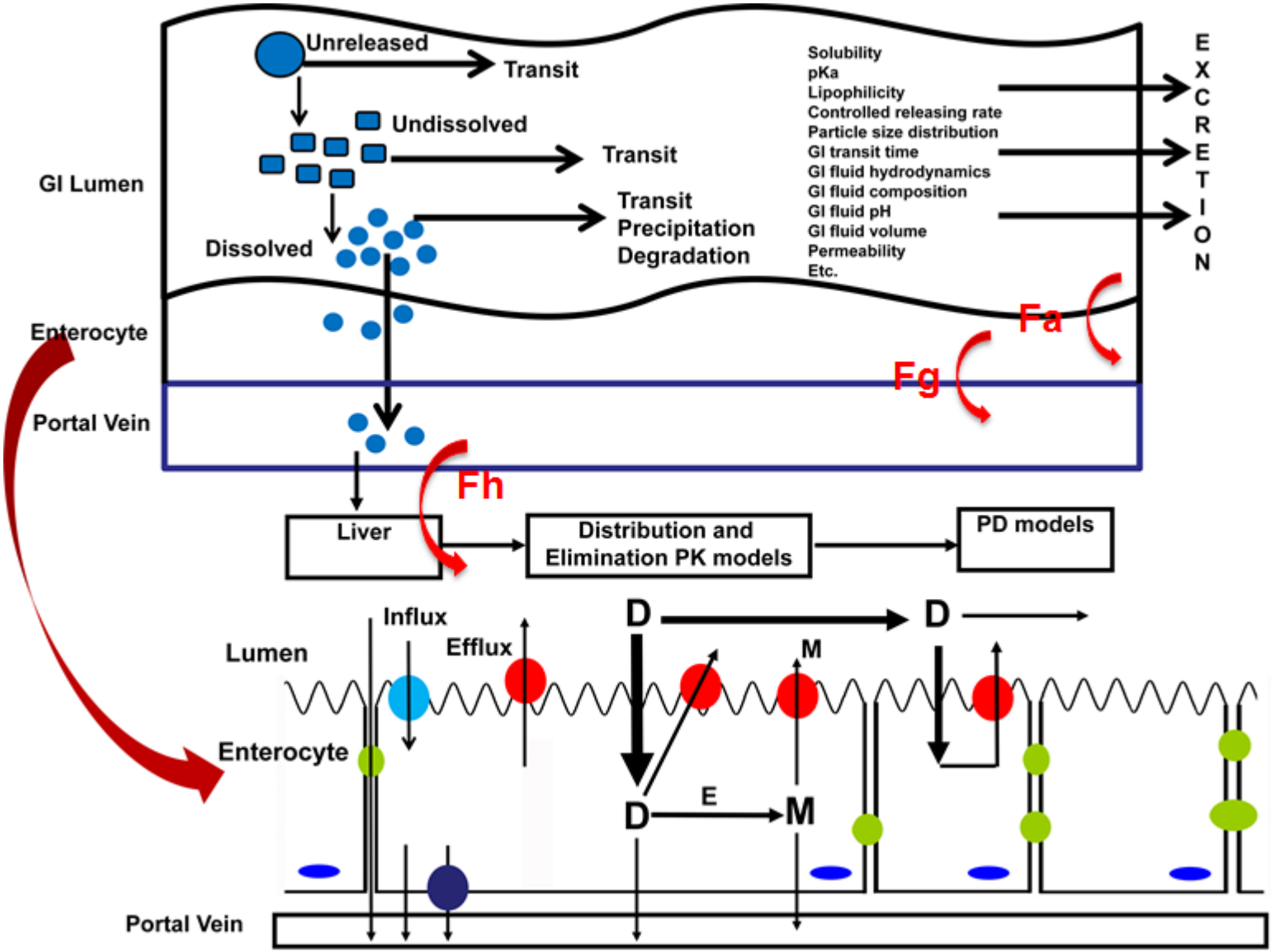
General PBPK Model Applications for Generic Products



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

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

Factors Affecting Oral Absorption



Source: Xinyuan (Susie) Zhang

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

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Quantitative Clinical Pharmacology

Quantitative Clinical Pharmacology TOOLKIT for Generics

Pharmacometrics Methods

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

What is a Virtual BE Study?

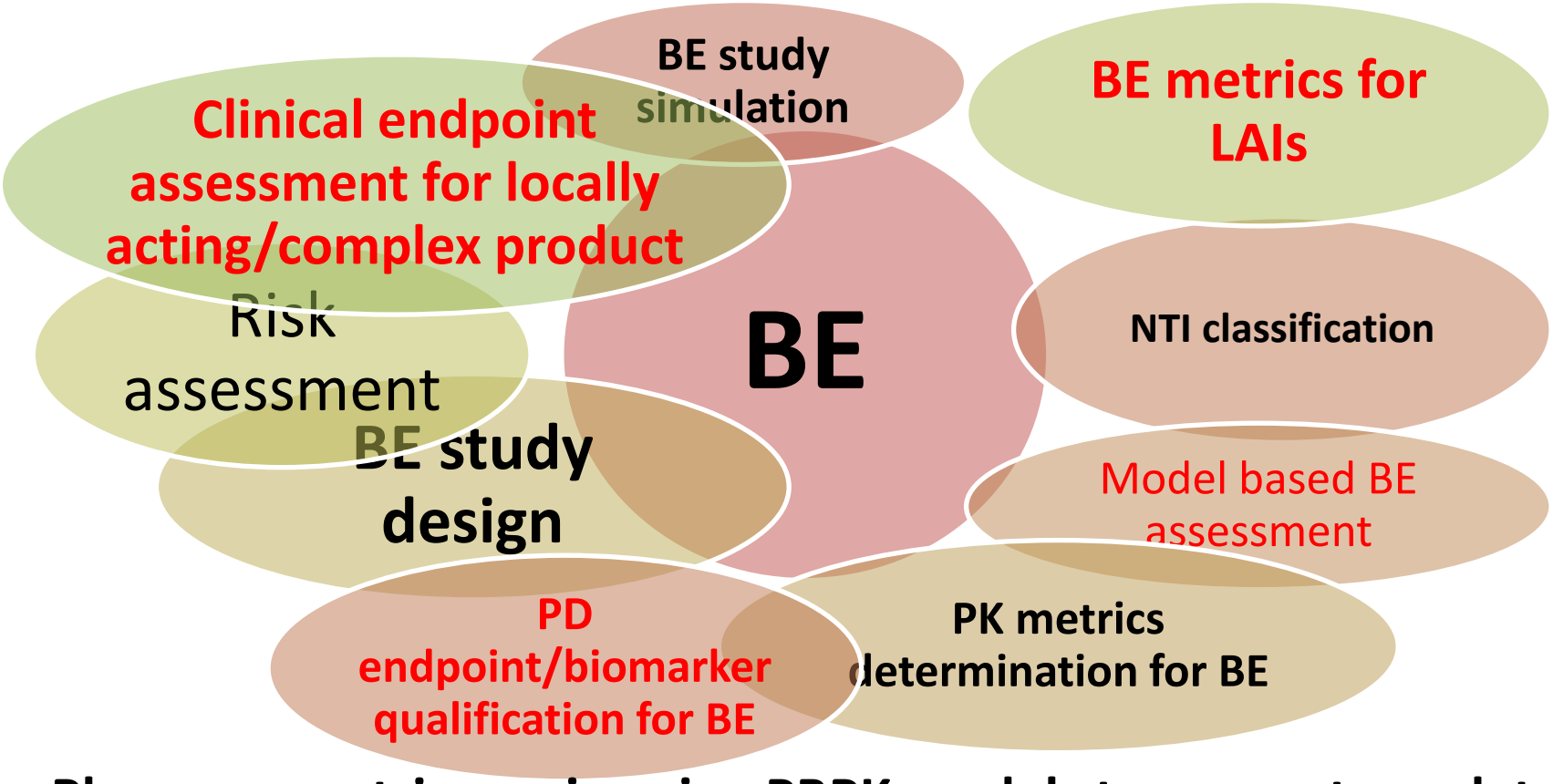
- Use of model to compare test and reference formulations
- The model must have a formulation variable that can be adjusted to represent the difference between T and R
- The model generates a population for BE study, compares T and R in that population
  - Simulate many studies to estimate probability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

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

Quantitative Clinical Pharmacology

- Established and useful for solid oral products
- Applications for locally acting and complex products

General QCP Model Applications for Generic Products



Pharmacometrics as in using PBPK models to support regulatory decision makings in the realm of generic drug development

QCP: quantitative clinical pharmacology

Highlights of QCP Impacts (Year 2016)

Category	Example Drug	Impact on regulatory decision making
PK metrics determination	Eletriptan	Evaluation on including pAUC for BE assessment and recommendation that standard Cmax, AUC0-t, and AUC0-inf PK measures, along with the examination of tmax, are sufficient to establish BE between the generic immediate release eletriptan tablets and the respective RLD product
Study design	Desoximetasone	Evaluation on interim analysis concluded that sponsor's analysis will not inflate the type one error. The reviewer also recommended not excluding the outlier from analysis which failed the BE assessment.
	Loteprednol Etabonate	Evaluation of the adequacy of the proposed sequential study design in BE evaluation of sparse in vivo PK data.
PK metrics determination	Mesalamine Suppositories	Recommendation on using AUCinf as a supporting BE metric for the particular ANDA
	Methylphenidate Hydrochloride	Recommend partial AUC be included for BE evaluation of generic MPH transdermal system to ensure comparable drug exposures during clinically relevant time windows
Clinical endpoint evaluation	Brimonidine	Pharmacodynamic (PD) model was used to extrapolate PD response at unstudies time point
PK metrics determination	Mesalamine Suppositories	Determination of PK metrics for BE evaluation
In vitro BE	Cyclosporine Ophthalmic Emulsion	Evaluation on particle size distribution to establish BE
BE assessment	Glucagon Powder	Recommendation of in vivo BE study design
PD based BE methods	Albuterol Sulfate Metered Inhalation Aerosol	Evaluation of data processing and statistical algorithm used in the dose scale analysis of in vivo PD endpoint.

QCP: quantitative clinical pharmacology; ER : extended release

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Health Outcomes and Big Data

Big Data

- Post market
- Big data models
  - Workload/research prediction
  - Pharmacoeconomics: generic areas for health care cost reduction
  - Area of improvement for regulatory communications

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

Further Research Needs

- BE demonstration for complex and locally acting products is challenging.
  - Further abbreviate clinical endpoint BE study program
  - Critical quality attribute identification
  - Innovative study design

- Recent advancement in science created several innovative pathways for BE of locally acting products in addition to clinical endpoints BE studies.
  - Better analytical tools
  - Better product characterization
  - **Quantitative methods and modeling**

- M & S Impact: Model based guidance development for complex and locally acting products will ensure timely availability of high quality and affordable generics for patients.

Research Priorities

- Develop PBPK models for complex routes of delivery (nasal, inhalation, dermal, ophthalmic) where there are limitations to generic competition
- Use quantitative pharmacology and bioequivalence trial simulation to optimize BE studies for complex products
- Leverage Big Data for decisions related to generic drugs

Key Questions for Inputs

- Opportunities to use modeling to inform regulatory decision making in both pre-ANDA and review stages (e.g. BE metrics determination)
- Gaps that needs to be closed for quantitative methods to provide evidentiary support for drug approval, especially for locally acting and complex products


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