# A Model- & Systems-based Approach to Assess & Ensure Generic Substitution

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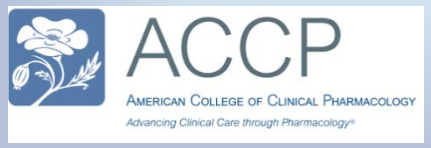


2018 Annual Meeting

# Disclosures:

The presenter has no financial interests in any of the presented materials and do not have any financial interests or relationships to disclose.

# Learning Objectives:

- Modeling and simulations (M&S) to assess and ensure effective and safe generic sameness via bioequivalence assessment through pre-marketing evaluation
- M&S to assess and ensure generic substitution through post-marketing evaluation
- Systems-based approaches to ensure generic substitution

# SYM08 Polling Question #1

I am a _____ !

A. Clinical pharmacologist
B. Pharmacometrician/Modeler
C. Pharmacist
D. Formulation scientist
E. Professional in regulatory affairs
F. Physician
G. Other

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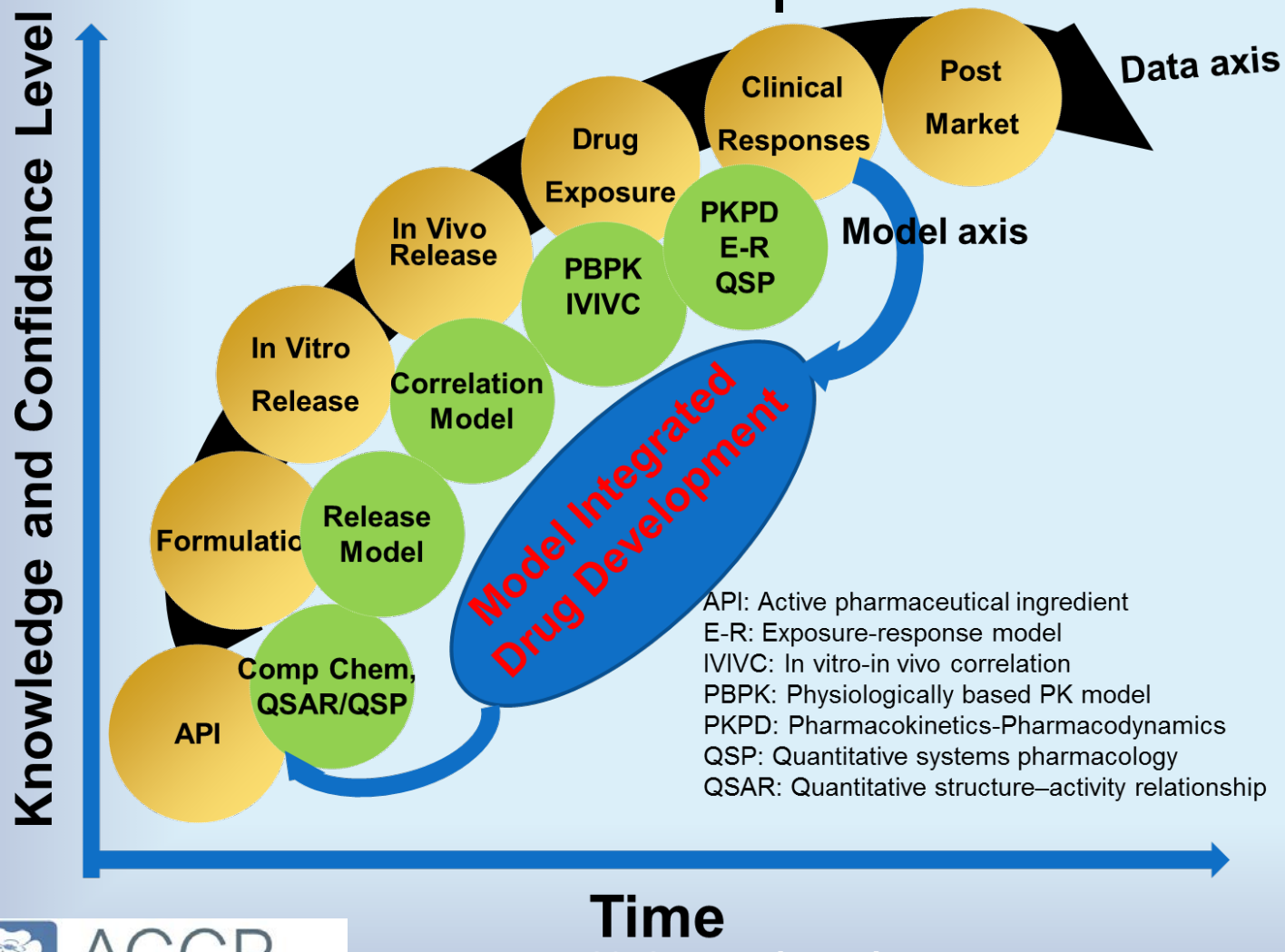
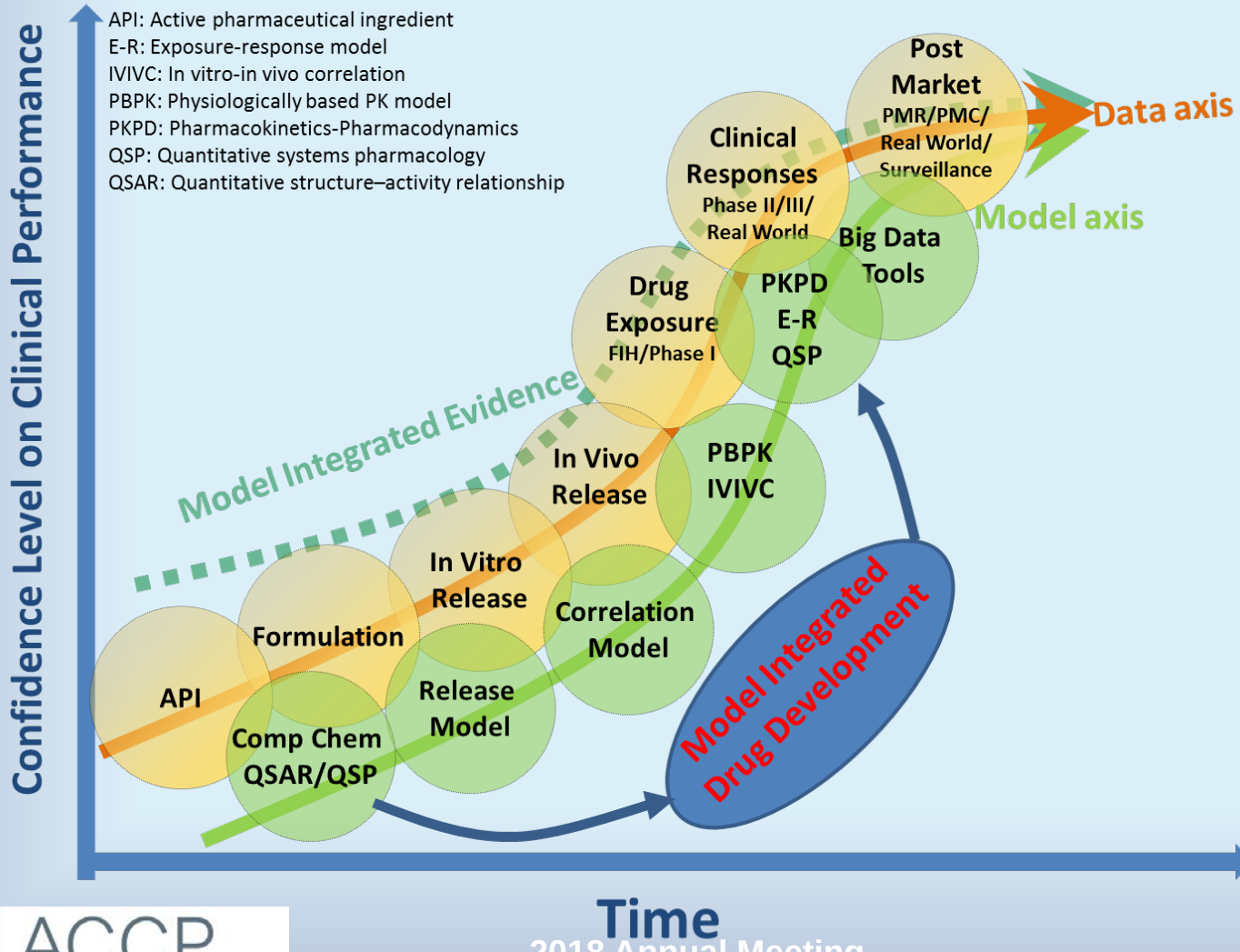
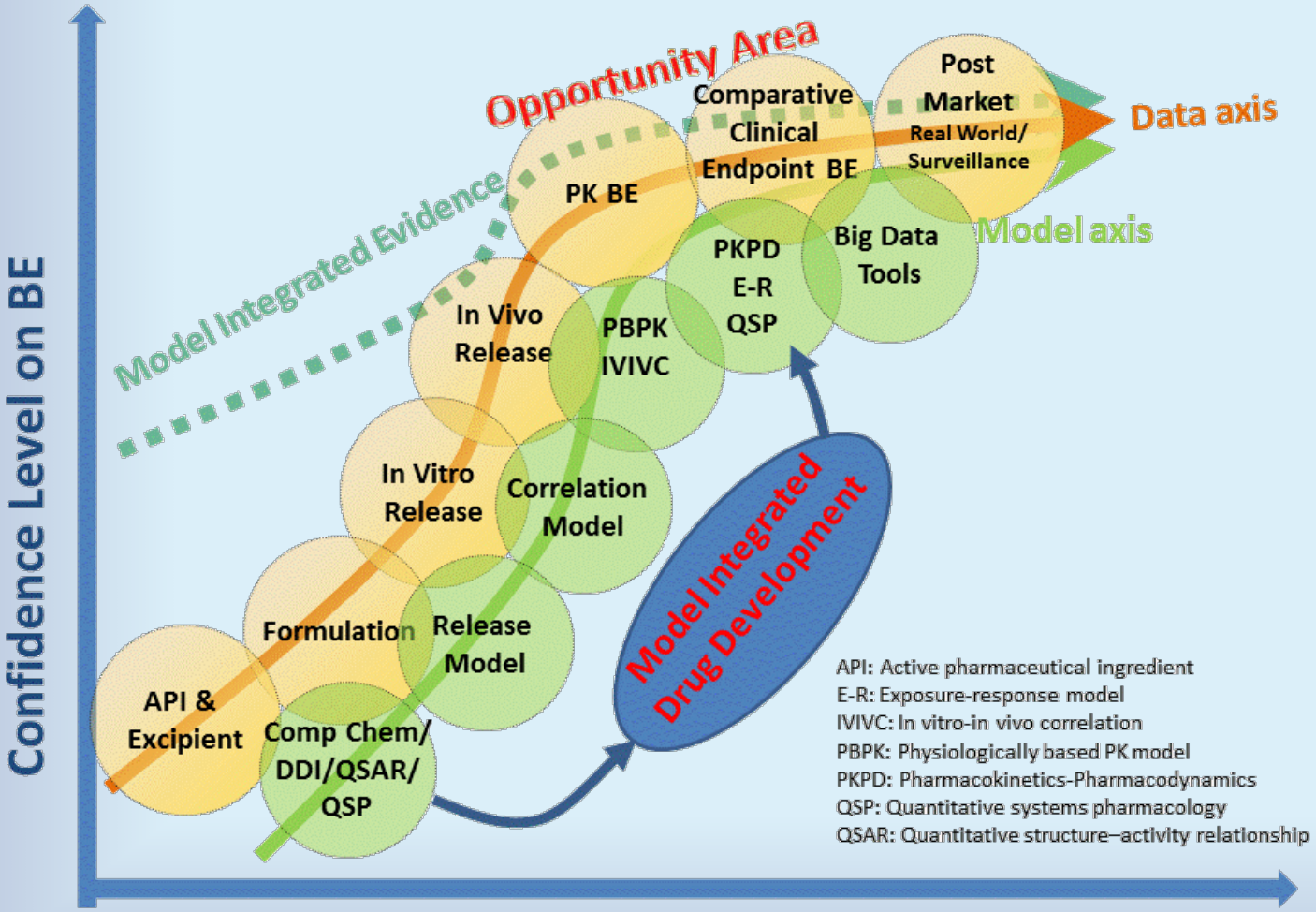
# Modeling Integrated System for Drug Development



# Modeling Integrated System for New Drug Development



# Modeling Integrated System for Generic Drug Development



# SYM08 Polling Question #2

What stays the same between an NDA and its corresponding ANDA submissions?

A. Regulatory requirements

B. Amount of data as included in the ANDA

C. Underlying models for formulation-PK-PD-clinical response relationships

D. The application fee

# M&S to Assess and Assure Generic Drug Substitutability during Premarketing

- Assist generic drug development
- Support product-specific guidance (PSG) development
- Support Pre-ANDA interactions
- Assist ANDA review
  - To assess risk of bioinequivalence
  - To bridge missing information and data
  - To support alternative BE approaches

*Cases will be introduced in the following slides*

# Use Case: PBPK in Assessing BE in the Presence of Proton Pump Inhibitors (PPIs)

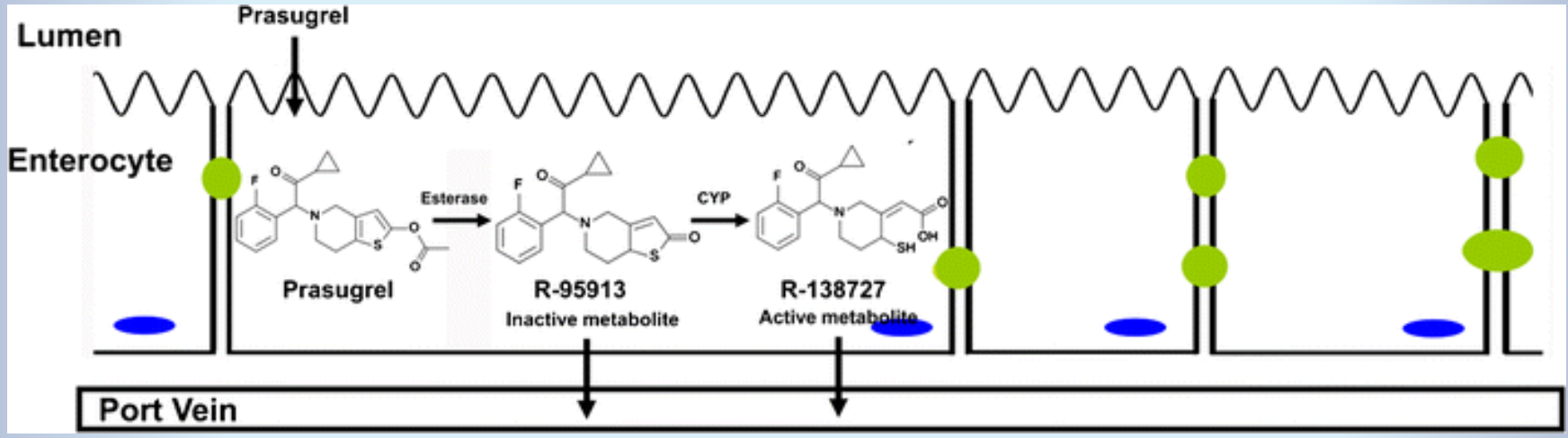
- Prasugrel tablets: for the reduction of the rate of thrombotic cardiovascular events in patients with acute coronary syndrome
- Prasugrel HCl salt tends to convert to prasugrel free base during manufacturing or storage, a process known as disproportionation

- PBPK Models were used to address question regarding threshold value on critical quality attribute to ensure BE



Fan et al, AAPS. J. **19** 1479-1486. (2017)

# Biotransformation Pathway of Prasugrel to its Inactive Intermediate Metabolite (R-95913) and Active Metabolite (R-138727)




- Following oral administration, prasugrel HCl is rapidly hydrolyzed by hydroxyesterases in the intestine to a thiolactone (R-95913), which is then converted to the active metabolite (R-138727) by a single step, primarily by CYP3A4 and CYP2B6 and to a lesser extent by CYP2C9 and CYP2C19.
- R-138727 is further metabolized to two inactive metabolites by S-methylation or conjugation with cysteine (R-119251 and R-106583)

Fan et al, AAPS. J. **19** 1479-1486. (2017)

# Clinical Findings

- Prasugrel HCl products with low (5%), intermediate (58%), and high (70%) degrees of conversion to base were
  - Bioequivalent to each other in terms o f $C_{max}$ and AUC of R-138727 with PPI
  - Still bioequivalent for AUC, but not bioequivalent for $C_{max}$ with PPI
    - The mean difference in $C_{max}$ between the low and the high conversion products, the medium and high conversion products, and the low and medium conversion products were 29% (90% confidence internal (CI) 0.62, 0.83), 20% (90% CI 0.69, 0.92), and 10% (90% CI 0.77, 1.04), respectively
- Analysis of the pharmacodynamics of prasugrel HCl product (60 mg) demonstrated that 29% differences in $C_{max}$ may result in a delay of perhaps 20 min in achieving maximal inhibition of platelet aggregation

***Question: What will be a conservative control for disproportionation % of prasugrel, when co-administered with PPI?***



Fan et al, AAPS. J. **19** 1479-1486. (2017)

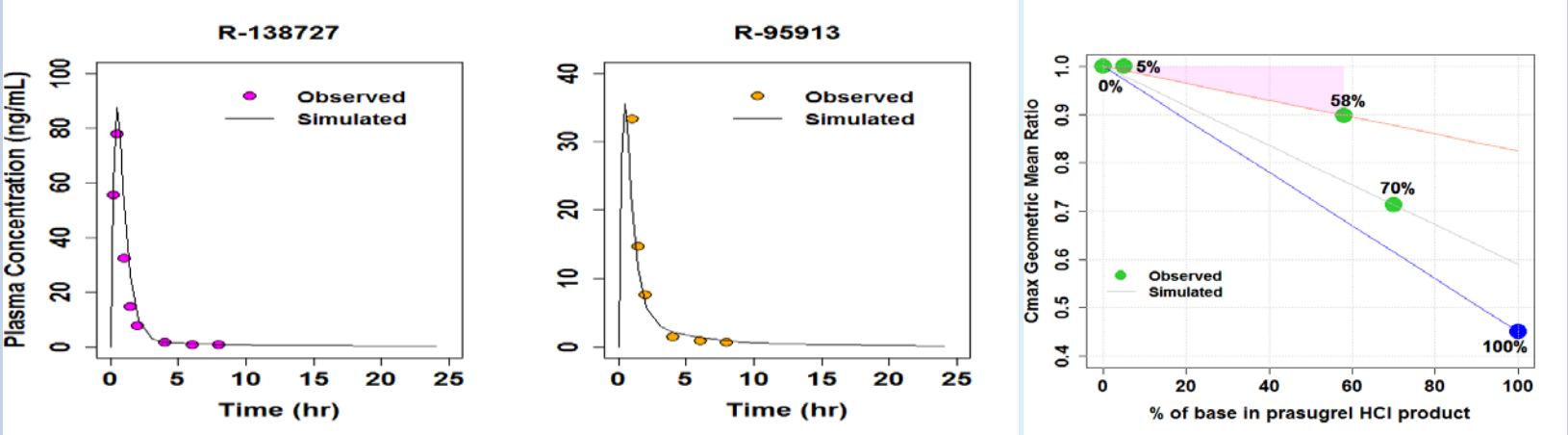
# Method

- A dynamic PBPK model was developed and validated for R-95913 and R138727
- The ADAM absorption model was selected with pH-dependent solubility, and an effective permeability ($P_{eff}$) in human was used as input parameters
- The distribution of prasugrel, primary metabolite, and secondary metabolite were described by a minimal PBPK model
  - The minimal PBPK model: a “lumped” model that has four compartments, predicting the systemic, portal vein, liver, and peripheral compartment concentrations
- The dissolution rate from solid dosage forms can be calculated using diffusion layer models (DLM)



Fan et al, AAPS. J. **19** 1479-1486. (2017)

# Observed and simulated values for 60-mg prasugrel HCl product with various levels of free base conversion in healthy subjects with PPI intake




- Intrinsic solubility of prasugrel HCl salt was deconvoluted based on the $C_{max}$s over the dose range of 10–60 mg for prasugrel HCl products containing 0% base in healthy subjects without taking PPI
- The only data available for prasugrel base are the data points plotted where the products were administered with PPI



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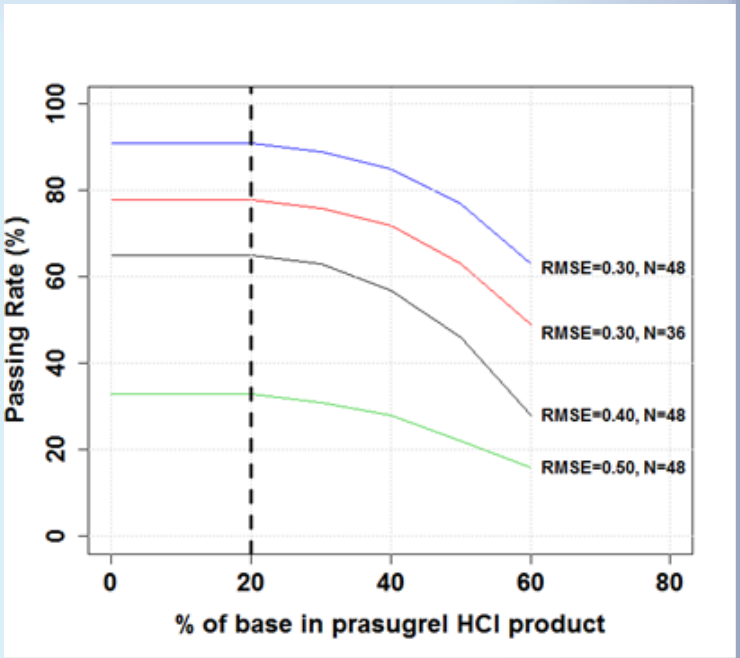
# Virtual BE Simulation Results

- The root mean squared error (RMSE) for R-138727 $C_{max}$ is 0.30 from multiple BE studies submitted to FDA, which was used in BE trial simulations to account for residual variability
- The deconvoluted intrinsic solubility of prasugrel base based on the PK profile of prasugrel HCl formulation containing 58% base for virtual bioequivalence (BE) trial simulation
- The simulation result predicted that 20% free base in the product results in 3% difference in Cmax between reference (0% base) and test product (20% base), which was considered as insignificant with respect to the impact of 20% base on BE evaluation




The sensitivity to detect formulation differences was assessed by comparing the passing rate of $C_{max}$ in each study based on average bioequivalence (ABE) criterion

**Critical quality attribute for salt to base conversion: <20% !**

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# SYM08 Polling Question #3

M&S isn't useful for what aspect of generic development and reviews?

A. Alternative BE approaches
B. Complex substance evaluation
C. PK metric determination for BE establishment
D. Save failed PK BE study
E. Evaluation of BE risks associated with comedication, specific population, and difference in PK curves

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# Generic Drug Substitutability

- In 2017, OGD received ~640 individual spontaneous case reports related to the quality of generic drugs each month
  - 55% described issues related to switching between brand and generic
- Over the past decade, several observational studies have been published that question the bioequivalence of generic drugs

# OGD Regulatory Actions on Three Products Related to Issues of Therapeutic Inequivalence (2011-2016)

1. Bupropion Hydrochloride Extended-Release tablets 300 mg Bioequivalence Studies. http://www.fda.gov/Drugs/DrugSafety/ucm322161.htm.
2. Methylphenidate Hydrochloride Extended Release Tablets (generic Concerta) made by Mallinckrodt and Kudco. http://www.fda.gov/Drugs/DrugSafety/ucm422568.htm.
3. Letter to Healthcare Professionals: Communication on lansoprazole delayed-release orally disintegrating tablets manufactured by Teva Pharmaceuticals. 2011. https://wayback.archive-it.org/7993/20170112031950/http://www.fda.gov/Drugs/DrugSafety/ucm251485.htm

**These cases highlight the importance of post marketing evaluation to ensure generic substitutability**

# SYM08 Polling Question #4

What isn't useful for a data source in post marketing analysis?

A. Adverse event report

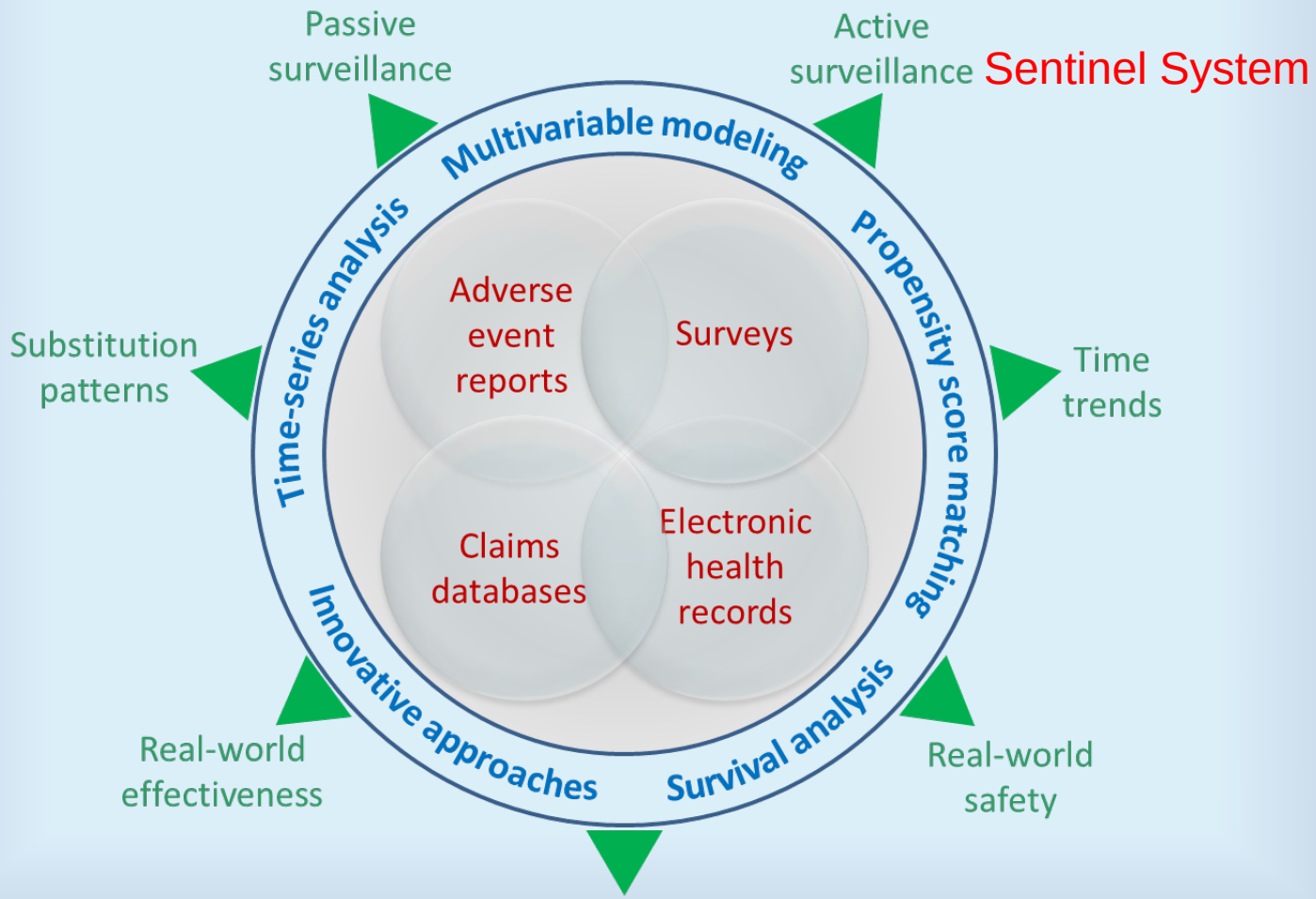
B. Surveys

C. Claim database

D. NDA or ANDA data in the application package

E. Electronic health records

# Analyzing data for postmarketing surveillance of generics



# GDUFAI Regulatory Science on Generic Drug Utilization and Substitution (FYs2013 - 2017)

- **A model- and systems-based approach to efficacy and safety questions related to generic substitution (**Grant 1U01FD005210, Univ. of Florida**)**
- **Pharmacometric modeling and simulation for generic drug substitutability and post marketing risk assessment (**Grant 1U01FD005192 , Univ. of Maryland)
- **Novel approaches for confounding control in observational studies of generic drugs (**Grant 1U01FD005555, Brigham & Women's Hospital )
- **Structural nested models for assessing the safety and effectiveness of generic drugs (**Grant 1U01FD005556, Johns Hopkins Univ**)**
- **Comparative surveillance of generic drugs by machine learning (**Contract HHSF223201510112C, Marshfield Clinic**)**
- **Generic drug substitution in specific populations (** Contract 1U01FD005875, IMPAQ International & Auburn Univ.)
- **Characterizing use, safety and efficacy of brand-name and generic drugs used to treat hypothyroidism** (CERSI-Mayo Clinic/Yale)
- **Identify and evaluate manufacturer-level drug utilization and switching patterns in Sentinel** (Internal Project)

# Case: Sentinel Tool Development

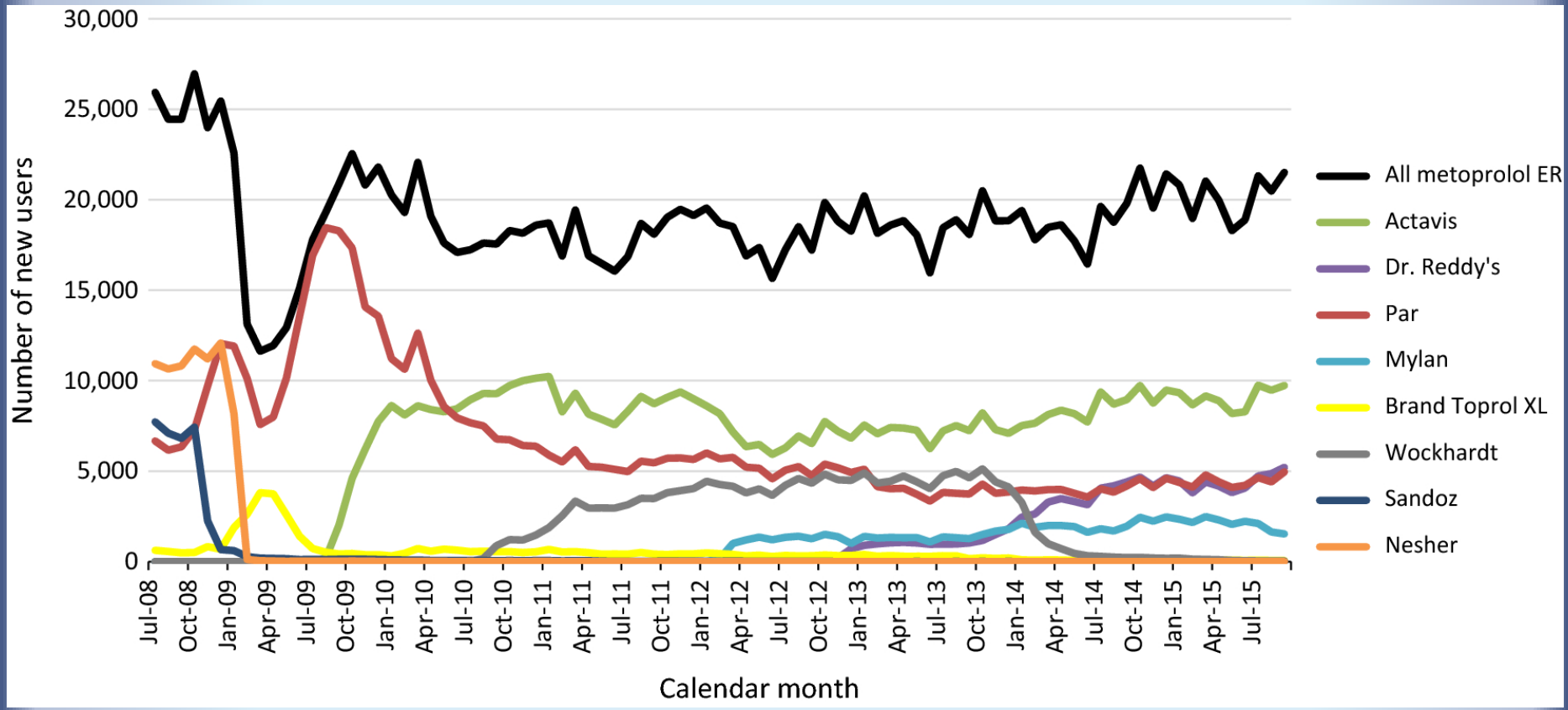
- Sentinel: FDA's active surveillance system for medical products
  - from a distributed data network of 18 data partners
- FDA's Sentinel Initiative - deliverables from completed contracts are publicly available
- Existing Sentinel tools were still limited in their ability to study brand and generic switching patterns
- **Objective: To develop and implement a modular, reusable tool for describing manufacturer-level drug utilization and switching patterns within the US FDA's Sentinel system**

# Use Cases: Metoprolol extended release (ER)

- Beta blocker indicated for the treatment of hypertension, angina pectoris, and heart failure
- First generic was approved July 31, 2006
- From 2008-2014, several manufacturers recalled some generic products due to failures in meeting quality standards

# Results: Metoprolol ER

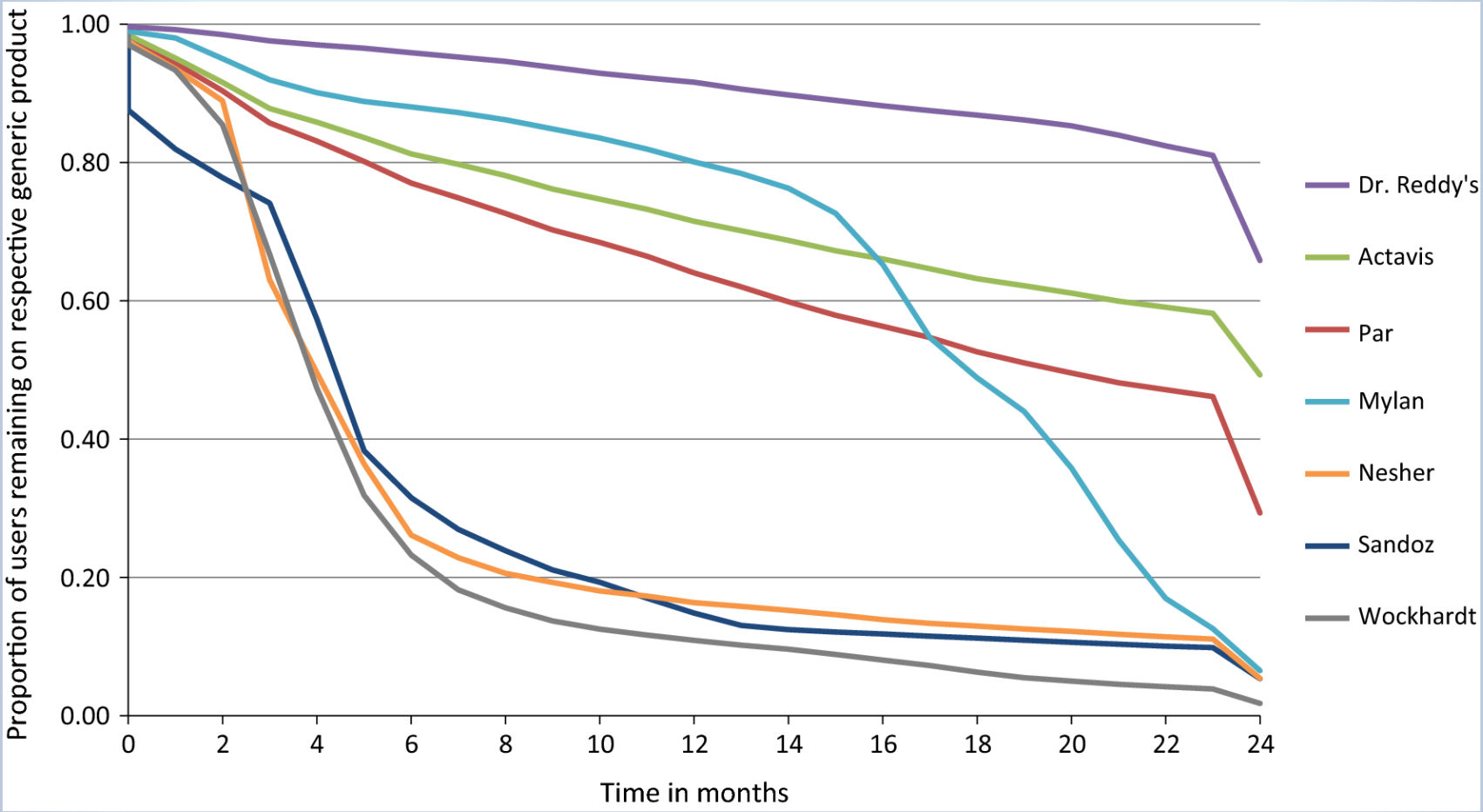
## Monthly Number of New Users, Metoprolol ER




Gagne et al. Drug Saf. 2018 Aug 17. doi: 10.1007/s40264-018-0709-4.

# Results: Metoprolol ER

## Time to Switch to Generic, Metoprolol ER

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# Metoprolol ER Summary

- Substantial changes in utilization following several manufacturer-specific production and availability issues
- High rates of switching from two generic products that were recalled and later discontinued
- Characterizing and evaluating switching or switchback patterns is an essential exploratory analysis of post-marketing surveillance of generic drugs
- Potential future enhancements



Andermann F, et al. *Epilepsia* 2007;48:464-9.
LeLorier J, et al. *Neurology* 2008;70(22 Pt 2):2179-86.

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# Systems-Based Approach

- Formulation: excipient
- Manufacture
- Systems biology/bioinformatics
- Systems pharmacology
- PBPK models
- PK-PD models/exposure-response models
- Postmarketing signals

# Example Workflow for A Systems Approach to Ensure Sameness (1)

Post Marketing (PM) signal as detected by advanced PM evaluation methods from data sources including:

- Sentinel system
- Standalone Claim/EHR databases
- FARES etc

**Causality of generic drug-AE pair**

PBPK Absorption/Drug-drug interaction models

Systems biology/ Bioinformatics?

**Potential (subgroup) PK exposure change**

PK-PD/ Exposure-response models to inform clinical relevance

**Interpretation, Report, and Decision Making based on Weight of Evidence**

*Representative Works from Dr. Stephan Schmidt, Univ. Florida in press/submission* (Grant 1U01FD005210)

Physiologically Based Pharmacokinetic Modeling to Evaluate Formulation Factors Influencing Bioequivalence of Metoprolol Extended-Release Products.

A Model and Systems Based Approach to Assess Impact of Changes in Formulation on Dissolution, Pharmacokinetics, Pharmacodynamics and Questions Regarding Generic Equivalence – A Metoprolol Extended Release Case Study

# An Example Workflow for A Systems Approach to Ensure Sameness (2)

Epilepsy/transplant community concerns for patients switching to generic antiepileptic drugs/ immunosuppressants

**PK data in healthy subjects/patients**

PBPK Absorption/Drug-drug interaction models

Population PK model to characterize PK variability

**PK profile and variability characterization for specific products**

**Virtual BE study simulations to evaluation generic bioequivalence**

*Representative Works under GDUFA regulatory science program:*
Tacrolimus (a narrow therapeutic index drug): PBPK model to assess impact of crystallinity extent on the oral absorption of the products; PopPK model was used to characterize PK profiles of different formulations and assess the formulation effect on drug exposure

Lamotrigene: PBPK based IVIVR model to evaluate BE for waived strengths of Lamotrigiene ER ; PopPK model was used to conduct in silico studies to assess equivalence between generics

# SYM08 Polling Question #5

What type of information is considered in a systems approach to assess generic drug substitution?

A. Excipient/ Dissolution profile
B. Color and shape of the tablet
C. Systems pharmacology
D. PBPK model/Exposure-response relationship
E. All

# Take Home Message

- M&S are integration of knowledge and experience gained from full product life cycle and should be used as key toolsets to ensure generic drug efficacy and safety
- Although M&S have been mostly used in premarketing stage to ensure quality approval, great needs exist in developing new methods for postmarketing evaluations
- A systems-based approach is a powerful tool by integrating all knowledge together to have an ultimate comprehensive evaluation of bioinequivalence risks that could impact generic drug substitution

# Acknowledgement


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- Lei Zhang

OGD/ORS/DTP

OGD/OB

OSE/OPE/DEPII

- Sarah Dutcher

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# 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: pro[illegible]itor; ER : extended release



Source: Lev[illegible]thods and Modeling to Modernize Generic Drug Development and Review; FDA Public Workshop, October 2 - 3, [illegible] modeling methodologies in generic drug development. May 17th, 2018.

# 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;



Source: Lev thods and Modeling to Modernize Generic Drug Development and Review; FDA Public Workshop, October 2 - 3, modeling methodologies in generic drug development. May 17th, 2018.