A Model- and Systems-Based Approach to Efficacy and Safety Questions Related to Generic Substitution

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Research at the University of Florida Center for Pharmacometrics and Systems Pharmacology

- To develop a quantitative and integrative approach that will separate post-marketing “signals from noise”
- If the “signal” is credible, develop a strategy using quantitative methods and modeling to provide insight into causal mechanisms

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The UF Research Strategy is Based on Three Pillars to Make Regulatory Decisions

Bioinformatics: develop associations between drugs, targets, pathways and "signals"

PBPK Models: develop oral absorption models to conduct PSA of API and formulations and feed into PK simulations

Pop-PK/PD Models: link to PD to predict impact of product differences in PK on drug response

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The Workflow for the Case Examples

ADE: FAERS, consumer complaints, www.peoplespharmacy.com, clinical studies, ISMP and other public databases

Confirmation – FAERS analysis

1

Replication – Truven® database

Enhanced FAERS analysis – Evidex™ by Advera Health

Confirm targets and pathways, and prediction of ADEs – MH Effect™

Causality of generic drug-AE pair

Prediction Modeling

PBPK Absorption Models: Sensitivity Analysis

PK/PD Models: Benefit and Risk

2

3

Model Interpretation and Report

Drugs and Formulations Selected To Demonstrate a Wide Range of Applications

Case I: anti-epileptic drugs considers BCS classification that can have a significant effect on absorption. BCS class II (carbamazepine, lamotrigine and phenytoin) and BCS class III (gabapentin and levetiracetam)

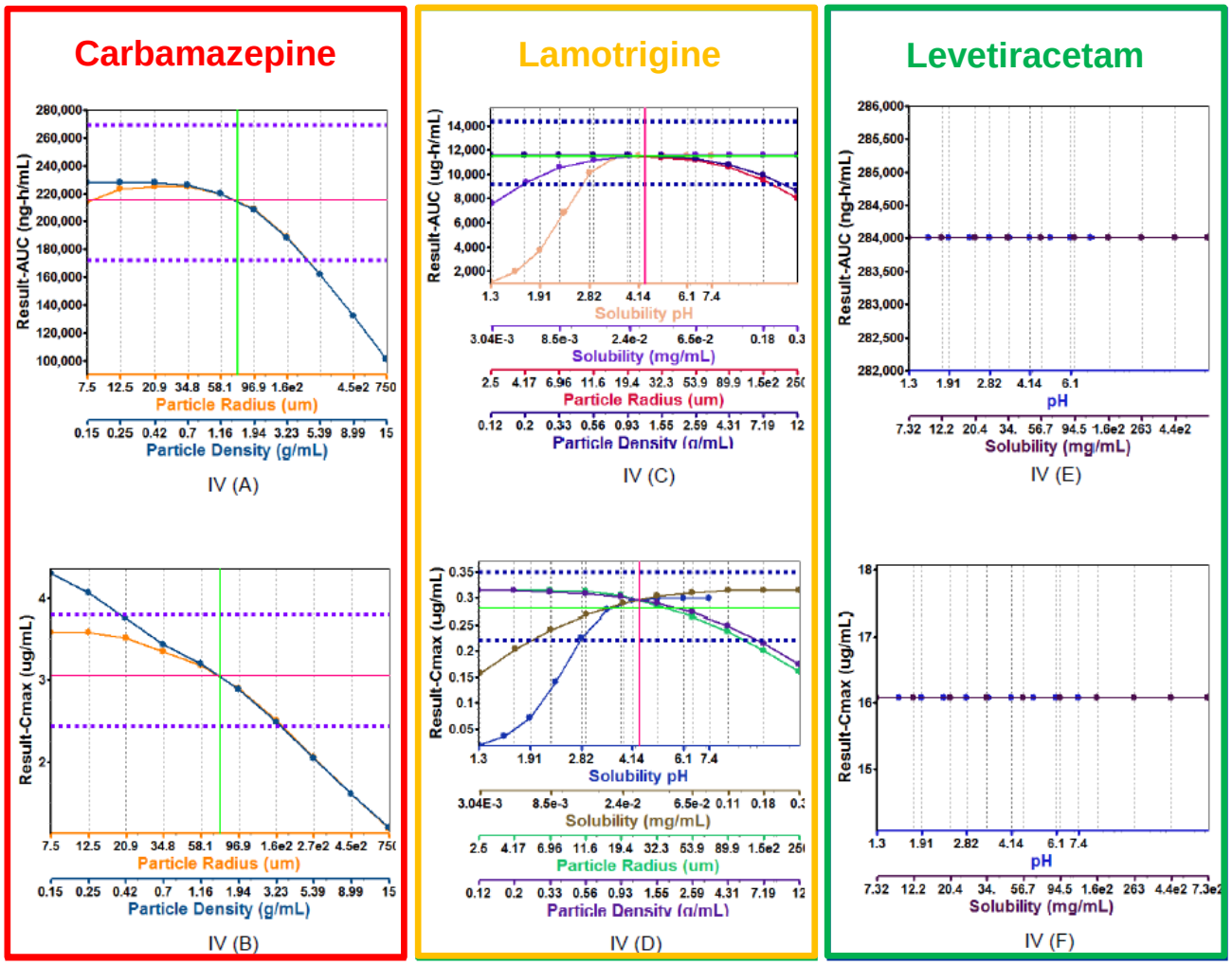
Case II: metoprolol XL examines a complex CR formulation to predict PK and PD profiles from a PSA and differences in *in vitro* dissolution

Case III: anticoagulants that belong to the same therapeutic class (DOACs) that are not yet available as generics to gain a mechanistic understanding of potential bioINequivalence

Medicines and Healthcare Products Regulatory Agency (MHRA) Considers BCS Classes for Risk Categorization

- ***Category 1 – definite concerns***
  - Phenytoin (BCS class II) [1]
  - Carbamazepine (BCS class II) [1]
- ***Category 2 - possible concerns***
  - Lamotrigine (BCS class II) [1]
  - Topiramate (BCS class III) [1]
  - Valproate (BCS class I) [2]
- ***Category 3 - unlikely to be concerns***
  - Levetiracetam (BCS class I/III) [1,3]
  - Lacosamid (BCS class I) [4]
  - Pregabalin (BCS class I) [5]
  - Gabapentin (BCS class III) [1]

Impact of Drug- and Formulation Parameters on AUC and C_{max}



Samant *et al.* Poster presented at the 2015 Annual Meeting of the American College of Clinical Pharmacology

Case I: Levetiracetam (BCS I/III, 2008)

ADE: FAERS, consumer complaints, www.peoplespharmacy.com, clinical studies, ISMP and other public databases

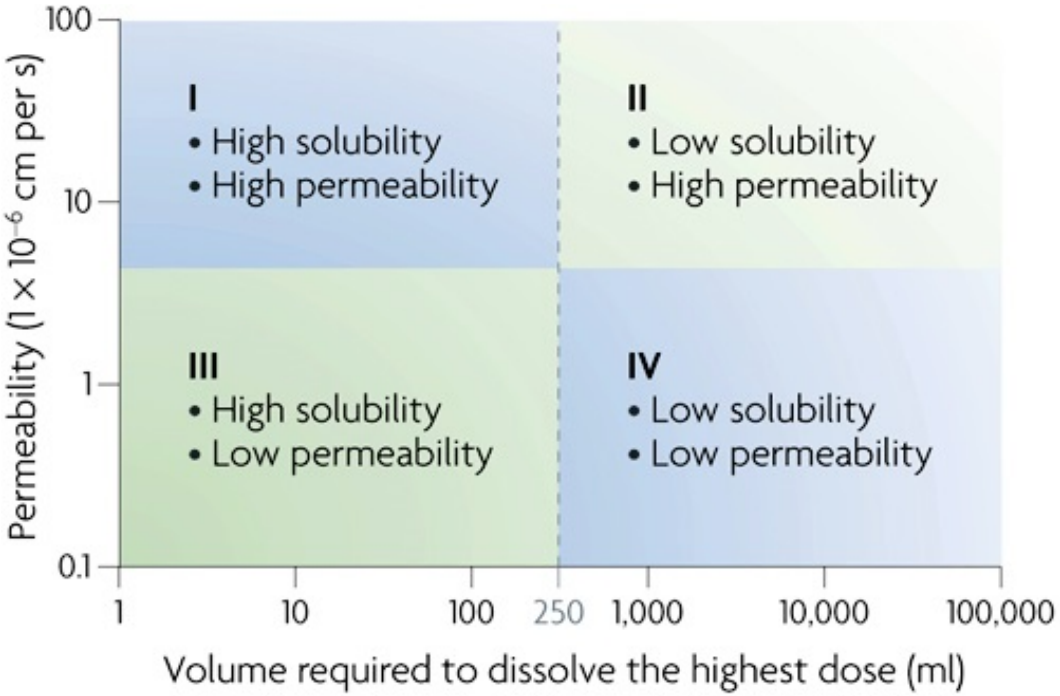
- Indication: antiepileptic drug (RCT: 1433 patients)
- Generics: 25 from variety of manufacturers

Unlikely

✧ Report from physician to FAERS on 08-24-2012

Patient: male
Complaints: frequent nosebleeds, easy bruising
✧ Reaction: decreased WBC, anemia, thrombocytopenia
AE resulted in: hospitalization
Suspect Drug: **levetiracetam after switch to generic**
Other Conmeds: Valproic acid

The Biopharmaceutics Classification System
(as defined by FDA after Amidon *et al.*)



BE study perspective: subjects serve as their own controls → permeability is unlikely to change within subjects during the study → it's a solubility problem

A systems perspective applied to BE studies: What is the rate limiting step for absorption? Solubility? Permeability? Other?

Rate-Limiting Step: Drug Release From Extended Release (ER) Formulations

The Korsmeyer-Peppas Model (The Power Law) is frequently used to describe drug release from ER dosage forms

$$M_t/M_\infty = Kt^N$$

M_t/M_∞ is the fraction of drug release at time t
K is the release constant and
N is the release exponent

Release exponent (N)	Drug transport mechanism	Rate as a function of time	
0.5	Fickian diffusion	$t^{-0.5}$	IR
0.5<N<1	Non-Fickian diffusion	t^{n-1}	
1	Case II transport	Zero order release	ER
>1	Super Case II transport	t^{n-1}	

Plain English, Please!

- N is indicative of the release mechanism
- N depends on the type, grade, and MW of the release controlling polymer → fairly reproducible
- K is indicative of the release rate from a swellable polymer matrix, such as HPMC
- K depends on the porosity and tortuosity of the polymer matrix → can be (highly) variable depending on processing conditions
- K may be subject to lab-to-lab or batch-to-batch variability → CMC

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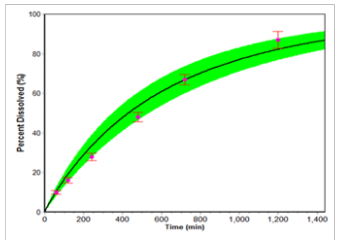
PBPK Model Flowchart to Evaluate the Impact of Formulation Factors on PK Profiles of Metoprolol ER

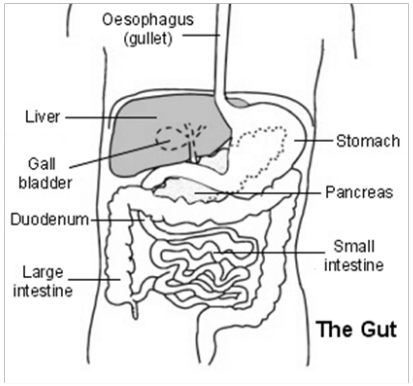
Formulation

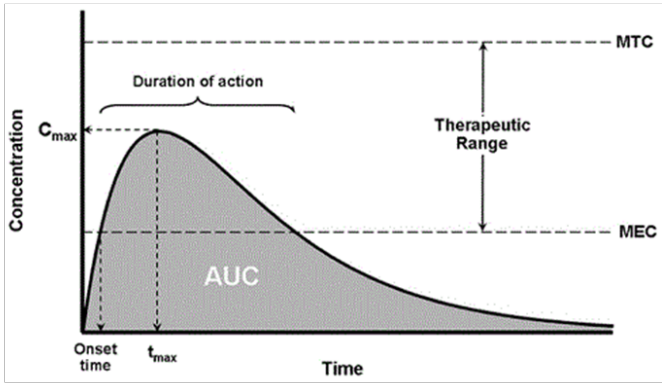
***In vitro* and *in silico* dissolution testing**

***In vivo* dissolution and *in silico* absorption modeling**

***In silico* bioequivalence testing**







DDDPlus™

Advanced Compartment and Transit (ACAT) module in GastroPlus™

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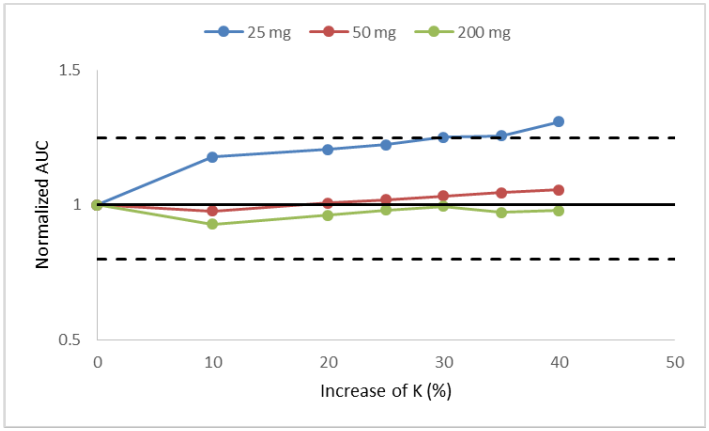
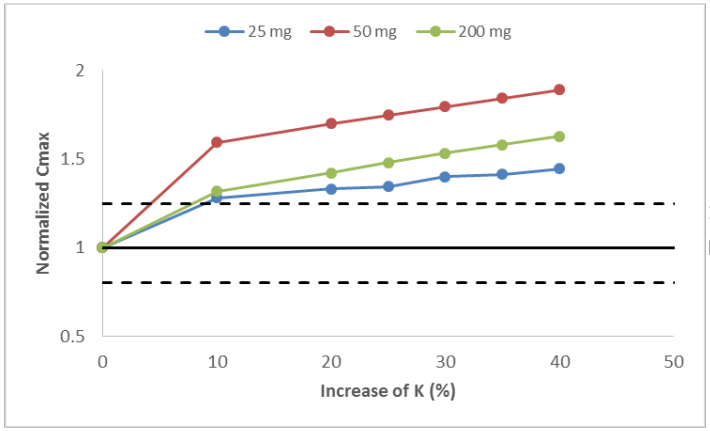
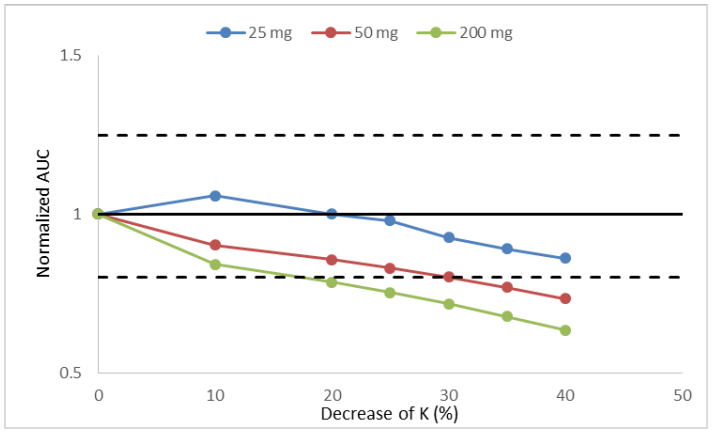
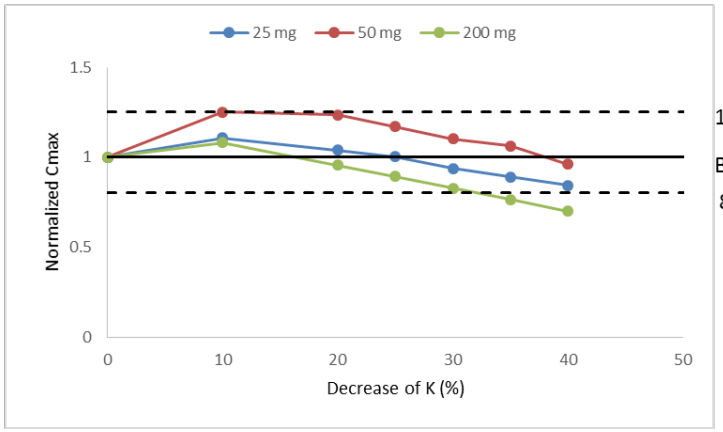
Impact of Changes in K on AUC and C_{max} of Metoprolol ER









→ FDA takes stringent measures to prevent post-approval changes [6,7]

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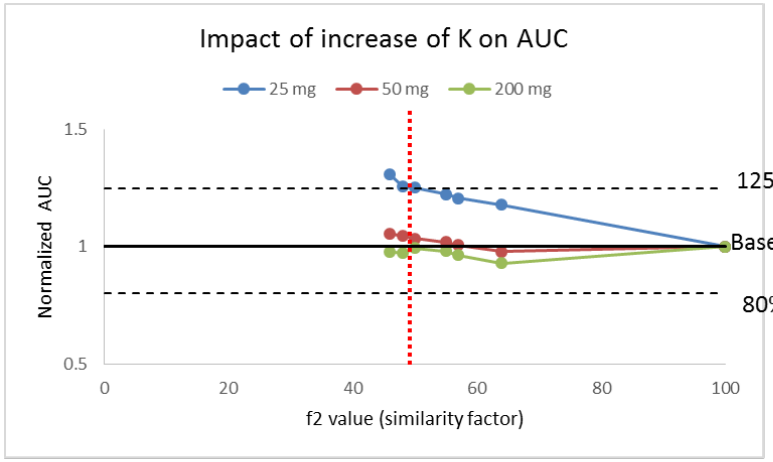
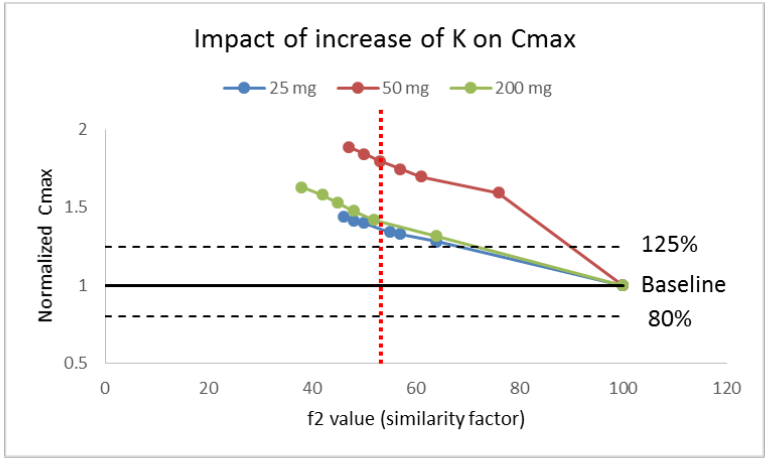
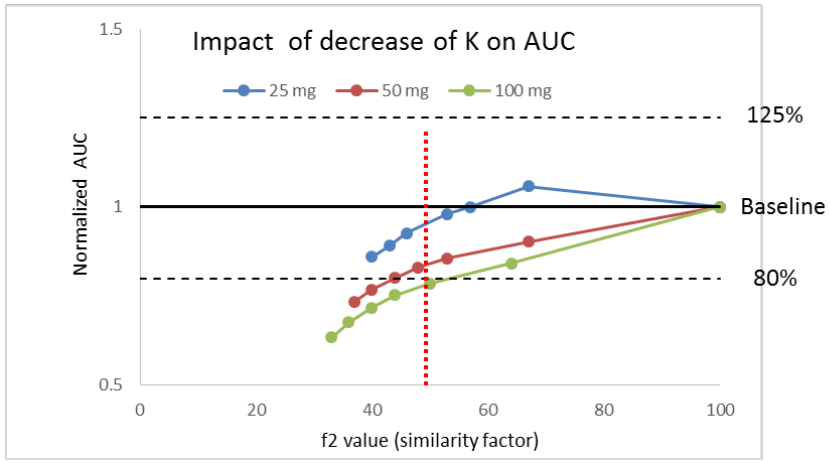
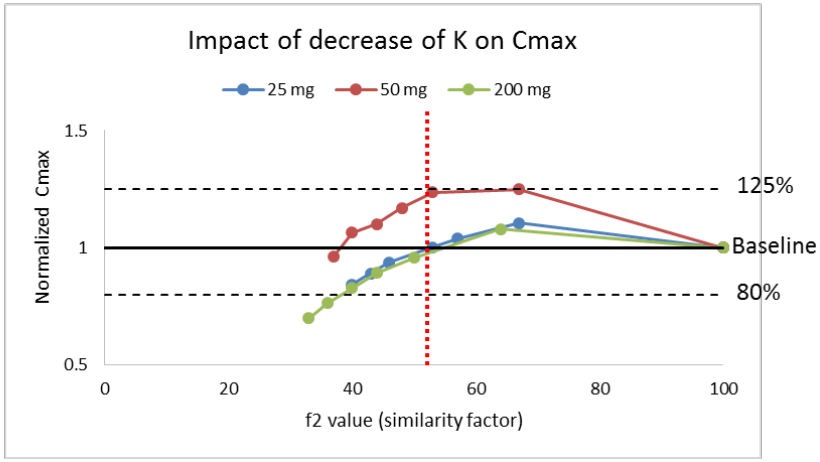
Dissolution Testing









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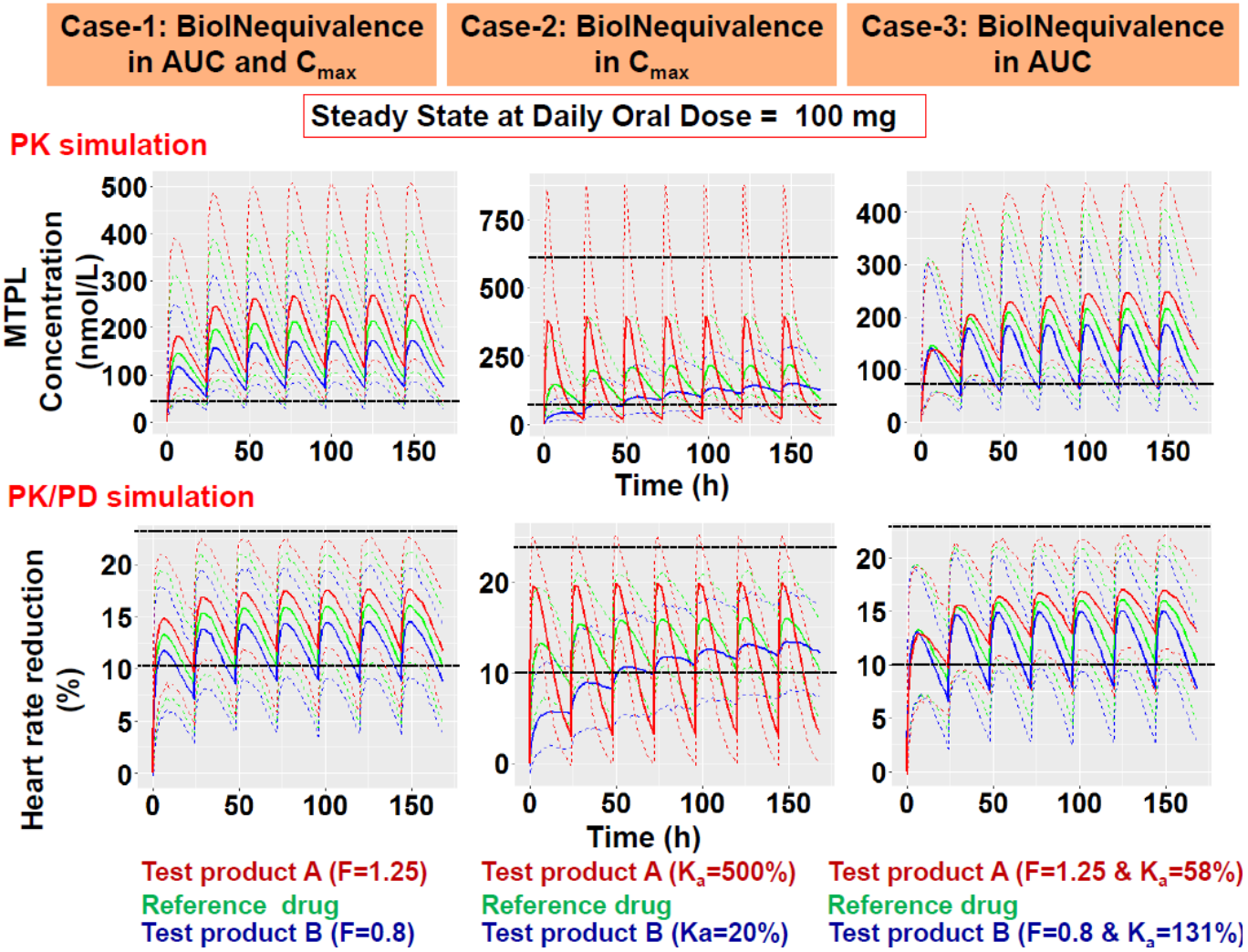
In Silico PK/PD Results



Sharma *et al.* manuscript in preparation

Case II: Metoprolol XL (BCS I, 2006)

2 **PBPK Absorption Models: Sensitivity Analysis** ⟷ **PK/PD Models: Benefit and Risk** 3

- Indication: antihypertensive
- Generics: at least 3 from various manufacturers

✧ Report from physician to FDA on 06-23-2014

Patient: male
Complaints: chest pains
Reaction: increase HR, increase BP, dizziness, migraine
AE resulted in: switch back to brand name product
Suspect Drug: **metoprolol after substitution**

Possible

https://www.nytimes.com/2014/06/24/health/warning-unheeded-heart-drugs-are-recalled.html

Can Our Approach Predict the Relative Risk of Bioinequivalence Before Generics Hit the Market?

Case III: DOACs – Work in Progress

Apixaban
Dabigatran
Edoxaban
Rivaroxaban

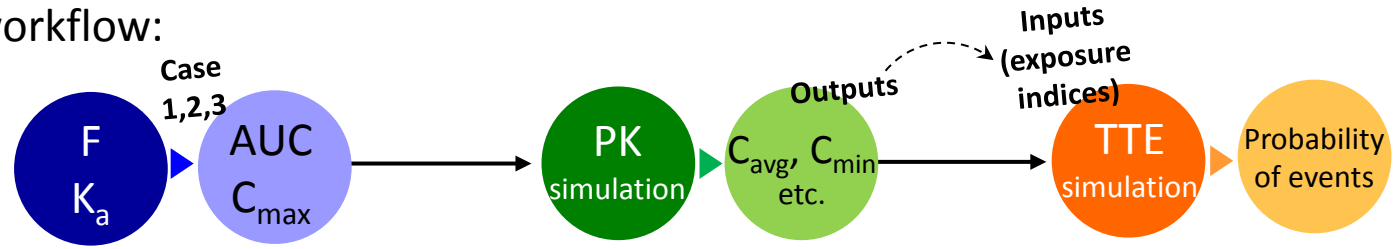
Case III: PK/PD Simulations to Evaluate the Impact of Bioinequivalence on Response to DOACs

PURPOSE

- The objective of this collaborative research was to determine **the impact of hypothetical bio-IN-equivalence (BIN)** in AUC and/or C_{max} **on the efficacy (ischemic stroke) and safety (major bleeding) profiles** of the direct oral anticoagulants (**DOACs**): dabigatran, edoxaban, rivaroxaban, and apixaban.

METHODS

- We simulated out **3 sets of BIN scenarios by altering the rate (k_a) and/or extent (F)**.
- **Changes in PK** were then implemented into **pop-PK/PD** and time to event (**TTE**) models available from the respective NDAs and literatures.
- **Comparison with real-world data:** additional statistical analyses were performed to compare the results to the real-world data from FDA Adverse Event Reporting System and Truven MarketScan Health Analytics.
- Overall workflow:



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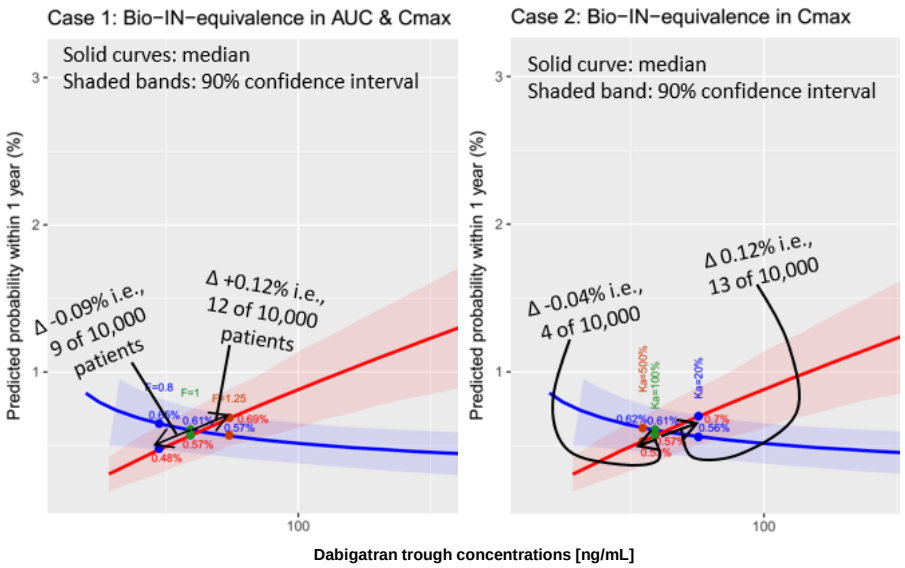
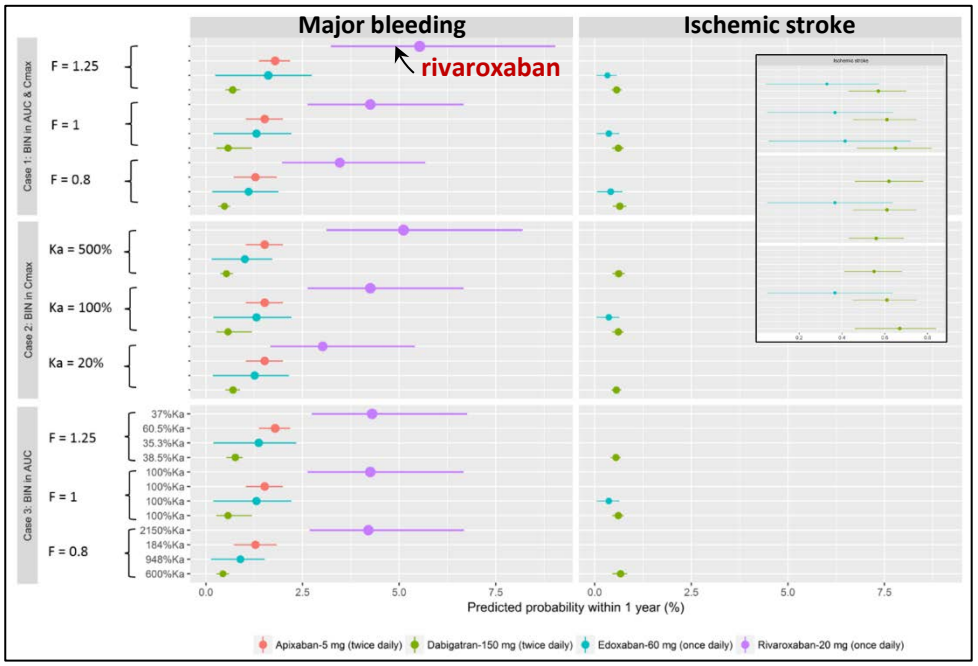
Case III: PK/PD Simulations to Evaluate the Impact of Bioinequivalence on Response to DOACs

Dabigatran Example



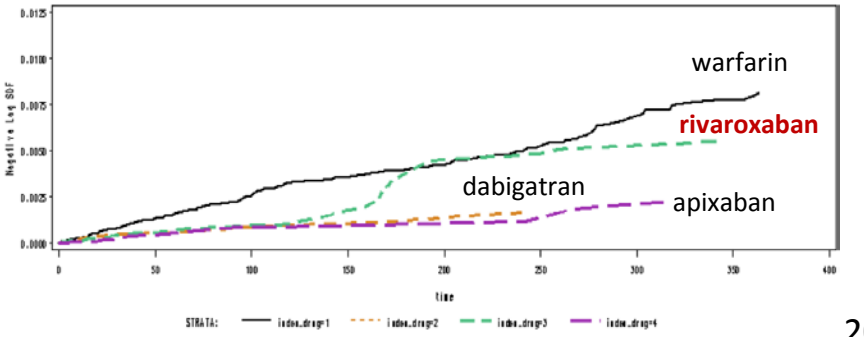


Note that the ER curves from the FDA reports were established using **different PK inputs**. Thus, **computed probabilities provide trends** but cannot be compared directly one another.

→ **Future work** has to be conducted in order to **harmonize employed PK/PD indices across DOACs**.

Real-world data (see below↓)

Survival curves for overall major bleeding in different treatment group



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Summary: Regulatory Use of Our Research

A. Mechanistic model-based “tool” to investigate purported post-marketing claims of bioINequivalence between generic and brand name products

B. “Tool” can be used to assess differences in BA between clinical trial formulations and to-be-marketed dosage forms of new brand name drugs

C. Scientific basis to define if new BE criteria are warranted to better assure interchangeability of generic and brand name product

D. Justification for future targeted post-marketing surveillance of high risk generic drugs

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2. PROPOSAL TO WAIVE IN VIVO BIOEQUIVALENCE REQUIREMENTSFOR THE WHO MODEL LIST OF ESSENTIAL MEDICINES IMMEDIATE RELEASE, SOLID ORAL DOSAGE FORMS **–WHO** http://www.who.int/medicines/services/expertcommittees/pharmprep/QAS04_109Rev1_Waive_invivo_bioequiv.pdf

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