



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

**Stephan Schmidt, B.Pharm., Ph.D., F.C.P.**

*Certara Professor*

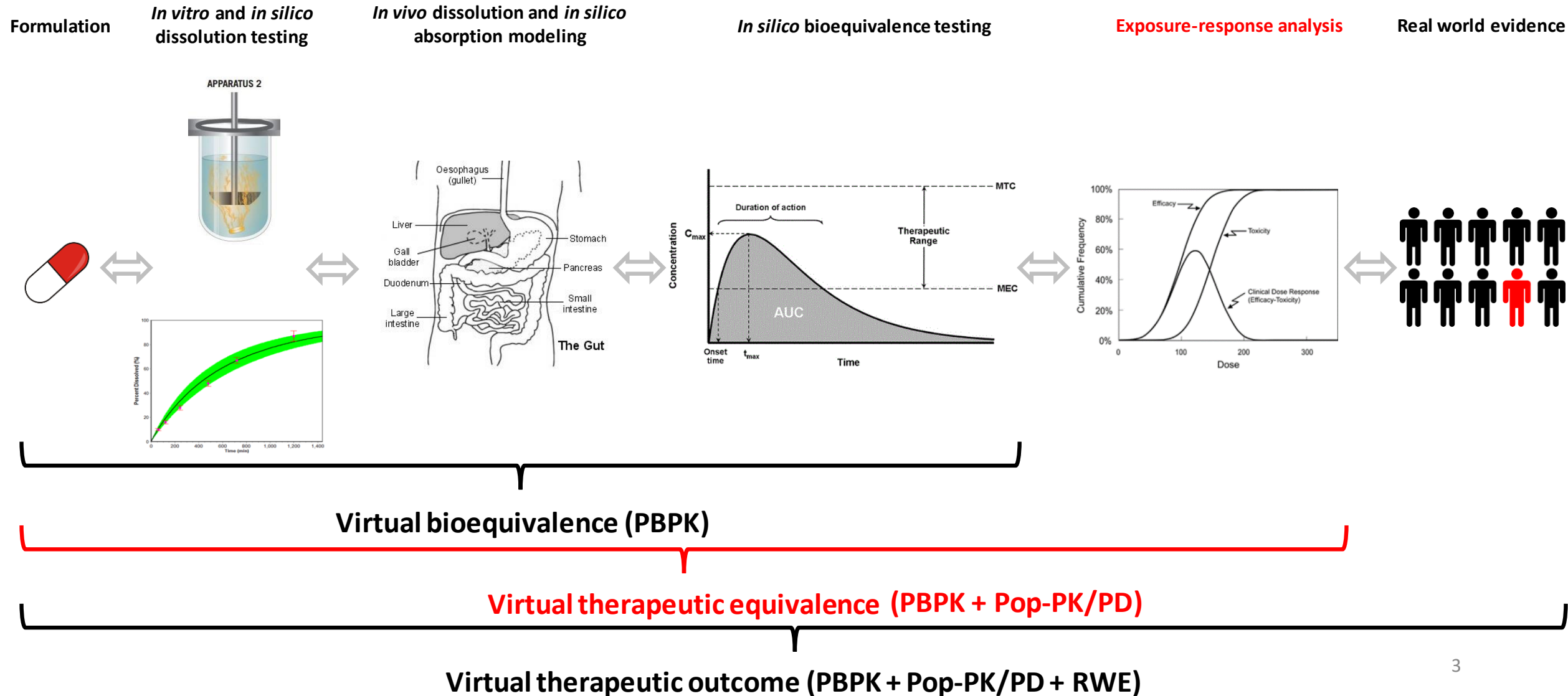
*Director Center for Pharmacometrics and Systems Pharmacology*

*Associate Professor, Department of Pharmaceutics (Lake Nona)*

*University of Florida at Lake Nona*

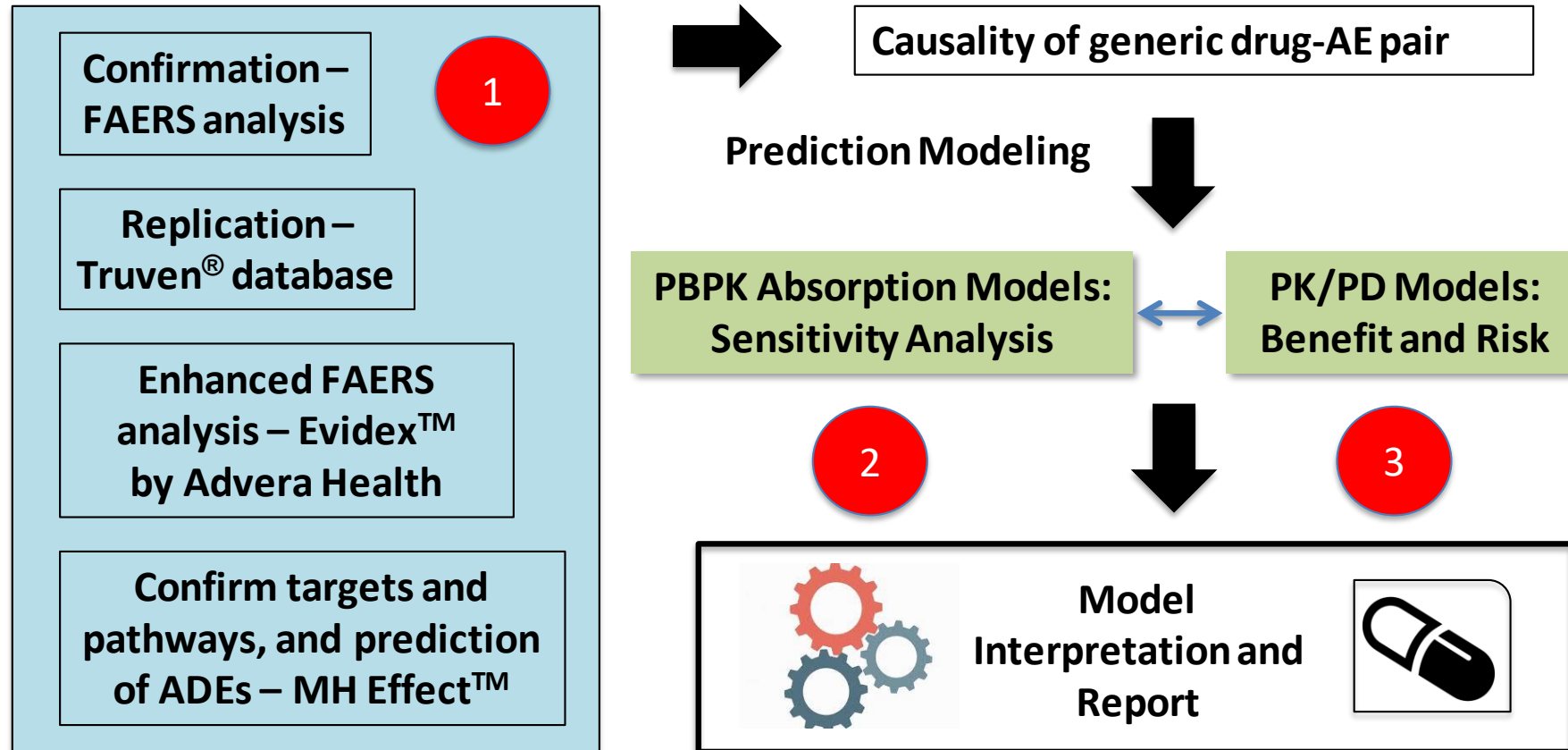
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# Quantitative Methods and Modeling



# Reengineering the Process

ADE: FAERS, consumer complaints, [www.peoplespharmacy.com](http://www.peoplespharmacy.com), clinical studies, ISMP and other public databases



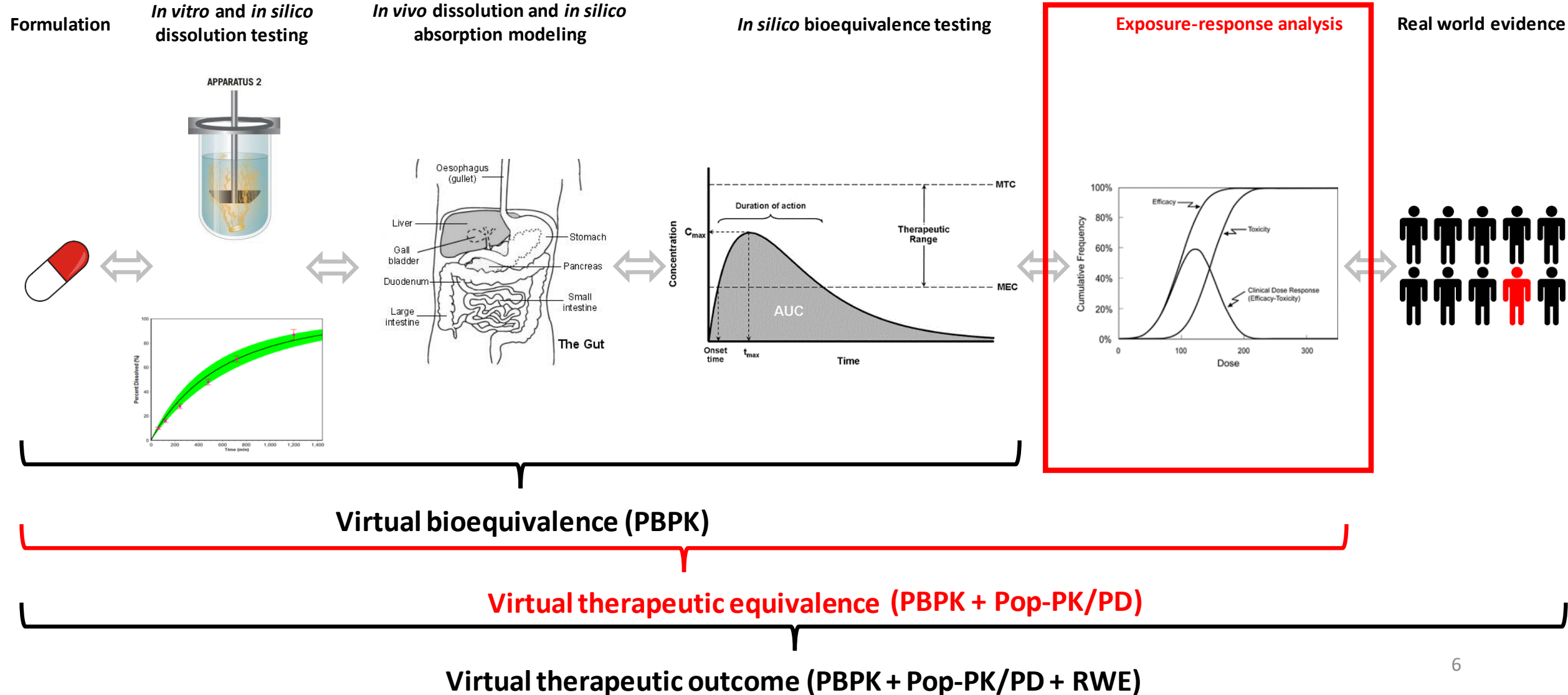
# Drugs and Formulations Selected To Demonstrate a Wide Range of Applications

**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

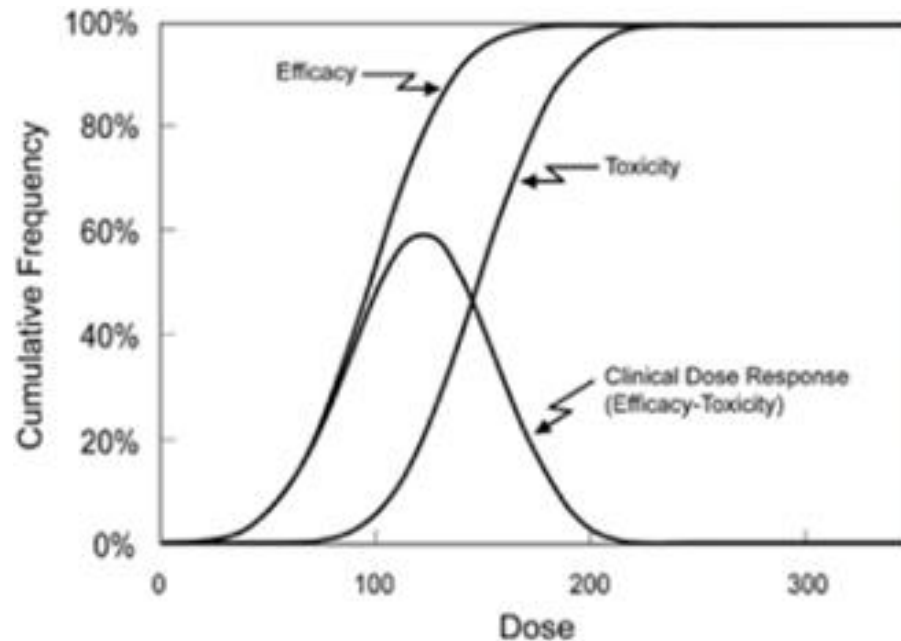
**Case III: anticoagulants** that belong to the same therapeutic class (DOACs) that are not yet available as generics to gain a mechanistic understanding of potential bioequivalence

# Impact of Exposure-Response on Bioequivalence Assessment

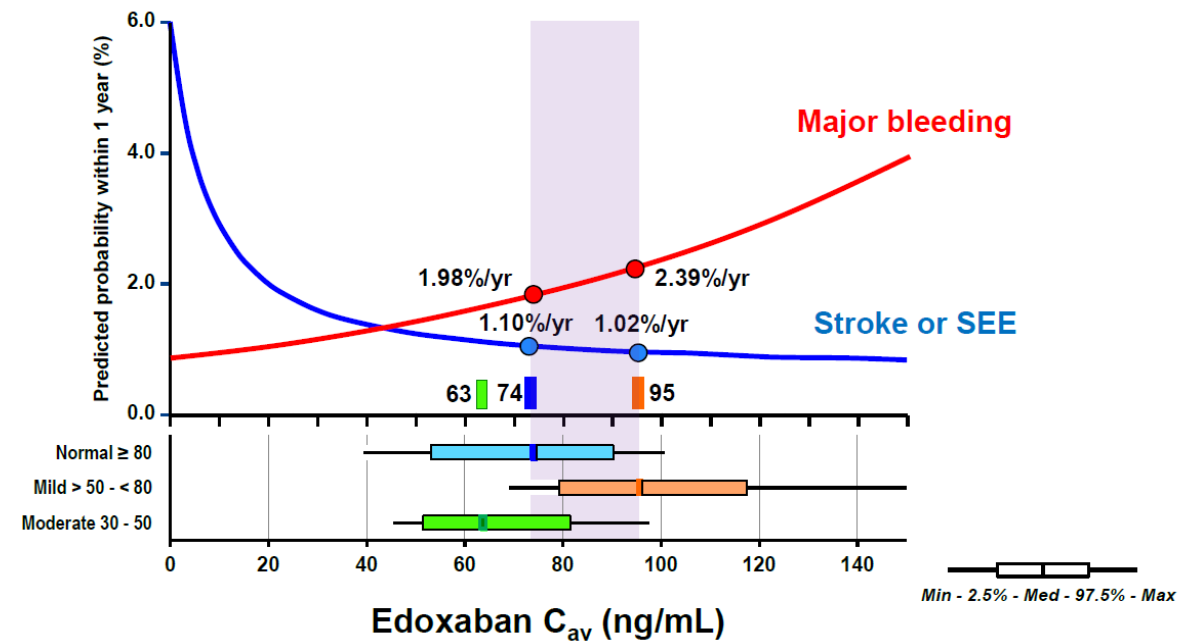


# Impact of Exposure-Response on Bioequivalence Assessment – Example: Edoxaban

## General



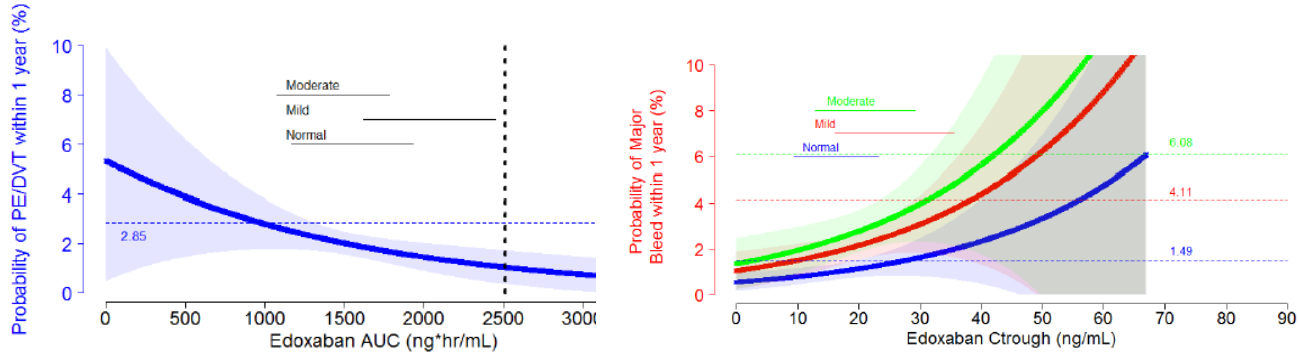
## Drug (class) specific



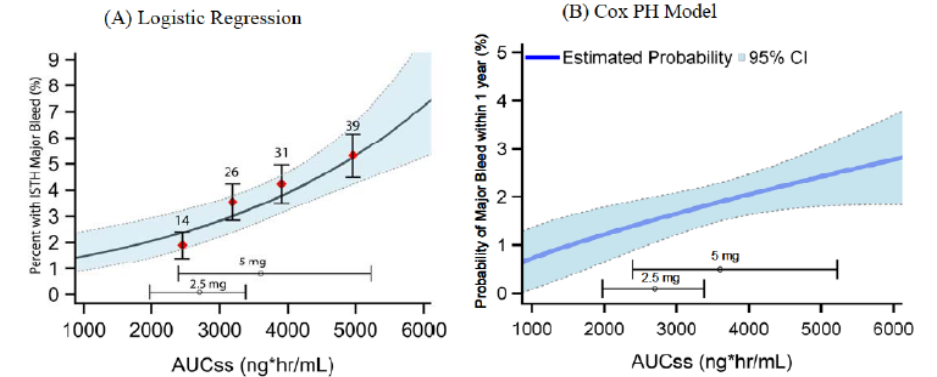


# We Have a Decisive Advantage Here

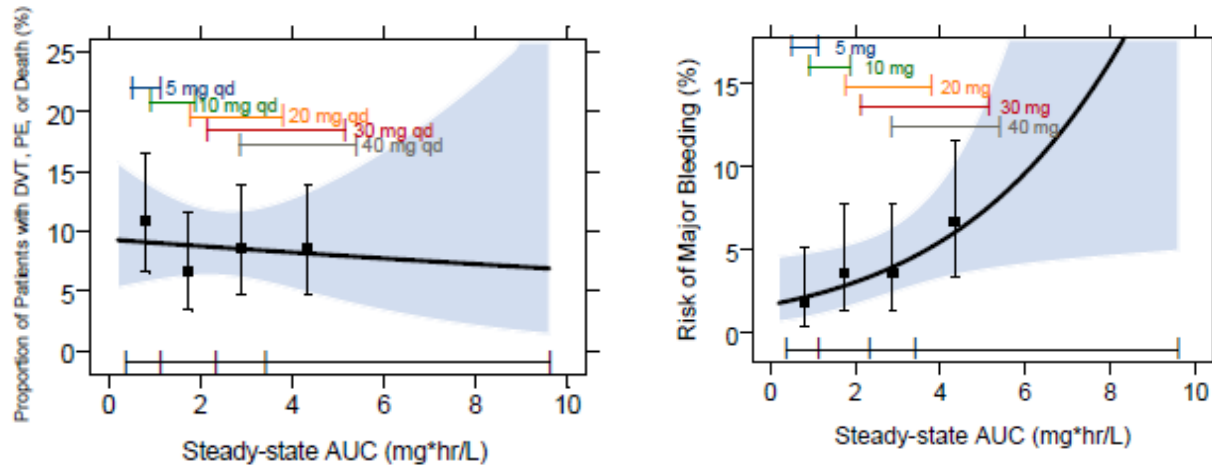
## Edoxaban



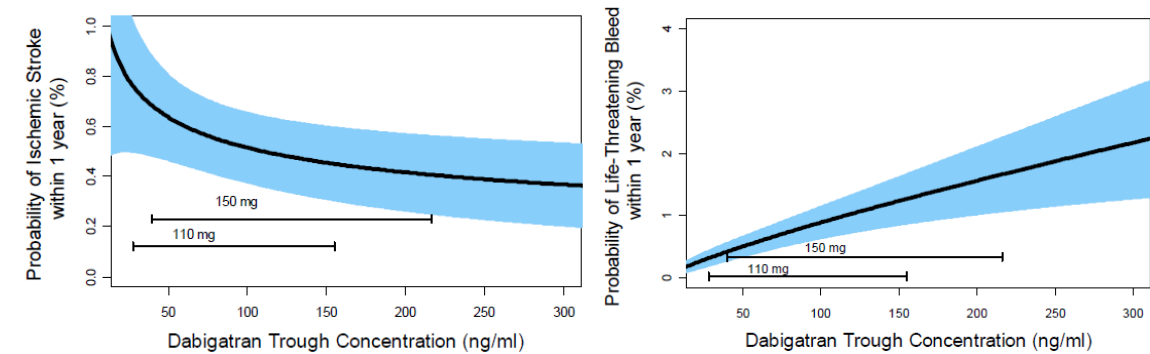
## Apixaban



## Rivaroxaban



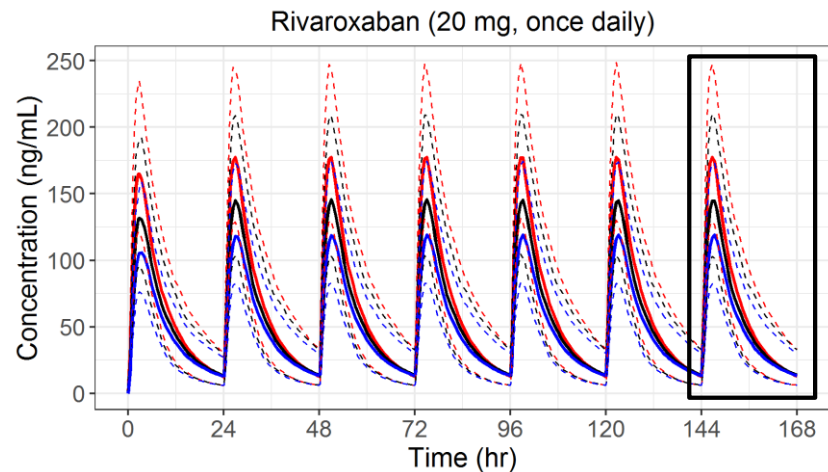
## Dabigatran





# So Let's Use It

## PBPK



Particle Radius (μm): — 2.95 — 3.88 — 4.8

Solid curve: median

Dashed curves: 5<sup>th</sup> percentile (lower), and 95<sup>th</sup> percentile (upper)

## Pop-PK/PD

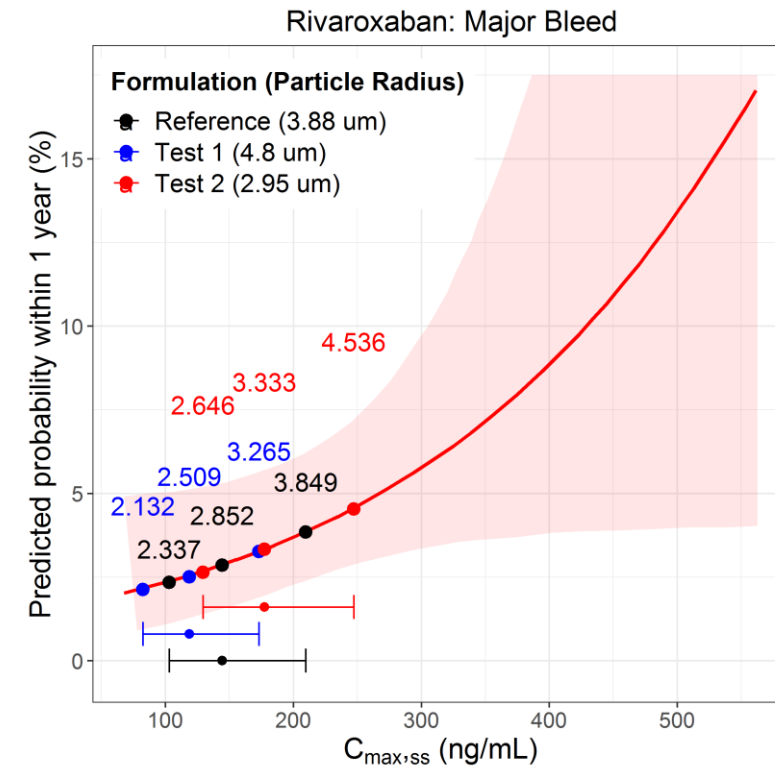
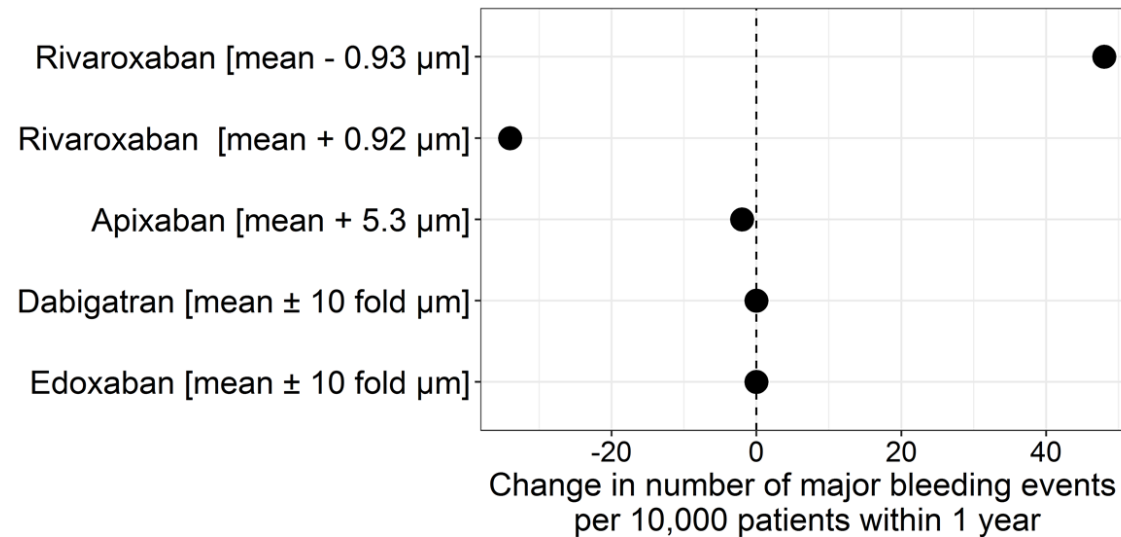


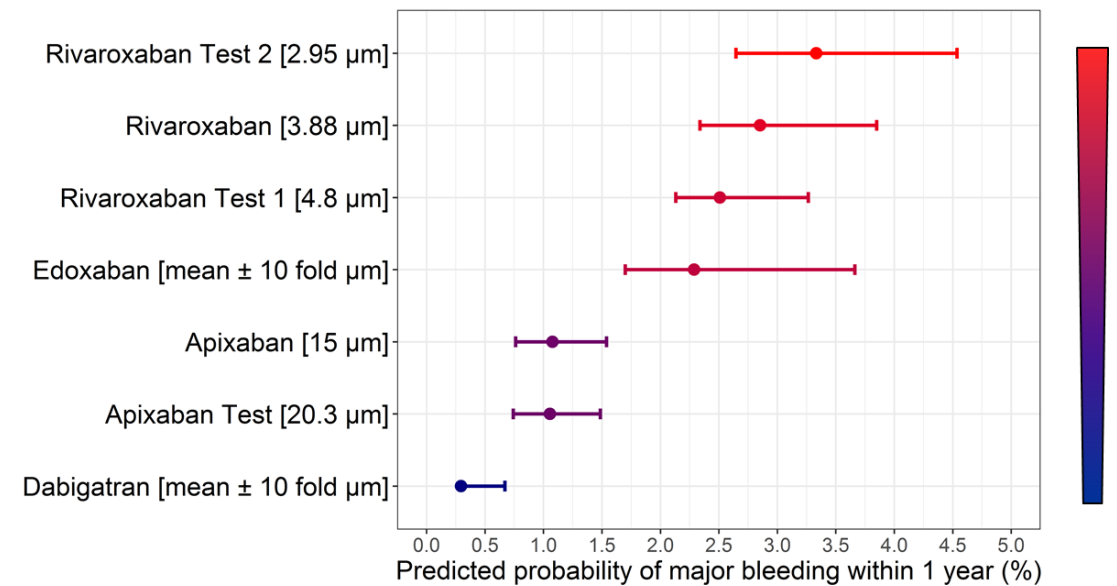
Figure adapted from NDA 22-406.

Solid curve: mean, shaded area: 95% confidence interval, bars on the bottom: 5<sup>th</sup> to 95<sup>th</sup> percentiles of rivaroxaban  $C_{max,ss}$  by formulation subgroup, and dots on the bars: medians of rivaroxaban  $C_{max,ss}$ .

# Evaluation of API Properties on Clinical Endpoints



**Rivaroxaban > Apixaban > Dabigatran ~ Edoxaban**

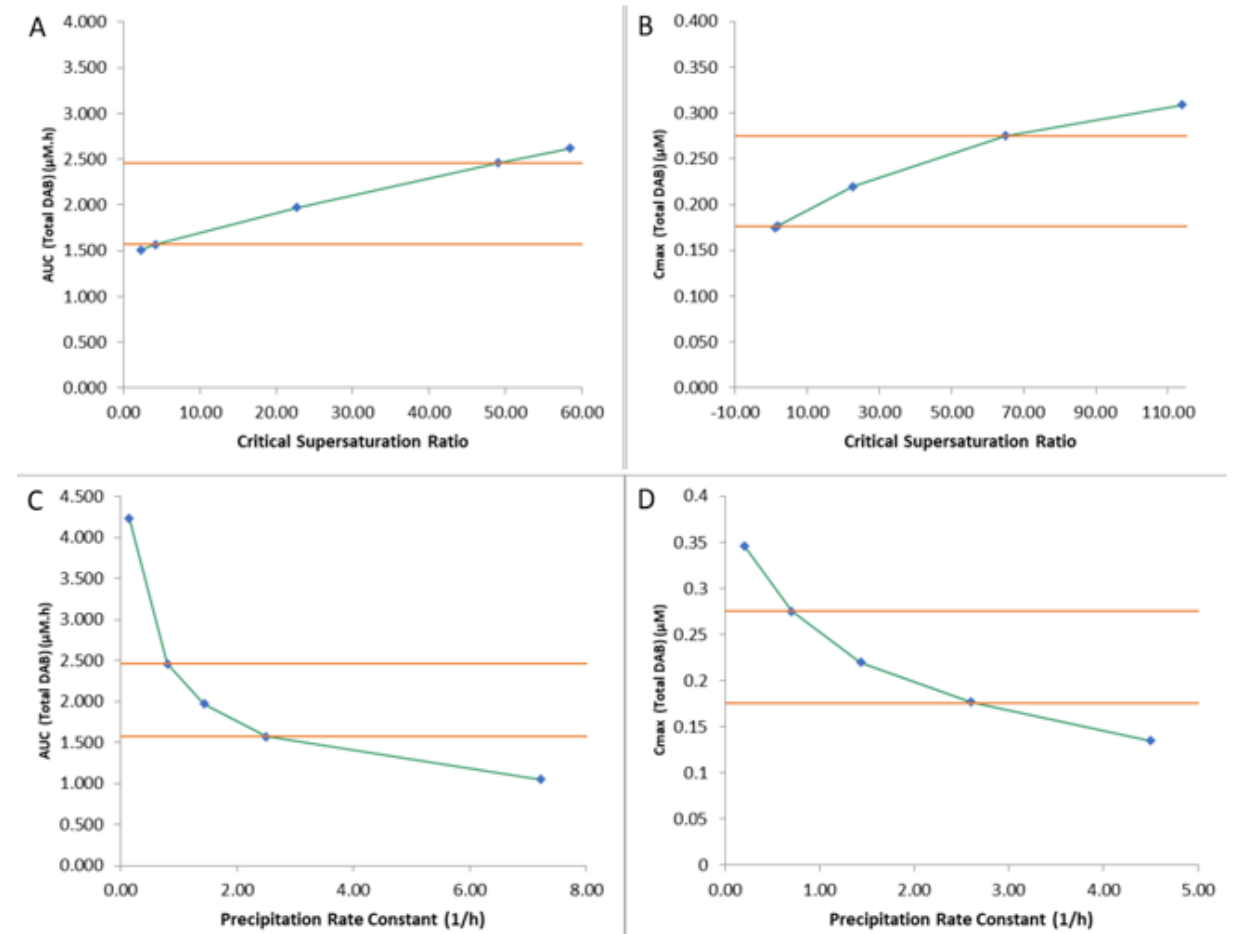


**Rivaroxaban > Edoxaban > Apixaban > Dabigatran**

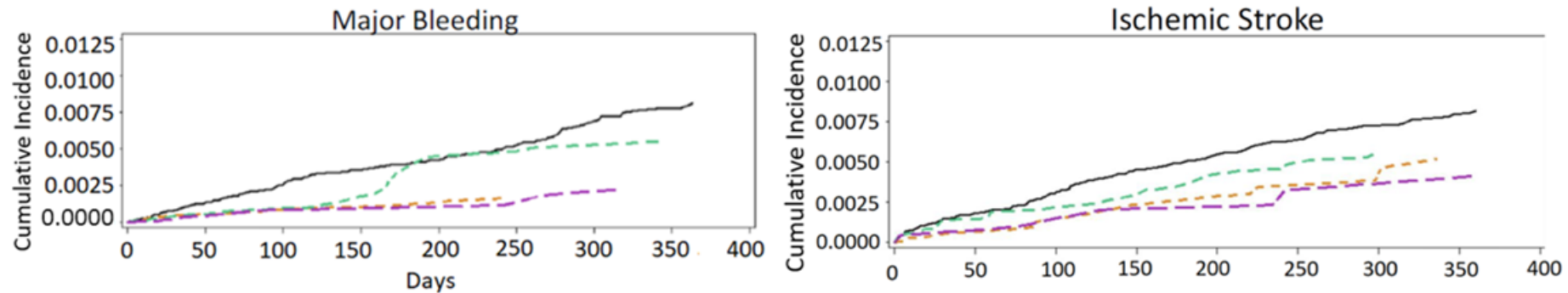
# Evaluation of Formulation Properties

## Example: Dabigatran

- ✓ Dabigatran (Pradaxa®) is a prodrug with low oral bioavailability due to low solubility and P-gp mediated efflux in the gut
- ✓ Formulated as DABE coated pellets with acidified inner core to improve in vivo dissolution
- ✓ Generic formulations may contain different excipients compared to RLD



# Opportunity: Use of RWE Data



Major bleeding and Ischemic stroke outcome cumulative incidence plots by anticoagulant treatment over the first 12 months of treatment. Note: Black = warfarin; Orange = dabigatran; Green = rivaroxaban; Purple = apixaban

Hypotheses for detecting formulation issues:

- ✓ **Generic uptake/market share** will be decreased
- ✓ Patients will **discontinue** treatment and/or **switch back** to trade formulations at a higher rate
- ✓ **Event rates** for indicated conditions will be **elevated** for generic vs. trade formulations

# Recommendations to FDA

- ✓ Concerns regarding generic drug substitutability and post-marketing risk assessment should be approached in an interdisciplinary fashion combining **real-world outcomes**, **pop-PK/PD**, and **mechanistic absorption** modeling.
- ✓ **Future research** should be conducted to gain a better understanding of the role of **excipients** on dissolution and permeability as well as variability therein.
- ✓ Close **collaboration** between **OGD** and **OCP** may be desirable since the BE standards and evaluation procedures outlined in this project also apply to new drug development when scaling between development and to-be-marketed formulations. → **anticipation** of **BE issues** prior to the brand name product coming off patent.
- ✓ Reciprocally, **exposure-response relationships** are available from NDAs and can be used to identify BE standards (product-specific guidances)



**Stephan Schmidt:**  
[sschmidt@cop.ufl.edu](mailto:sschmidt@cop.ufl.edu)  
Office: 407-313-7012  
Cell: 352-408-2833