# The Science of Therapeutic Equivalence

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- In this presentation I am relaying personal views and opinion. This presentation is not intended to convey official US FDA policy, and no official support or endorsement by the US FDA is provided or should be inferred.

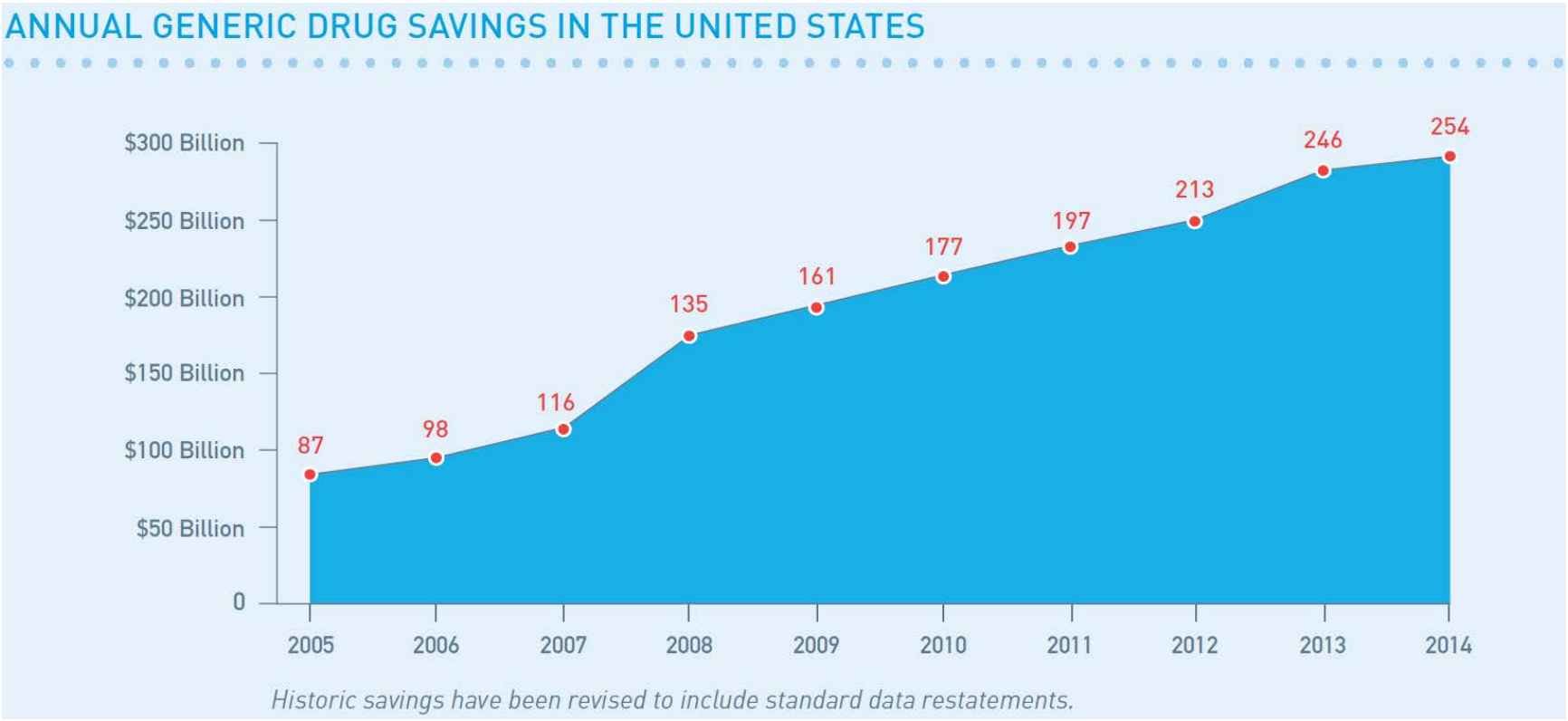
- The materials presented are available in the public domain.

- I do not have any financial interest or conflict of interest with any pharmaceutical company.

# Outline

- ANDA and Bioequivalence
- Demonstrating BE for complex dosage forms
  - Examples: Draft Guidance for Demonstrating BE
- Roles of modeling and simulation in generic drug regulatory science
- Generic Drug Regulatory Science

# Significance of the Generic Drug Program




http://www.gphaonline.org/media/wysiwyg/PDF/GPhA_Savings_Report_2015.pdf

# ANDAs vs RLDs

- Per 21 CFR 314.92 ANDAs may be submitted when the generic drug is the same as the reference listed drug (RLD) in
  - active ingredient(s)
    - ***Might differ in inactive ingredients*** (21 CFR 314.94(a)(9))
  - strength
  - dosage form
  - route of administration
  - conditions of use

- *However, ANDA maybe different from RLD in formulation design*
  - What is the impact of formulation design on BE?

# Bioequivalence

- Per 21 CFR 320.1 , “Bioequivalence” is defined as
  - The absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

# Product Specific BE Guidance

*FDA Guidance for Industry: Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA (2013)*

- Pharmacokinetic Studies
  - Fasting vs fed
  - Single-dose vs steady-state
  - Study population
- Other Approaches to Demonstrate BE
  - In Vitro-In Vivo Correlation Studies
  - Pharmacodynamic studies
  - Comparative clinical studies
  - In vitro studies

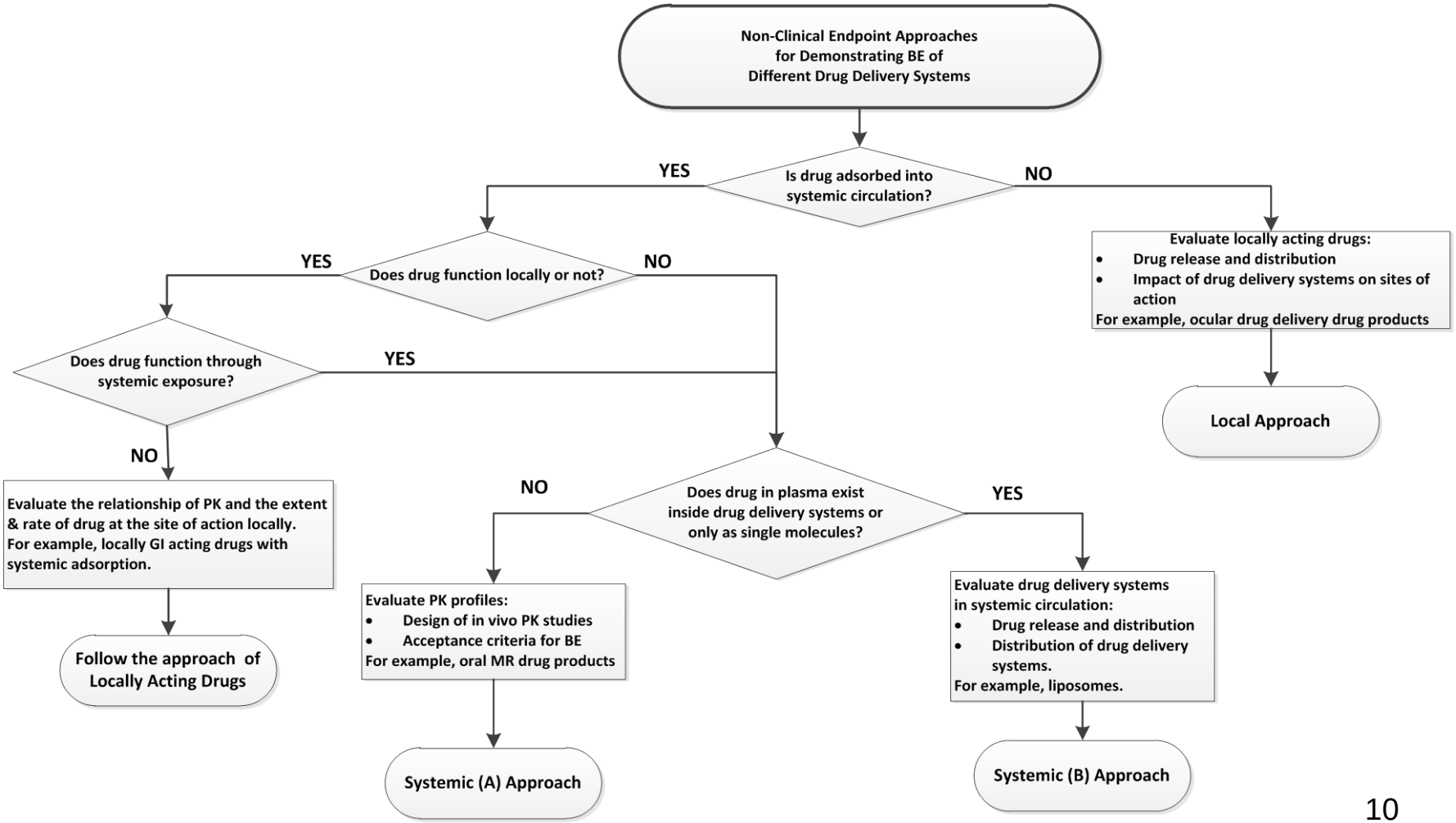
# Regulatory Science for Generic Drugs

- GDUFA Regulatory Science Priorities for Fiscal Year 2016
  - Post-market evaluation of generic drugs
  - ***Equivalence of complex products***
  - ***Equivalence of locally-acting products***
  - ***Therapeutic equivalence evaluation and standards***
  - Computational and analytical tools
  - Complex drug delivery systems pose challenges on consistent quality and therapeutic performance for both brand and generic drugs

# List of Classifications for Drug Delivery Systems

| Route of Administration | Dosage Form | BE Approach |
|---|---|---|
| **Oral** | Capsule, tablet, suspension, solution | Local or Systemic (A) |
| **Buccal** | Film, tablet, chewing gum | Local or Systemic (A) |
| **Sublingual** | Film, tablet | Systemic (A) |
| **Dental** | Paste, powder, insert | Local |
| **Inhalation (oral)** | Aerosol, powder, suspension, spray | Local or Systemic (A) |
| **Nasal** | Spray, drop, ointment | Local or Systemic (A) |
| **Endocervical** | Gel | Local |
| **Injection, intravenous** | Liposome, suspension, solution | Systemic (A) or Systemic (B) |
| **Injection, subcutaneous** | Injection, implant | Systemic (A) |
| **Injection, intramuscular** | Solution, suspension, implantation | Systemic (A) |
| **Ophthalmic** | Suspension, solution, ointment | Local |
| **Otic** | Suspensions/drops | Local |
| **Topical** | Lotion, cream, gel, spray | Local |
| **Transdermal** | Film, gel, ointment, solution | Systemic (A) |
| **Rectal** | Enema, gel, suppository | Local or Systemic (A) |
| **Vaginal** | Cream, gel, ring, insert, suppository, tablet, capsule | Local or Systemic (A) |

# Non-clinical Endpoint Systematical Approaches To demonstrate BE of different drug delivery systems



# BE for Different Drug Delivery Systems
## - examples

- Drug delivery systems exist in systemic circulation, e.g. doxorubicin liposome
- Locally GI acting drugs, e.g. fidaxomicin
- Drug device combinations, e.g. ventolin HFA (albuterol sulfate) inhalation
- Oral modified release formulations, e.g. methylphenidate HCl (Concerta) tablet

# Drug Delivery Systems Exist in Systemic Circulation

| Drug Delivery System | Example |
|---|---|
| **Nano-suspensions** | Abraxane (paclitaxel) |
| **Liposomes** | Marqibo (vincristine), Doxil (doxorubicin hydrochloride) |
| **Iron carbohydrate complexes** | Venofer® (iron sucrose) |
| **Complexations & ion paring** | Vfend® (voriconazole) |
| **Polymeric micelles** | No approved drug yet. Many candidates in clinical trials. |
| **Emulsions & microemulsions** | Diazemuls® (diazepam) |

# Example: Draft Guidance on Doxorubicin HCl *Liposome*

- When the test and reference pegylated liposome products are
  - Same drug product composition:
    - Lipid excipients are critical in the liposome formulation.
  - Active liposome loading process with an ammonium sulfate gradient
  - Equivalent liposome characteristics
- *The following clinical and in vitro studies are recommended to demonstrate bioequivalence:*
- In Vivo Bioequivalence Study: Fasting
  - Analytes to measure (in appropriate biological fluid): Free doxorubicin and liposome encapsulated doxorubicin.
  - Bioequivalence based on (90% CI): AUC and Cmax for free doxorubicin and liposome encapsulated doxorubicin.
- In Vitro Study:
  - Type of study: Liposome Size Distribution

# Locally GI Acting Drugs

## - Three Scenarios

- No or minimal systemic exposure
- Measurable pharmacokinetic profiles, but the region of absorption may overlap with the site of action in human GI tract
- Measurable pharmacokinetic profiles, but the region of absorption may not overlap with the site of action in human GI tract

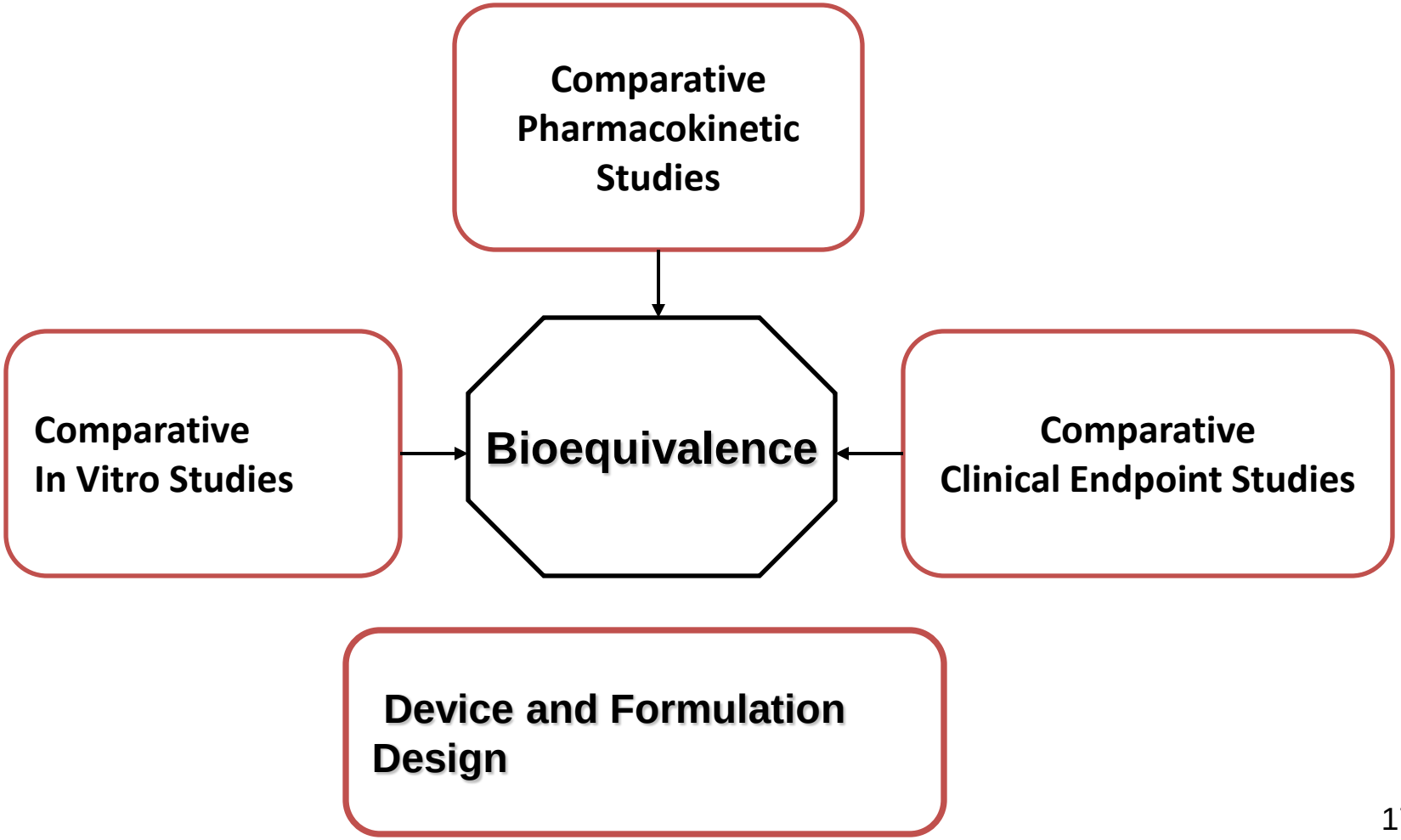
# Example: Draft Guidance on Fidaxomicin
## *Tablet*

- BE Option 1 for Q1/Q2 generic:
  - In vitro dissolution study
  - In vivo BE study with PK endpoint: both Fasting and Fed
    - Analytes to measure (in appropriate biological fluid): Fidaxomicin and its active metabolite, OP-1118 in plasma
    - Bioequivalence based on (90% CI): Fidaxomicin
- BE Option 2 for non-Q1/Q2 generic:
  - BE should be established by conducting an in vivo study with clinical endpoints in patients with Clostridium difficile Associated Diarrhea (CDAD).

# Drug Device Combinations

| Drug Device Combination | Example |
|---|---|
| **Inhalation** | Ventolin HFA (albuterol sulfate) |
| **Transdermal patch** | Daytrana (methylphenidate) |
| **Ring** | Nuvaring (Ethinyl Estradiol; Etonogestrel) |
| **Stent** | Endeavor (sirolimus) |

# Regulatory Considerations for Generic DPIs



# Example: Draft Guidance on Albuterol Sulfate
## *Inhalation*

- Formulation and Device
  - The T product is recommended to be Q1/Q2 as the RLD, and be similar in shape and size to the RLD.
- In Vitro Studies
  - Single actuation content (SAC), Aerodynamic particle size distribution (APSD), Spray pattern, Plume geometry, Priming and repriming
- In Vivo Studies:
  - Pharmacokinetic (PK) BE Study: Fasting
  - Pharmacodynamic (PD) BE Study
    - Bronchoprovocation study
    - Bronchodilatation study

# Oral Modified Release (MR) Formulations

- Terminology
  - Controlled Release (CR), Delayed Release (DR), Sustained Release (SR), Extended Release (ER), Pulsatile Delivery
- Short half life – $T_{1/2}$
  - Multiple doses
- Narrow therapeutic window -- $C_{max}$
  - Adverse effects
- Benefits:
  - Improve patient compliance
  - Less likely to be abused or misused
    - HysinglaTM ER (hydrocodone bitartrate) ER Tablets CII
  - Improved drug tolerance, reduced peak-to-trough variations
  - Increased duration of drug therapeutic effect through maintaining plasma levels within therapeutic ranges.

http://www.medscape.com/viewarticle/781850_6 Advantages and Disadvantages of Using Controlled-release Medications

# Example: Draft Guidance on Methylphenidate HCl (Concerta) *Tablet*

- Two in vivo studies:
  - Fasting and Fed
- Additional comments regarding the bioequivalence study:
  - Additional Bioequivalence Metrics – Partial AUCs
    - The 90% confidence intervals of the geometric mean test/reference (T/R) ratios for the five metrics (Cmax, AUC0-T1, AUCT1-T2, AUCT2-T3, AUC0-∞) should fall within the limits of 80-125%.
  - Statistical Analysis of Pharmacokinetic Data – subject-by-formulation interaction variance

# MR Related Nine Active Research Grants/Contracts (FY 13-15)

1. BE study of **lamotrigine** extended-release tablets in healthy subjects, awarded to Vince & Associates (#HHSF223201210030I) in FY 2015.
2. Comparative surveillance of generic drugs by machine learning (AED drugs), Awarded to Marshfield Clinic (#HHSF223201510112C) in FY 2015.
3. BE and characterization of generic drugs (**methylphenidate**), Awarded to Vince & Associates. (#HHSF223201210030I, #HHSF22301001T) in FY 2014.
4. PK/PD studies of generic cardiovascular drugs in hypertensive patients (**metoprolol**), Awarded to University of Florida (5U01FD005235-02) in FY 2014.
5. PK/PD studies of **methylphenidate** extended release products in pediatric ADHD Patients, Awarded to Massachusetts General Hospital (5U01FD005240-02) in FY 2014.
6. Post-market surveillance evaluation of authorized generic drug products, Awarded to Brigham and Women's Hospital (5U01FD005279-02) and Auburn University (5U01FD005272-02) in FY 2014.
7. BE of generic **bupropion**, Awarded to Washington University (4U01FD004899-03) in FY 2013.
8. PK Study of **bupropion** hydrochloride products with different release patterns, Awarded to University of Michigan (HHSF223201310164C) in FY 2013.
9. Investigation of inequivalence of **bupropion** hydrochloride extended release tablets: In vitro metabolism quantification, Awarded to University of Michigan (HHSF223201310183C) in FY 2013.

# Outlook

- Identify and justify approaches to demonstrate BE for complex products, locally-acting products, etc.
  - Demonstrate BE using clinical endpoints may hinder the development of generic drug products
- Develop acceptance criteria
- Assure BE for drug products qualify for biowaiver

# The Science of Therapeutic Equivalence

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September 14, 2016

Disclaimer: The views expressed in this presentation are those of the speaker and not necessarily those of the Food and Drug Administration (FDA).

# Roles of modeling and simulation in generic drug regulatory science

- Modeling and Simulation (M&S) in OGD
- Mechanistic Oral Absorption M&S
- Case Examples
- GDUFA Regulatory Science

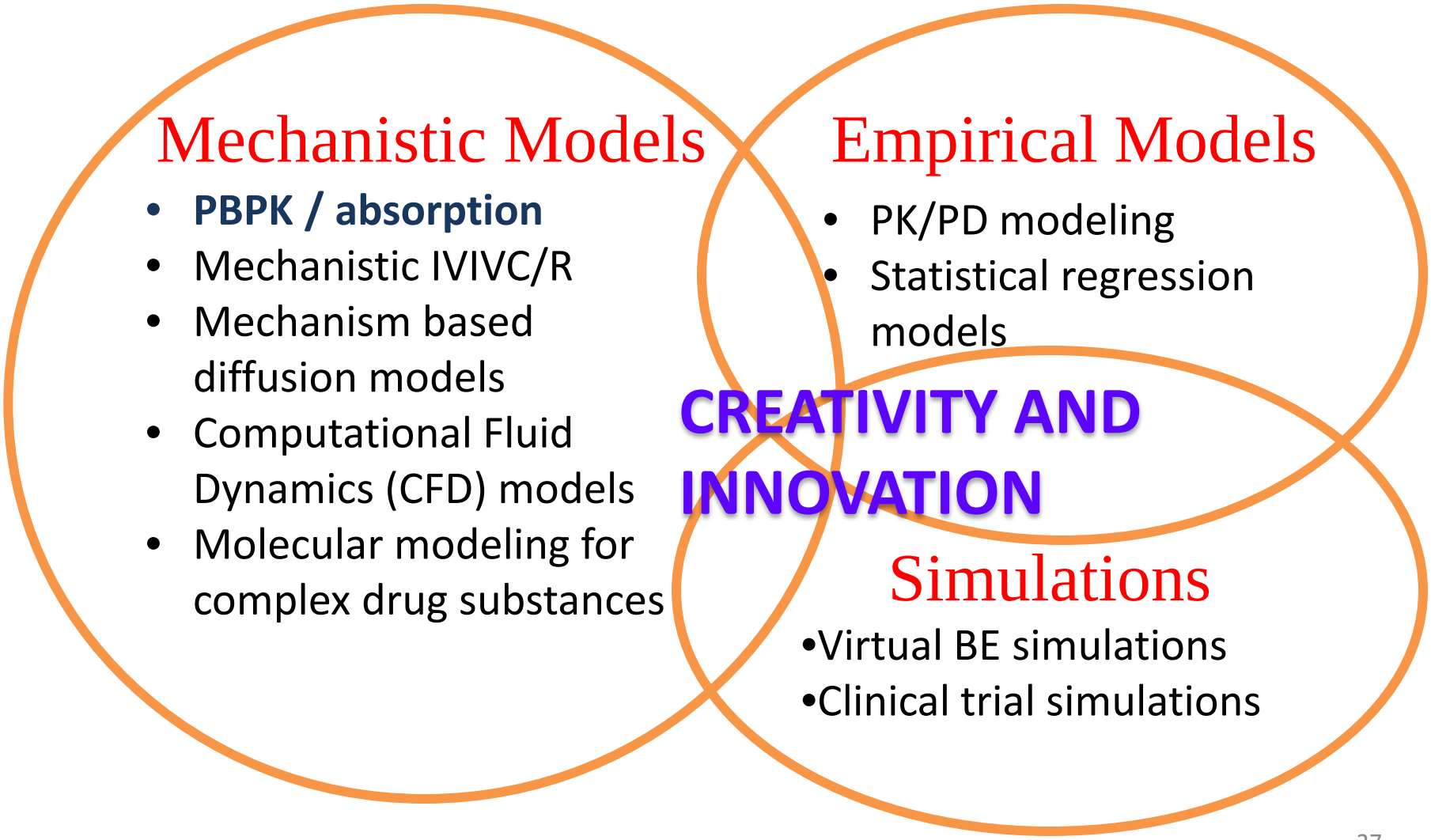
# Modeling and Simulation (M&S) in OGD

# M&S impact various regulatory activities in OGD.

| Type | No. | Examples |
|---|---|---|
| ANDA Reviews | 20 | ❖ PD modeling and simulation for Methylphenidate ER product and asthma controllers |
| CP, CC, Pre-ANDA meetings | 54 | ❖ Development of BE criteria for pain killers<br>❖ Assessment of BE standards for GI locally acting products<br>❖ Simulation of in vivo alcohol dose dumping studies |
| BE Guidances | 33 | ❖ Simulations for the development of BE criteria for HVDs and NTI drugs |
| Regulatory Research Study | 37 | ❖ PK/PD modeling and simulation to determine the appropriate study design and evaluate BE between generic anti-epilepsy drugs and immunosuppressant drugs in patients |

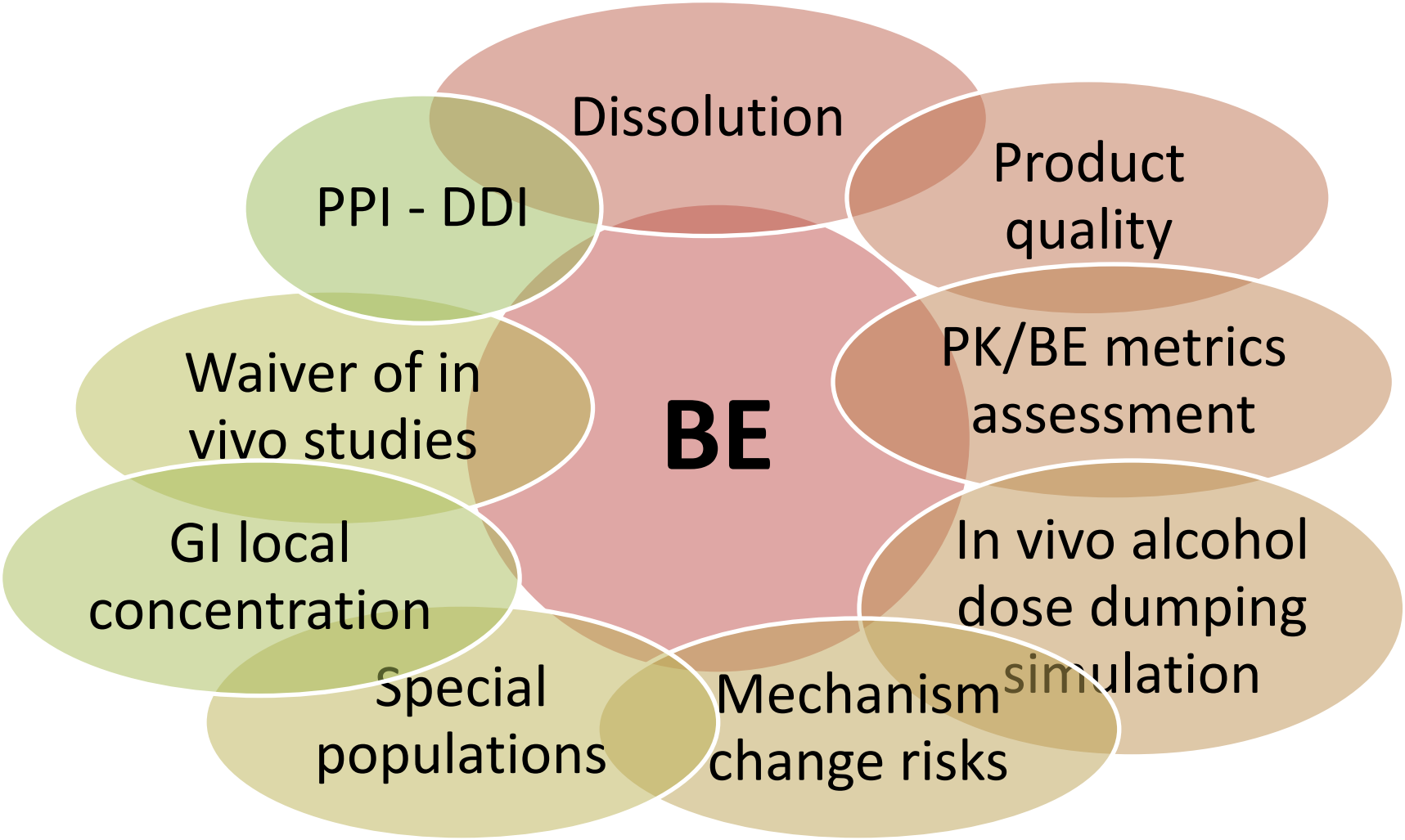
Zhao L. FDA Public Workshop Mechanistic Oral Absorption Modeling and Simulation for Formulation Development and Bioequivalence Evaluation. http://www.fda.gov/downloads/Drugs/NewsEvents/UCM505000.pdf

# A broad spectrum of M&S is applied.



# Mechanistic Oral Absorption Modeling and Simulation

# A broad spectrum of issues have been assessed using absorption modeling



# PBPK modeling for oral dosage forms

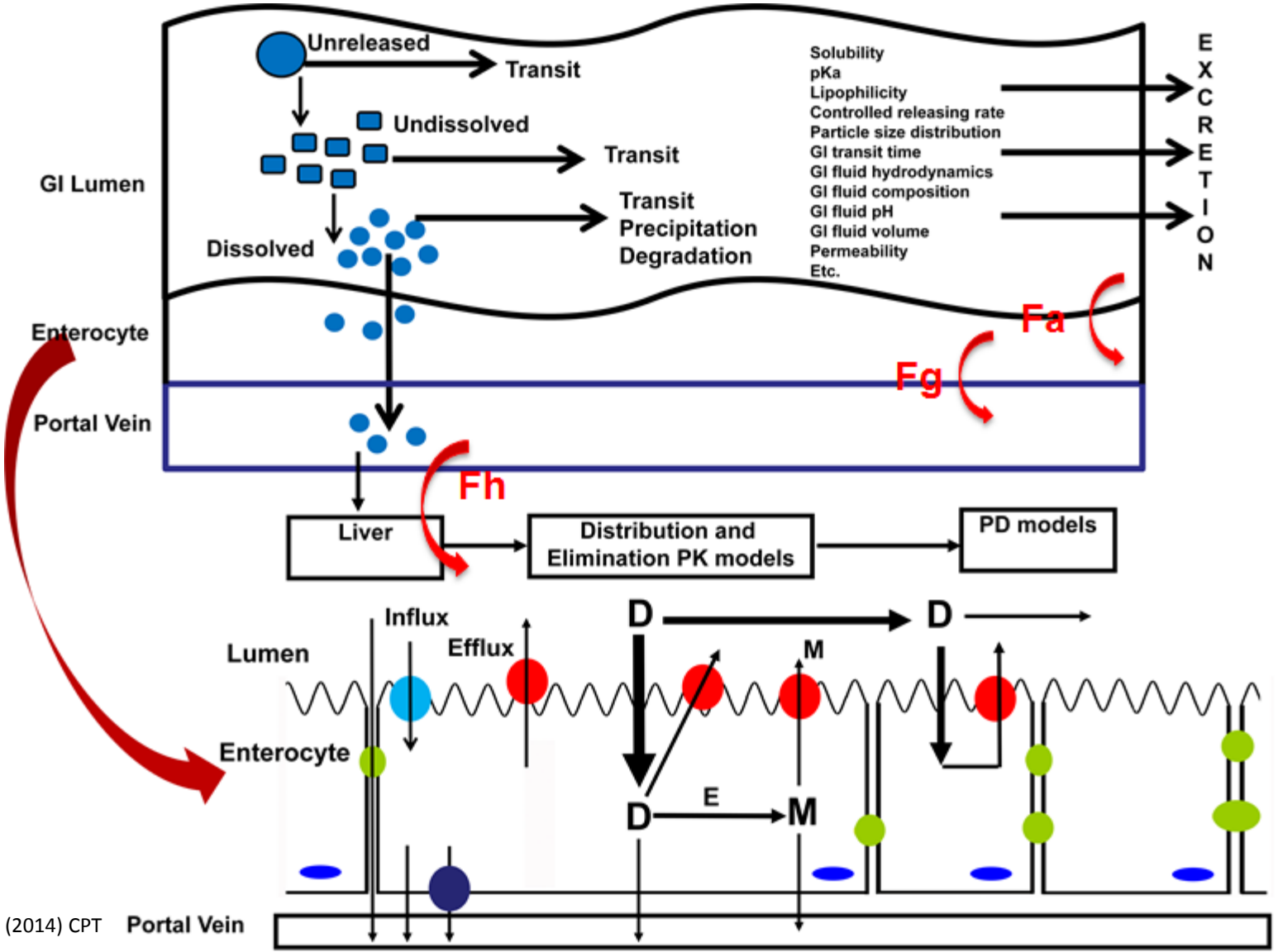
## Modeling and Simulation of Biopharmaceutical Performance

X Zhang[1] and RA Lionberger[1]

**Biopharmaceutical performance refers to the influence of pharmaceutical formulation variables on *in vivo* performance. New drug product success depends on formulation design for sufficient bioavailability for clinically desired dosing. Regulatory interest in biopharmaceutical performance includes batch-to-batch consistency, acceptability of postapproval changes, and evaluation of bioequivalence (BE) for generic drug products. This Commentary summarizes biopharmaceutical modeling and simulation in the US Food and Drug Administration (FDA) Office of Generic Drugs (OGD) for orally administered generic drugs.**

Zhang X. et al. (2014) Clinical Pharmacology & Therapeutics

# Simplified Absorption Process




Zhang X. et al. (2014) CPT

# Mechanistic Oral Absorption Models

$$dissolution\,rate = \frac{dM}{dt} = \frac{DS}{h}(C_s - C_t)$$

$$absorption\,rate = \frac{dM}{dt} = \iint_A J_w dA = \iint_A P_w C_w dA$$

- Quasi-equilibrium models
- Steady-state models
- Dynamic models
  - Compartment models
    - Mass balance
    - First-order transit along the GIT
    - Passive and active transport through enterocytes

# Inputs and Outputs

**Drug substance and product information:**

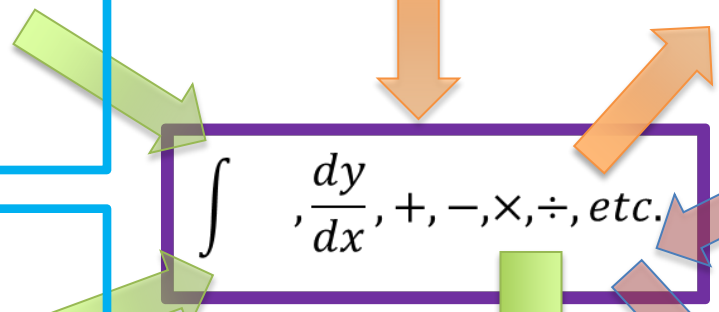
- Dose and dose volume
- Solubility vs. pH profiles
- logP, pKa
- Dissolution: MR: dissolution profiles; IR: particle size and density
- Diffusion coefficient
- Permeability
- Metabolic kinetics

**Physiological parameters**

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

**PK parameters**

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



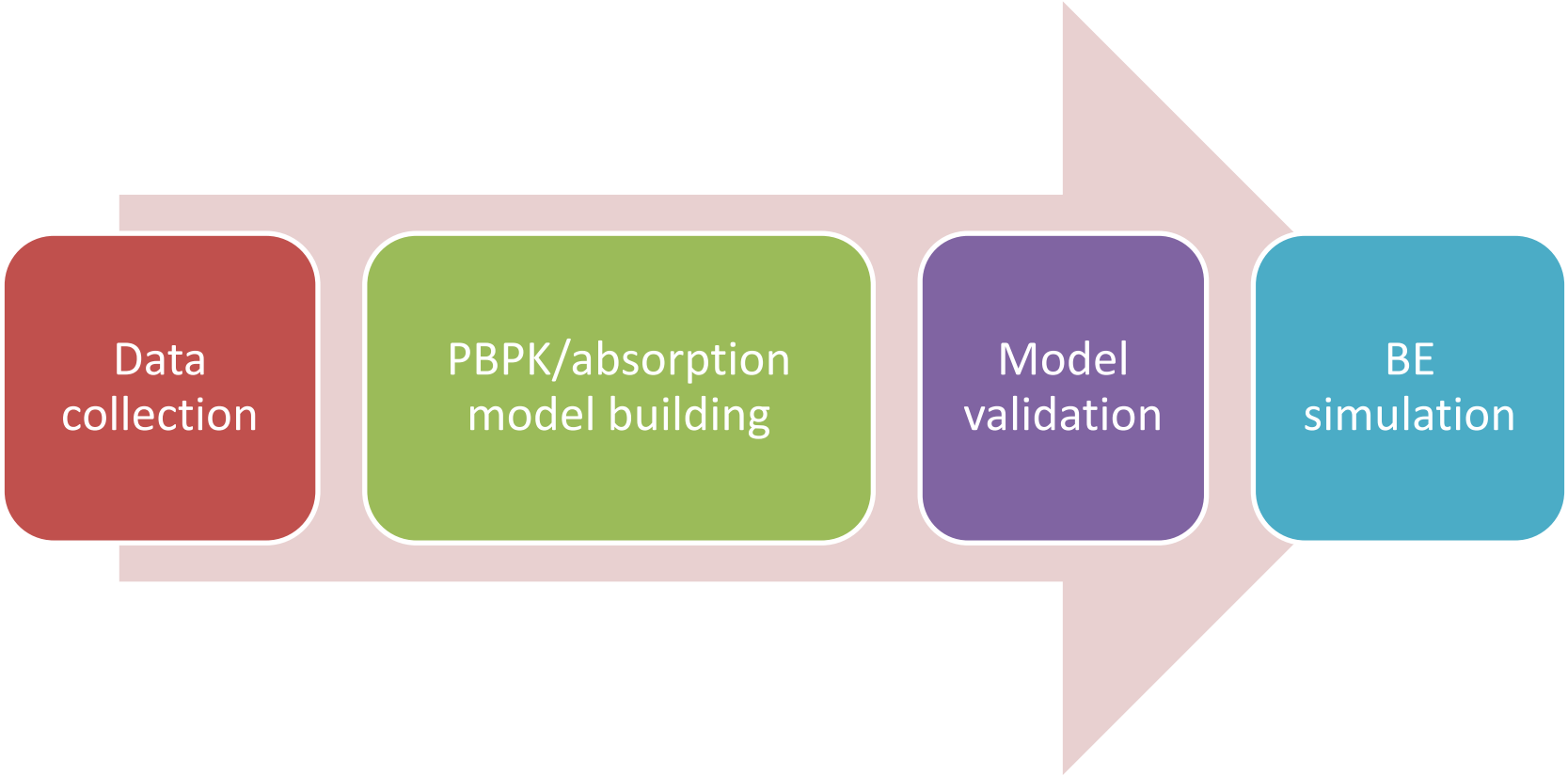

- Fh, BA
- PK profiles

**Metabolite Info**

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

Parent and metabolite PK

# General Practice




Zhang X. et al. (2011) The AAPS Journal
Babiskin A. et al. (2015) J Pharm Sci.

# Case Examples:

**1. Evaluate the correlation between GI lumen concentration and plasma concentration (mesalamine ER capsules)**

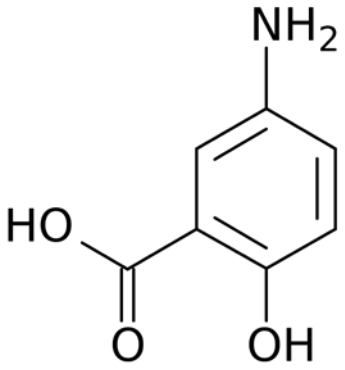
**2. Evaluate the PPI impact on BE (prasugrel HCl tablets, fingolimod capsules)**

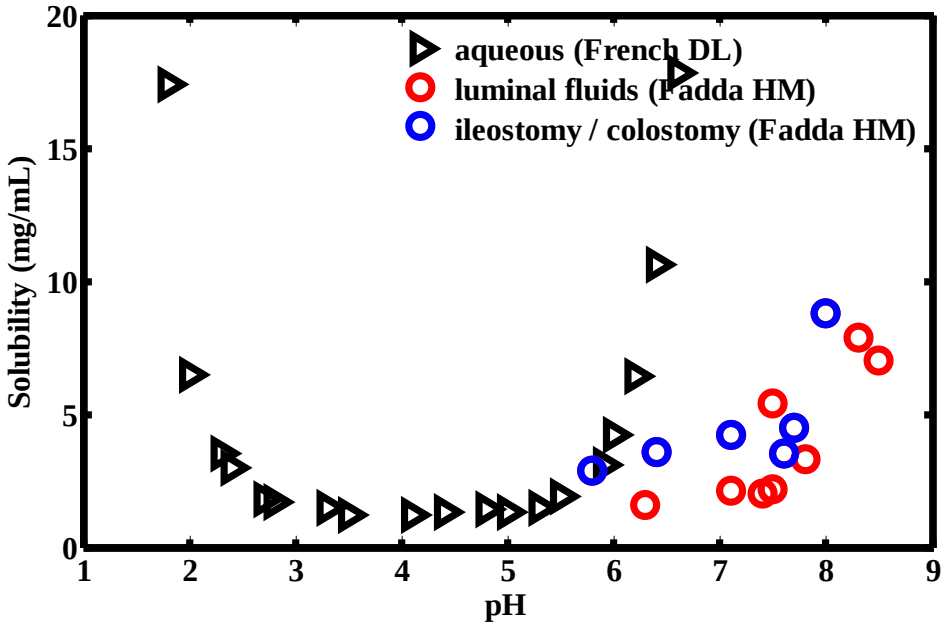
# Case Study: Mesalamine ER capsules

- Specific aims
  - Assess relationship between GI luminal concentration and plasma concentration for mesalamine extended release capsules.

# Mesalamine ER capsules

- pKa: 2.7, 5.8, and 12
- pH dependent solubility
- Half life: 42 mins after iv
- Metabolized by N-Acetyltransferases
- Targets lower GIT and acts topically for ulcerative colitis (UC)
- Modified release dosage form



# Approaches

Model was developed based on i.v., suspension, and suppository PK data.

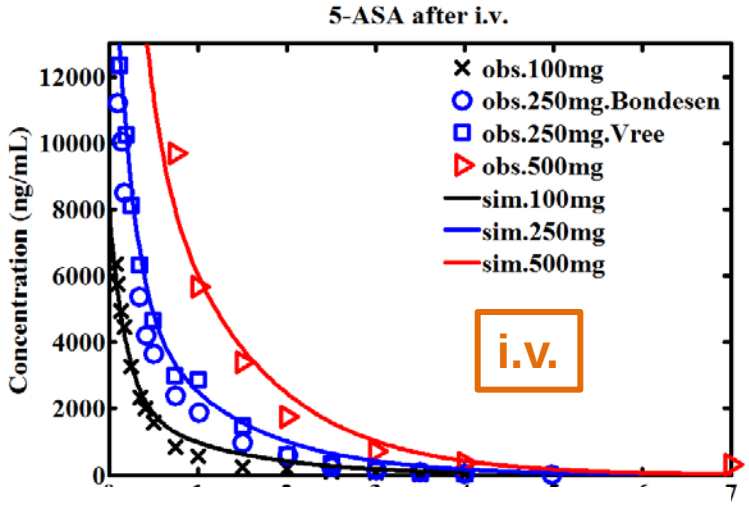
Fit pH dependent dissolution profiles as model input for in vitro dissolution.

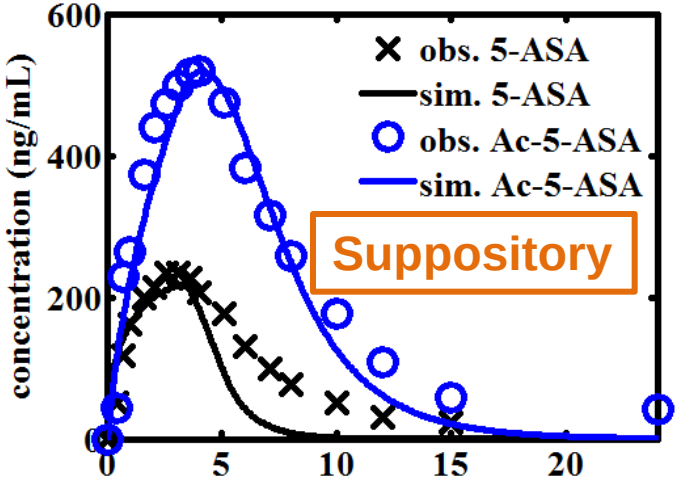
$$\frac{dM}{dt} = zM_{u,0}\left(\frac{M_{u,t}}{M_{u,0}}\right)^{\frac{2}{3}}(C_s - C)$$

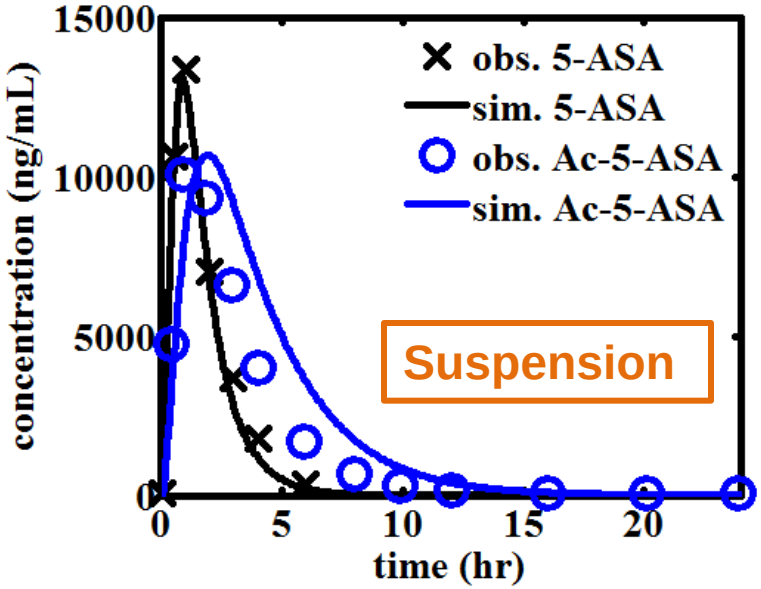
Adjust pH in the GI lumen against observed PK profiles for each subject.

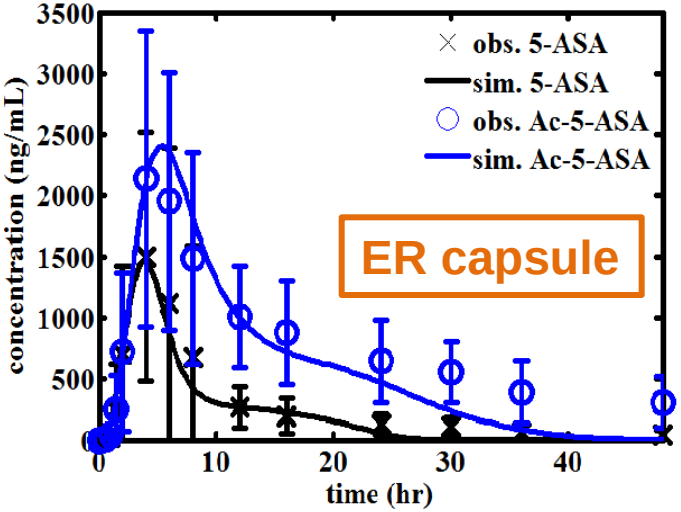
Perform simulation to answer specific questions.

# Model Development and Validation

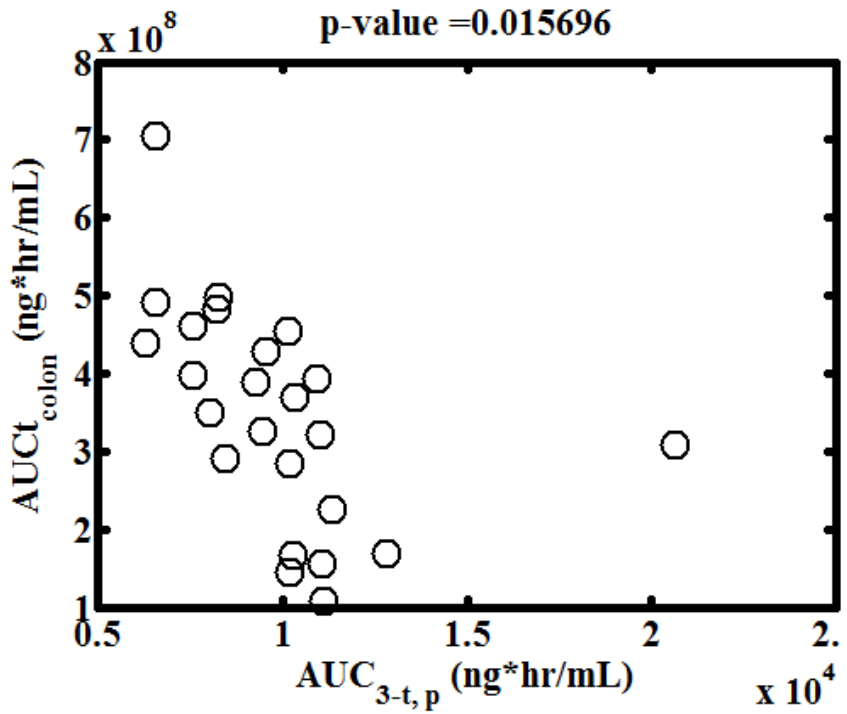


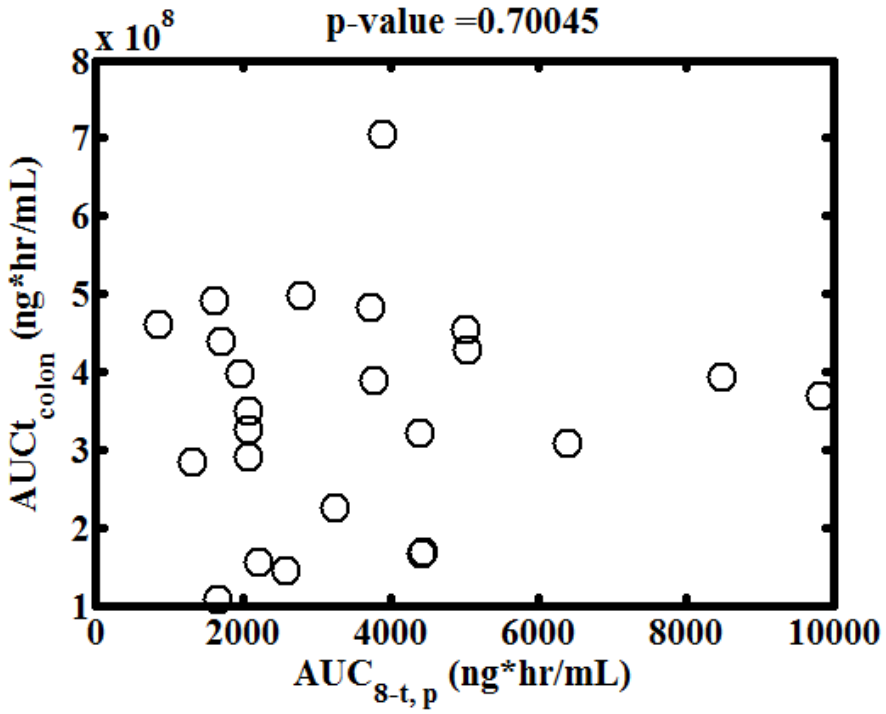



# Colon and plasma exposure correlation



# Conclusions

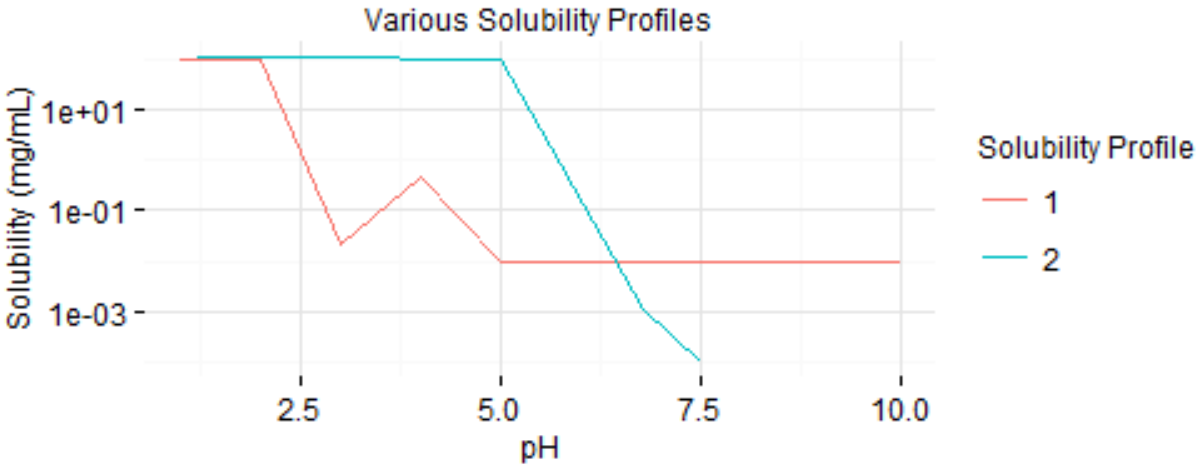
- Based on the in vivo GI tube study, GI local concentration measurement results are qualitatively correlated with PK metrics (certain partial AUCs).
- Based on modeling and simulation, $AUC_{3\text{-}t,p}$ correlates with colon exposure for ER capsules.
- In vivo GI tubing study and absorption modeling and simulation confirmed that PK endpoint study is a reasonable surrogate to reflect GI local concentration.

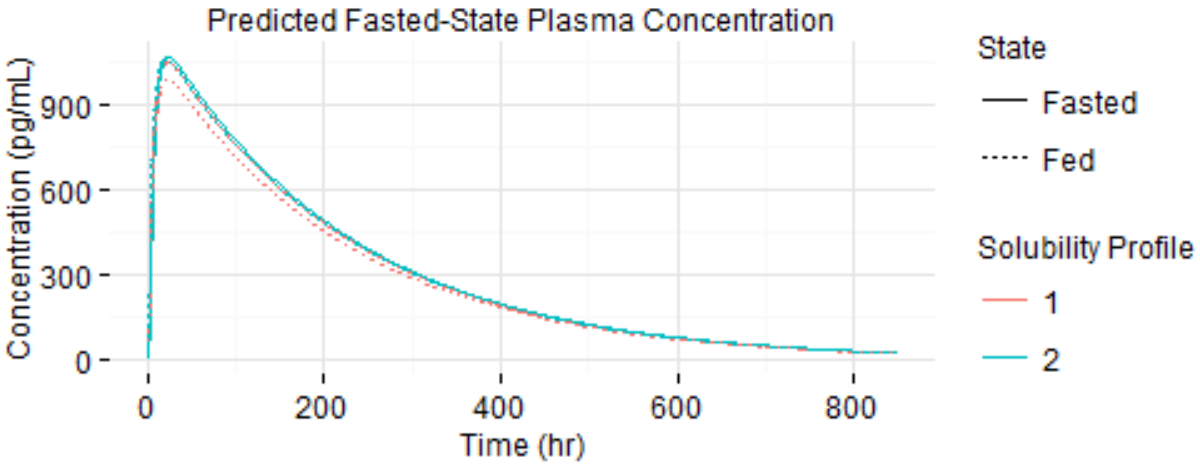
# Evaluate PPI impact on BE (prasugrel HCl tablets, fingolimod capsules)

# Assess the impact of elevated stomach pH on BA/BE

| | **Prasugrel HCl tablets** | **Fingolimod capsules** |
|---|---|---|
| Indication | Reduce thrombotic cardiovascular events | multiple sclerosis |
| pKa | 5.1 | 7.82 |
| Solubility | High in low pH, low in high pH | High in low pH, low in high pH |
| Half-life | 7 hours (range 2-15 hours) | 6 to 9 days |
| **Issues** | **Salt to base conversion leads to lower solubility** | **Slow dissolution observed in high pH condition** |
| Approaches | Conduct mechanism-based absorption modeling to assess the impact of solubility and elevated stomach pH on PK | |
| **Recommendation** | **Salt to base conversion should be controlled** | **Elevated stomach pH is less likely to impact PK significantly** |

# Fingolimod PK is not sensitive to solubility

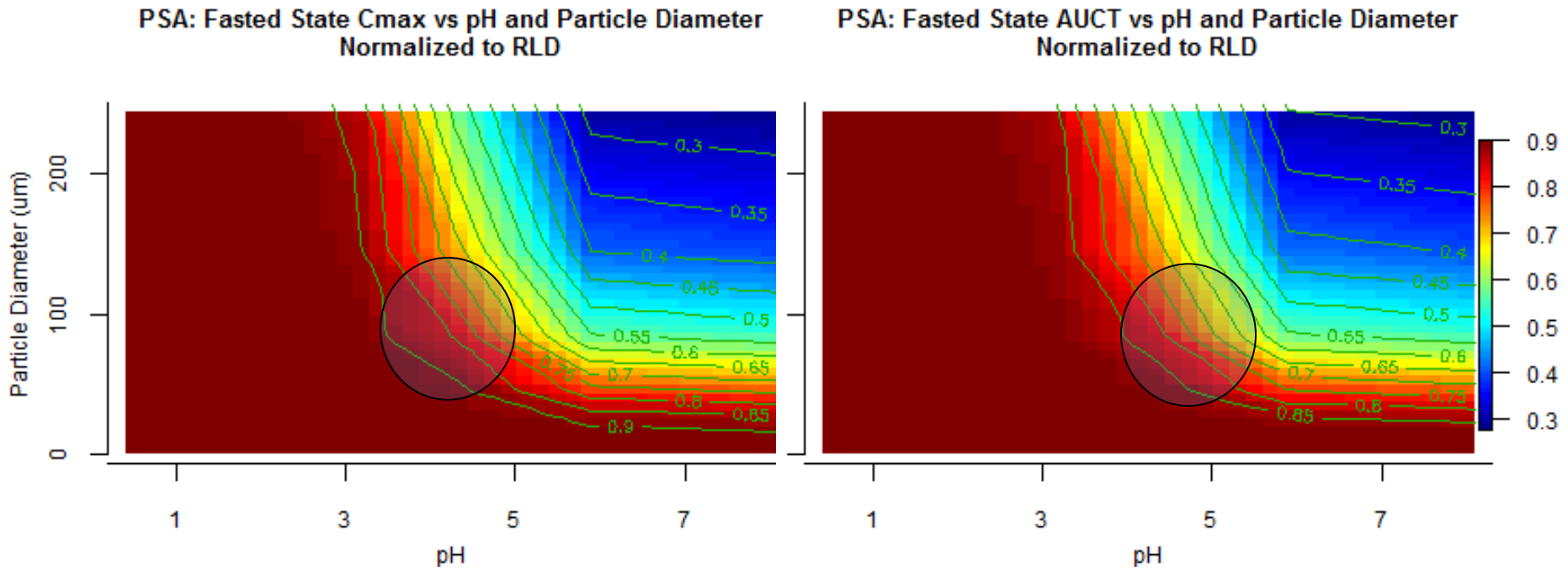



**Fingolimod**

# Fingolimod Fasted State Sensitivity Analysis

- Particle size will determine sensitivity to gastric pH
- Diameter greater than ~ 100 µm may have potential risk for $C_{max}$ and $AUC_t$ at elevated pH




**Fingolimod**

# Conclusions (PPI impact assessment)

- For BCS II immediate-release formulations, mechanism-based modeling could be challenging as in vitro solubility and dissolution might not be predictive.

- Multiple datasets are desired for model calibration.

- Evaluation of in vivo predicative dissolution will be based on whether the new dissolution approaches improve model predictions.

# GDUFA Regulatory Science

# Regulatory Science for Generic Drugs

- GDUFA Regulatory Science Priorities for Fiscal Year 2016
  - Post-market evaluation of generic drugs
  - Equivalence of complex products
  - Equivalence of locally-acting products
  - Therapeutic equivalence evaluation and standards
  - Computational and analytical tools
  - Complex drug delivery systems pose challenges on consistent quality and therapeutic performance for both brand and generic drugs

# Ongoing Studies to Improve Oral Absorption Prediction

- Multiple BE studies (lamotrigine, methylphenidate, warfarin, metoprolol, tacrolimus, bupropion) could be potentially used for model verification
- Effect of different preparation methods on the in vitro and in vivo performance of solid dispersion formulations
- Measurement of GI physiology (intra-subject variance)
- Innovative sampling methods for GI concentrations
- Correlation of mesalamine pharmacokinetics with local availability
- Excipients – target, excipients – transporters interaction

# FY16 Request For Proposals

- RFA-FD-16-025: Integrating supersaturation-precipitation mechanisms in mechanistic oral absorption models for predicting in vivo performance of supersaturating formulations (U01)
- RFA-FD-16-026: Implementing Population Pharmacokinetic Modeling Algorithm in Physiologically-based Pharmacokinetic Models to Allow Parameter Estimation at Individual Data Level (U01)

# Internal Research Efforts on Oral Absorption

- Evaluation of modified release products
- BCS III
- PBPK database
- Alcohol dose dumping simulation

# Summary

- OGD has routinely applied mechanism-based absorption modeling and simulation to address various issues raised in regulatory activities.
- OGD is actively improving the science of predictions for oral solid dosage forms.
- OGD is willing to collaborate with internal and external stakeholders to advance the application of mechanism-based absorption modeling and simulation in drug product development and regulatory review.

# Acknowledgments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