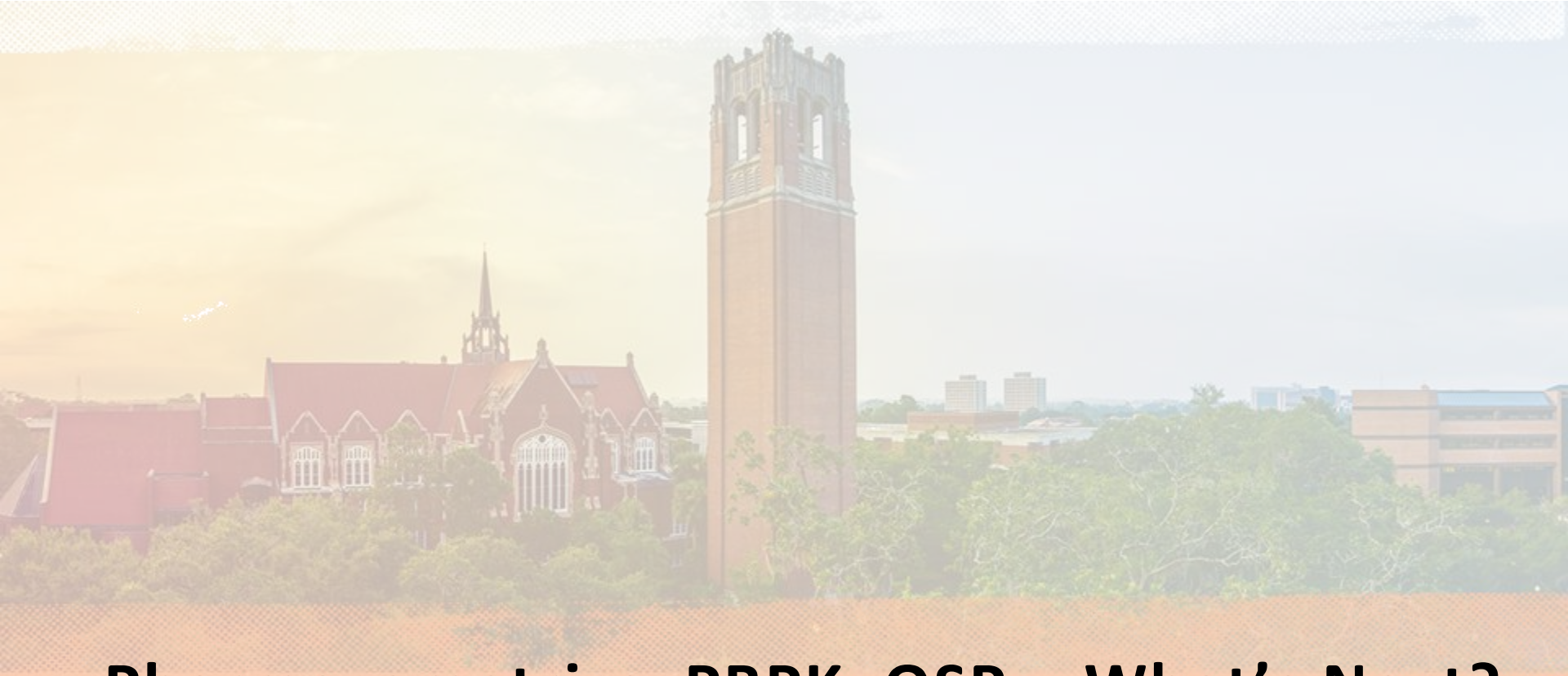


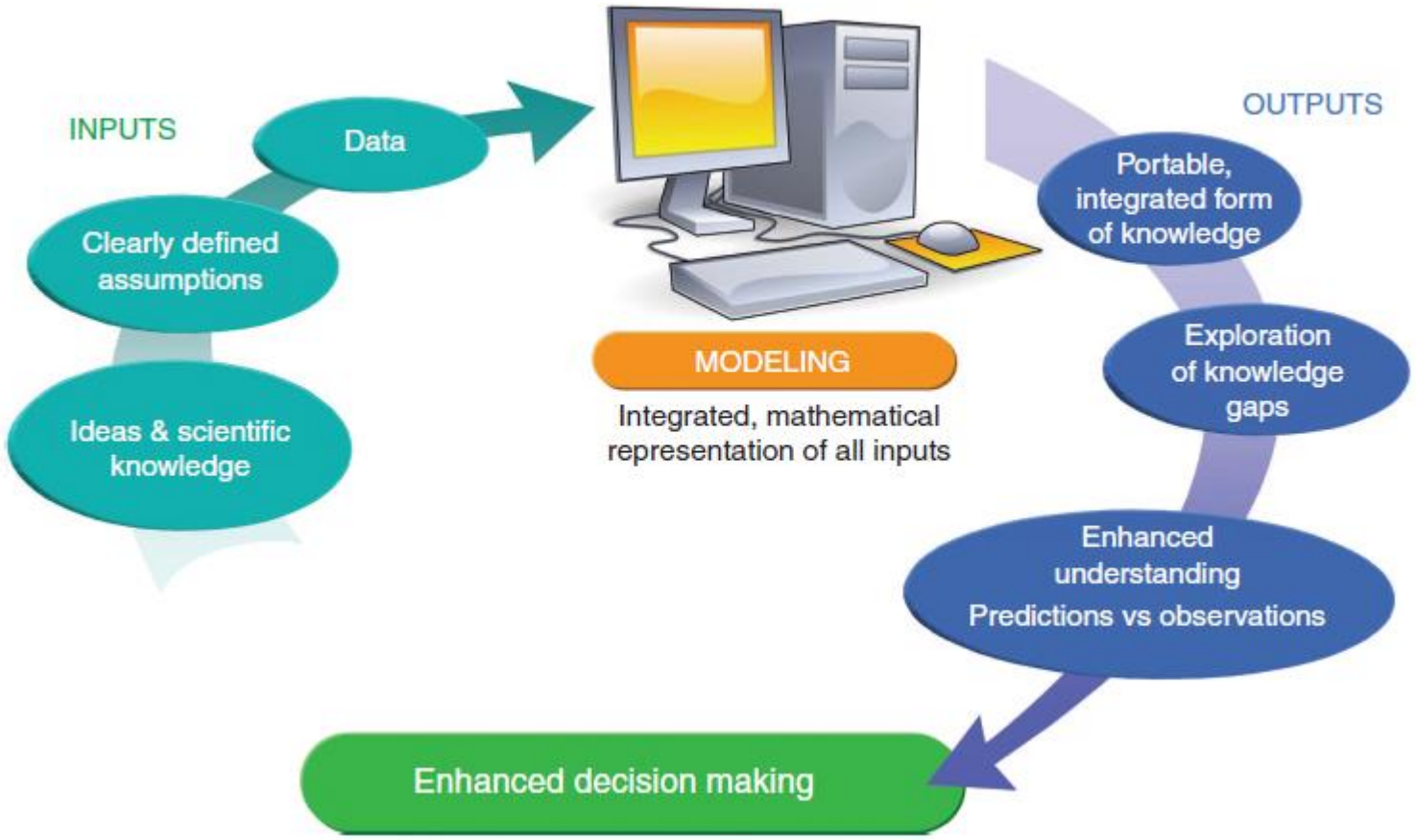
Pharmacometrics, PBPK, QSP – What's Next?

Stephan Schmidt, BPharm, PhD, FCP
Certara Professor
Associate Professor & Associate Director CPSP
Department of Pharmaceutics
University of Florida

Disclaimer

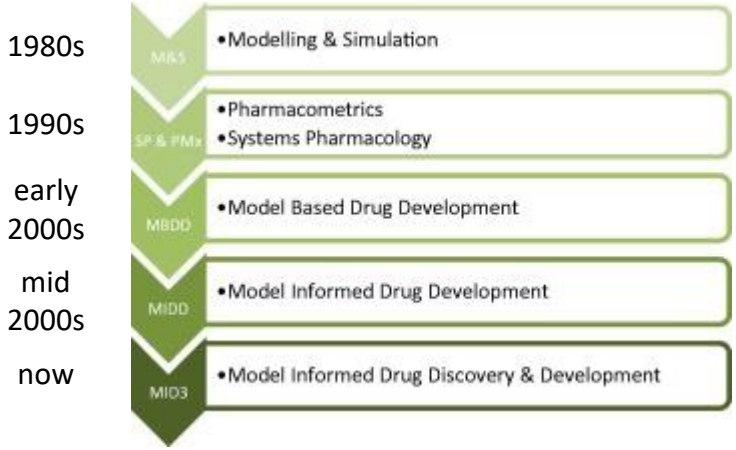
- I am a consultant to pharmaceutical industry
- I like applied & interdisciplinary research

The Idea Behind Using Models



Visser et al. (2014) CPT Pharmaco Sys Pharmacol

A Reflection on Where We "…" :



… "Were":

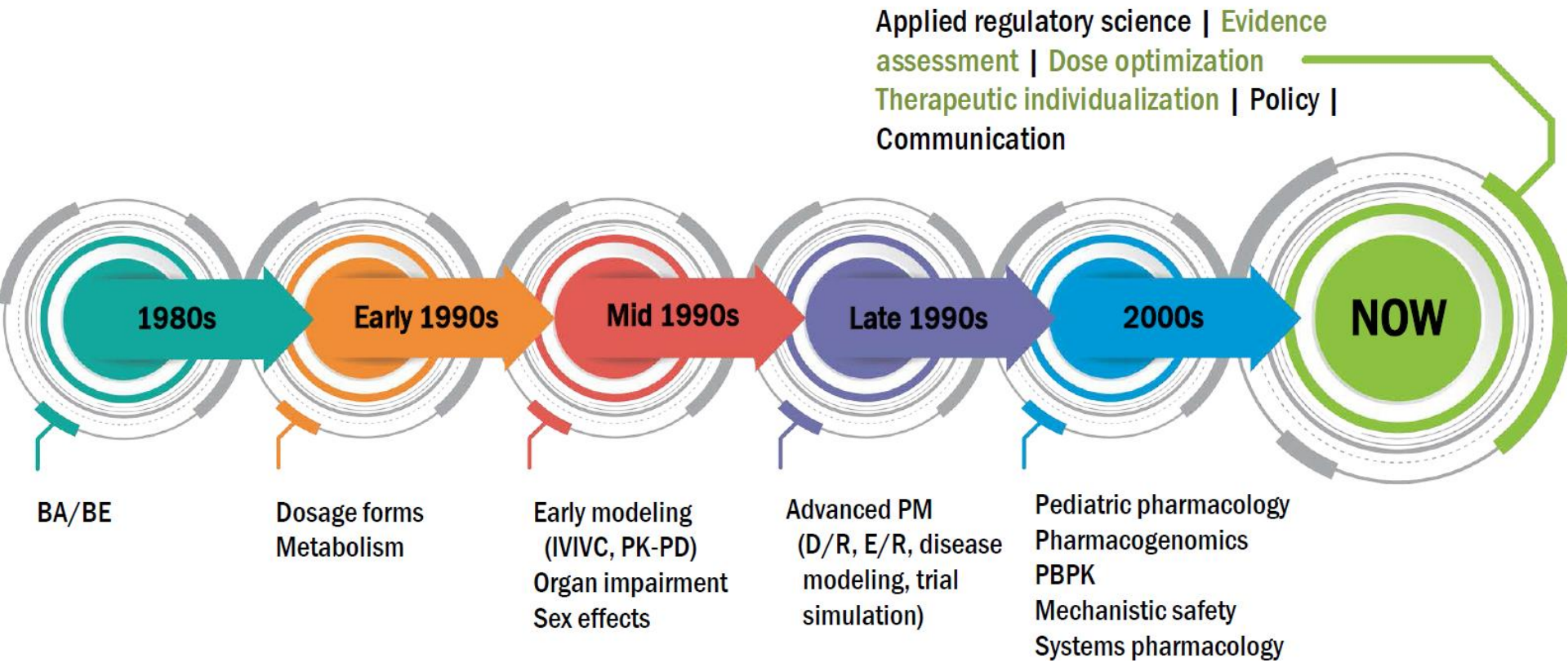
The **learn & confirm** paradigm as the basis for modern M&S:

1) What do we want to know?
2) How confident do we want to be?
3) What are we willing to assume?

… "Are":

MID3: "A quantitative framework for prediction and extrapolation, centered on knowledge and inference generated from integrated models of compound, mechanism and disease level data and aimed at improving the quality, efficiency and cost effectiveness of decision making"

Regulatory Buy-In Along the Way



Courtesy of Joe Grillo, FDA

Application of Modeling and Simulation

Within Programs:

Can be viewed as "Progressive reduction in uncertainty about benefits and risks of drugs" – or as "increasing levels of confidence about clinical outcomes"

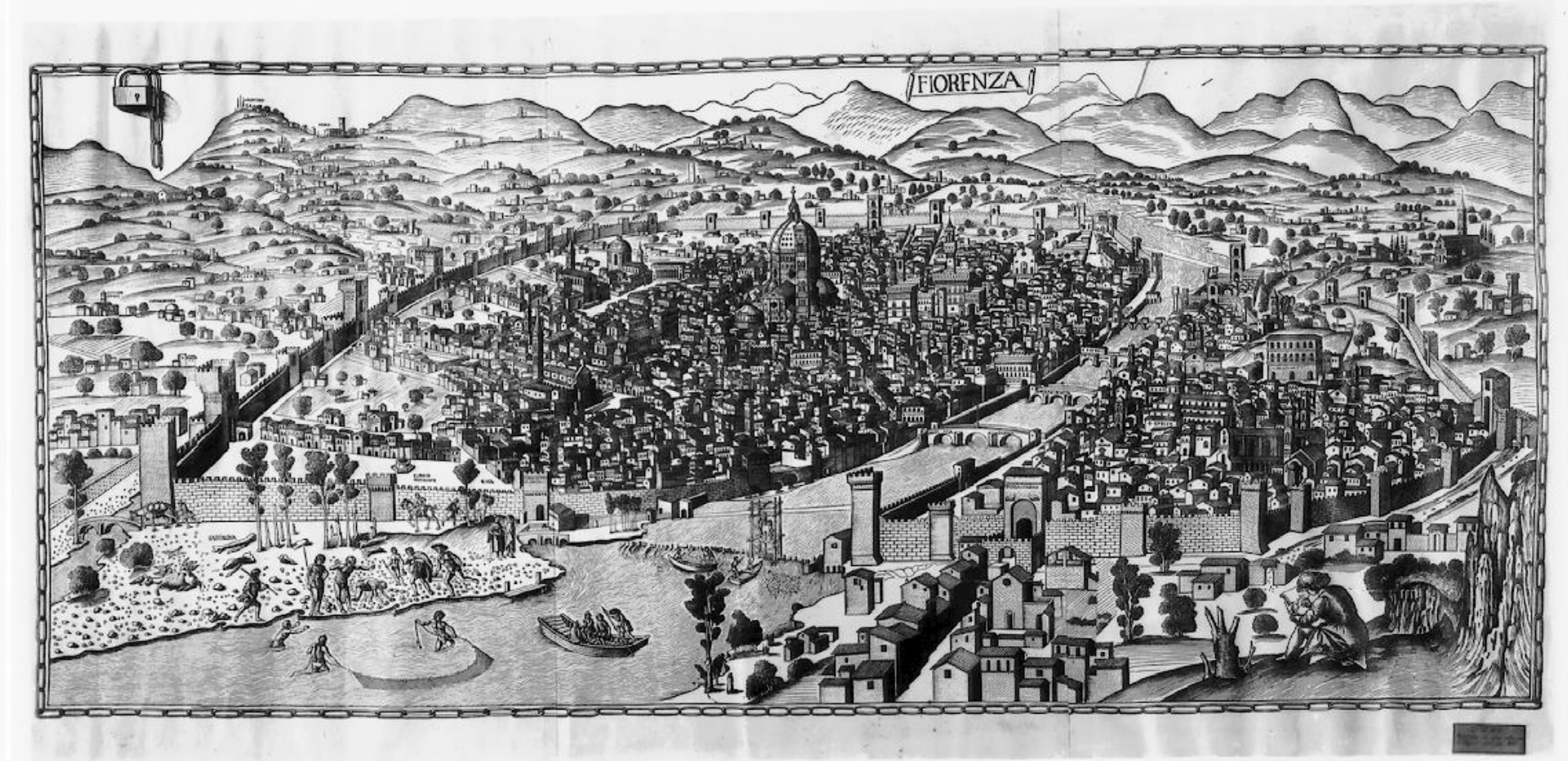
Across Programs:

Can be viewed as "Step-wise identification of clinically-relevant sources of variability for given indication and drug class"

In My Mind, This Begs an Additional Set of Questions

1) What are the clinically-relevant sources of variability?
2) How much of this variability can we capture in controlled clinical trials, even under optimal design conditions?
3) How can we implement what we have learned into clinical practice in a cost-effective fashion?

Call for Innovation: Lessons From The Past – Opportunities For The Future



Commissioner's Blog on *In Silico* Tools

How FDA Plans to Help Consumers Capitalize on Advances in Science

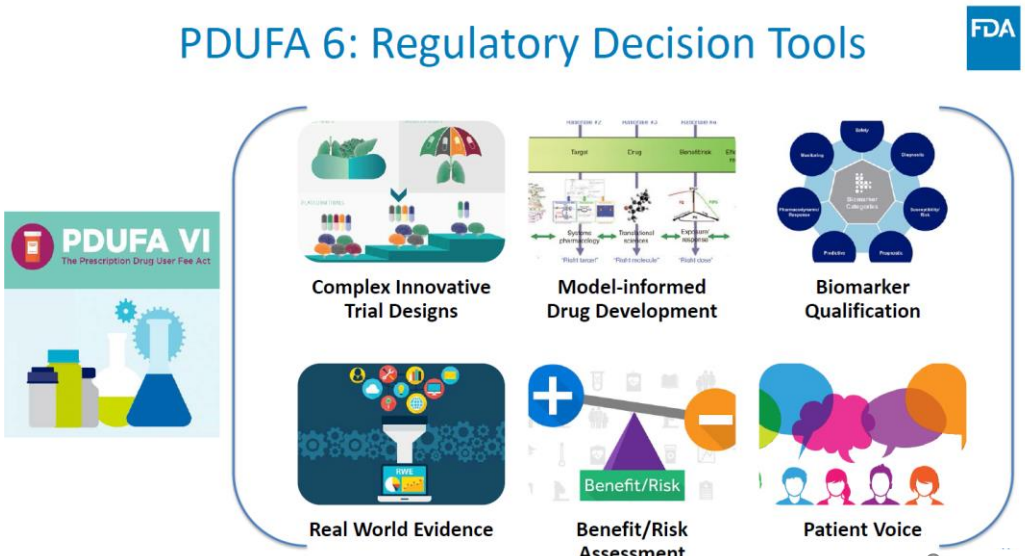
Posted on **July 7, 2017** by **FDA Voice**

By: Scott Gottlieb, M.D.

We're at a point in science where new medical technologies hold out the promise of better treatments for a widening number of vexing conditions. Over the last few decades, science has enabled fundamental advances in our understanding of the genetic and protein bases of human disease. These developments are already being translated into new medicines. In more cases, these treatments target the underlying mechanisms that drive different diseases. These advances hold out the promise of arresting and even curing a growing number of diseases.

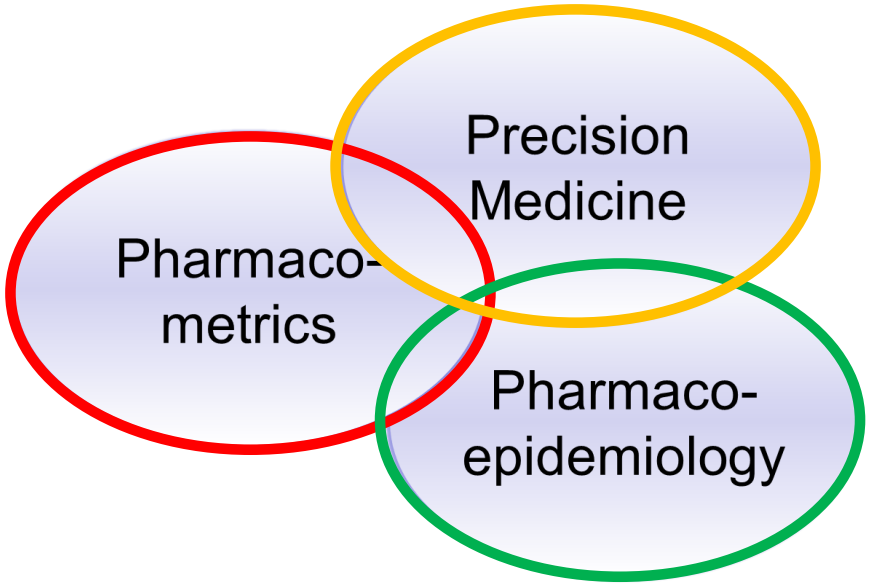
To build upon such opportunities, FDA will soon unveil a comprehensive Innovation Initiative. It will be aimed at making sure our regulatory processes are modern and efficient, so that safe and effective new technologies can reach patients in a timely fashion. We need to make sure that our regulatory principles are efficient and informed by the most up to date science. We don't want to present regulatory barriers to beneficial new medical innovations that add to the time, cost, and uncertainty of bringing these technologies forward if they don't add to our understanding of the product's safety and benefits.

- **Innovation Initiative**
- Use of ***in silico* tools** in clinical trials for improving drug development and making regulation more efficient
- M&S to **predict** clinical outcomes, inform clinical trial designs, support evidence of effectiveness, optimize dosing, predict product safety, and evaluate potential adverse event mechanisms
- Creation of natural history databases to support **model-informed drug development**



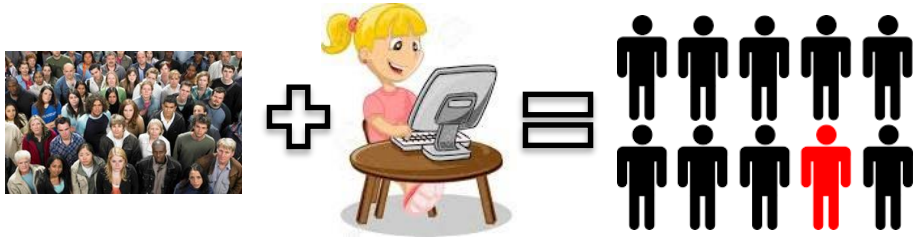
https://blogs.fda.gov/fdavoice/index.php/tag/in-silico-tools/

Opportunities Within the College



Pharmacometrics (Inductive reasoning):

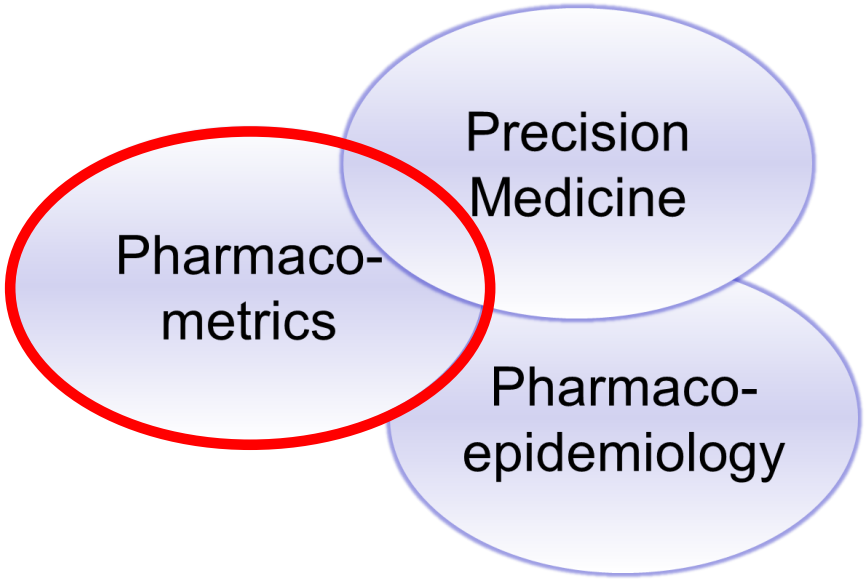
Pharmacoepidemiology (iterative reduction of bias):



Precision medicine:

- ✓ Genetic & non-genetic sources of variability in pharmacokinetics and drug response
- ✓ Clinical implementation

Creating Synergy



Selected Case Examples:

- Development of a drug-disease-trial model for postmenopausal osteoporosis
- Optimization of voriconazole therapy for the treatment of invasive fungal infections in adults
- How informative are DDIs of GDIs?
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Development of a Drug-Disease-Trial Model for Postmenopausal Osteoporosis

Background:

Osteoporosis is a chronic disorder with bones weakening over time. It is more prominent in women due to steep declines in endogenous estrogen production after menopause.

Current challenges in drug development in osteoporosis:

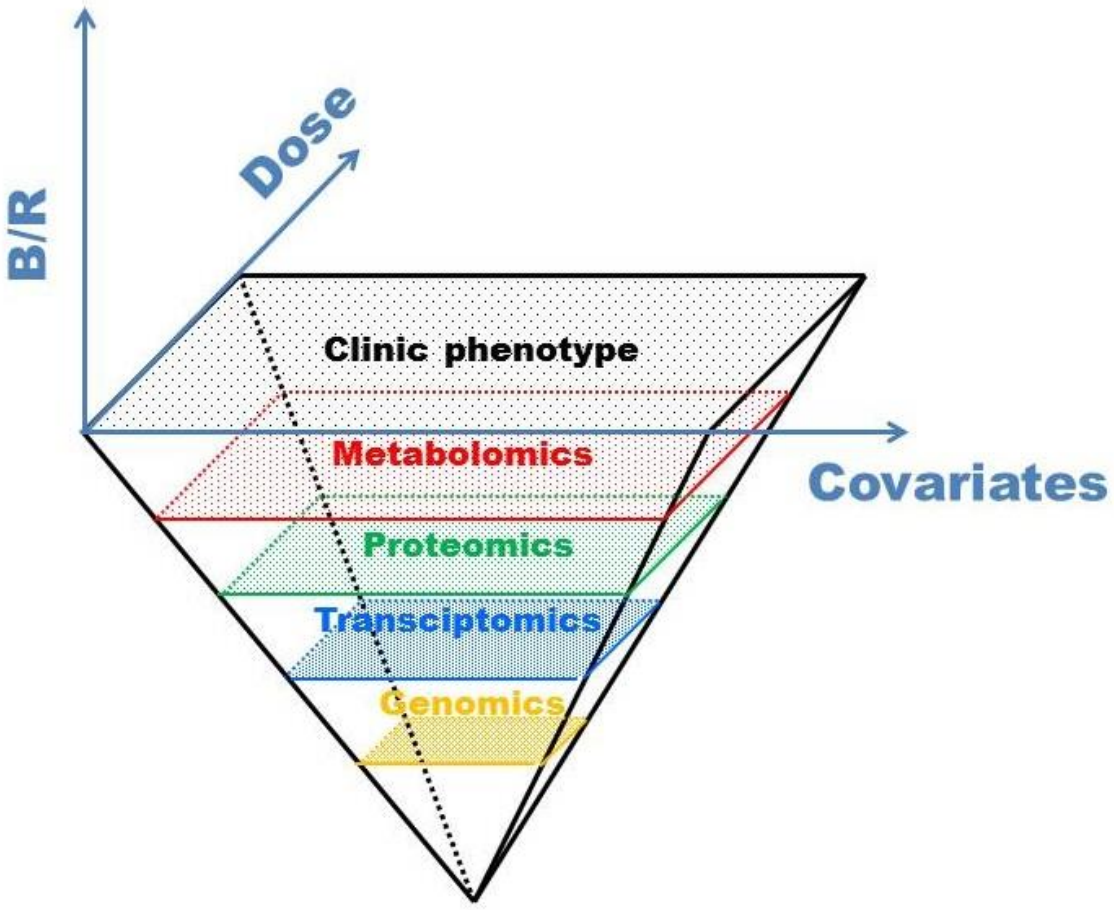
Osteoporosis drug development trials are long and large sample size is needed to evaluate current endpoints such as fracture risk or bone mineral density (BMD) change.

- ✓ Phase 3 trials with fracture risk as efficacy endpoint take 2-3 years.
- ✓ Phase 2 dose-finding trials with BMD as endpoint take 1-2 years.
- ✓ BMD is an imperfect surrogate marker for fracture

Opportunity:

Reliable predictions of the impact of disease progression and drug treatment on bone require the use of quantitative models.

Quantitative Models Can Be Established at Various Levels of Complexity



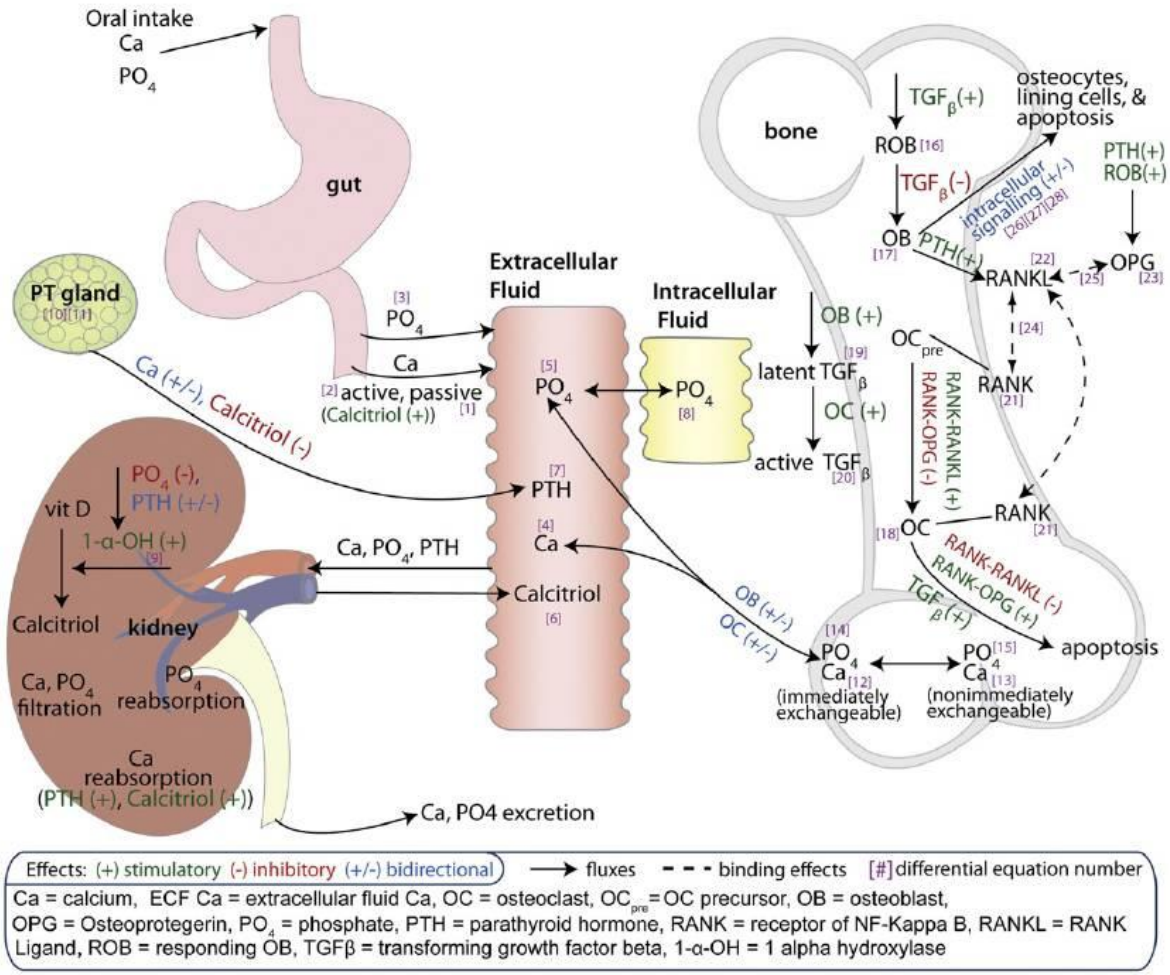
Pharmacometric Models
(Drug-Centric)

ePK/PD Models
(Mechanism-Centric)

Systems Pharmacology Models
(Network-Centric)

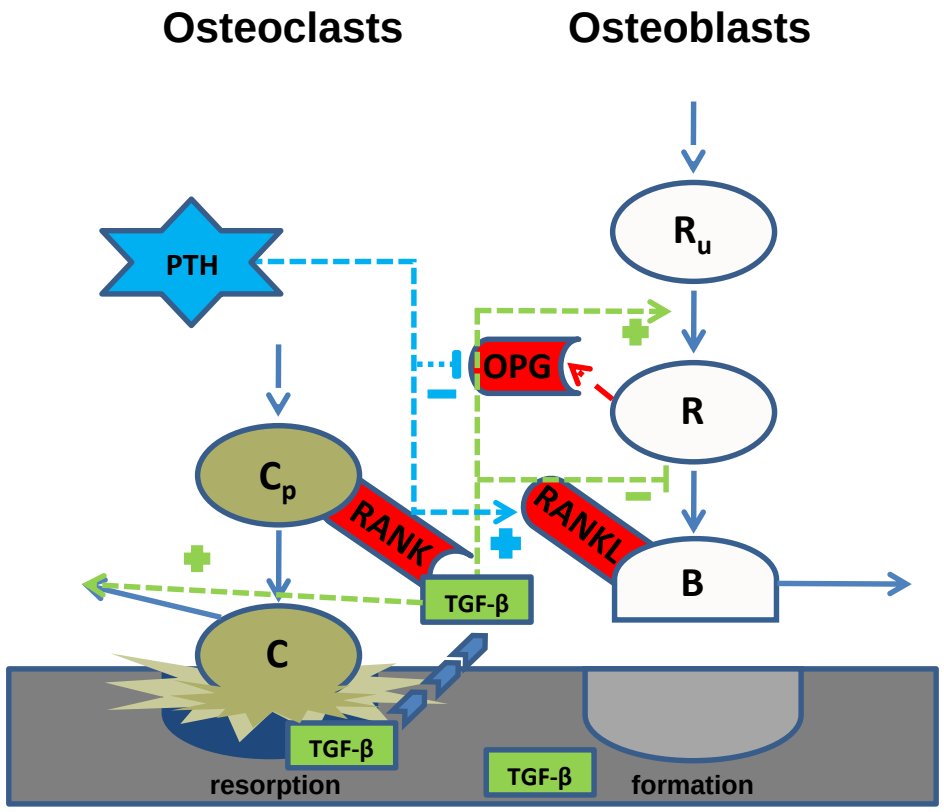
Adapted from: Post et al.; Pharm Res (2005) 22:1038-1049
Lesko and Schmidt; Clin Pharmacol Ther (2012) 92:458-466

Challenges Con't



*Peterson and Riggs (2010) Bone **46**:49-63.*

The Conceptual Bone Cell Interaction Model by Lemaire *et al.*



***R**: responding osteoblasts, **B**: active osteoblasts, **C**: active osteoclasts, **RANK**: receptor activator of NF-κB, **RANKL**: RANK ligand, **OPG**: osteoprotegerin, **PTH**: parathyroid hormone, **TGF-β**: transforming growth factor β*

Adapted from: Lemaire et al. (2004) J Theor Biol 229:293-309.

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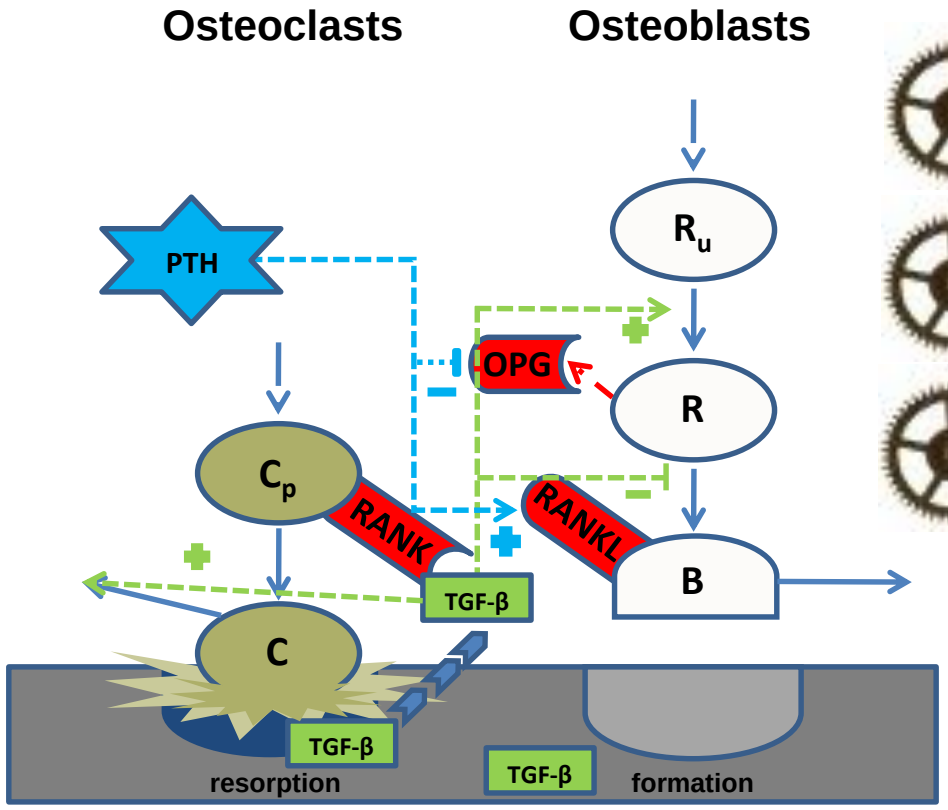


$$\frac{dR}{dt} = D_R \cdot \pi_C - \frac{D_B}{\pi_C} \cdot R$$

$$\frac{dB}{dt} = \frac{D_B}{\pi_C} \cdot R - k_B \cdot B$$

$$\frac{dC}{dt} = D_C \cdot \pi_L - D_A \cdot \pi_C \cdot C$$

with

$$\pi_C = \frac{C + f_0 C^s}{C + C^s}, \quad \pi_L = \frac{\alpha B}{1 + \beta R}$$

***R**: responding osteoblasts, **B**: active osteoblasts, **C**: active osteoclasts, **RANK**: receptor activator of NF-κB, **RANKL**: RANK ligand, **OPG**: osteoprotegerin, **PTH**: parathyroid hormone, **TGF-β**: transforming growth factor β, π_C: TGF- β receptor occupancy, π_L: RANK occupancy*

Adapted from: Lemaire et al. (2004) J Theor Biol 229:293-309.

Understanding the Critical Processes & their Relative Speeds

Systems Pharmacology … *is the quantitative analysis of the dynamic interactions between drug(s) and a biological system to understand the behaviour of the system as a whole, as opposed to the behaviour of its individual constituents* … .

Van der Graaf and Benson Pharm Res (2011) 28:1460-1464

J Pharmacokinet Pharmacodyn (2011) 38:873–900
DOI 10.1007/s10928-011-9224-2

Coping with time scales in disease systems analysis: application to bone remodeling

Stephan Schmidt · Teun M. Post ·
Lambertus A. Peletier · Massoud A. Boroujerdi ·
Meindert Danhof

Full system

- ✓ 5 differential equations
- ✓ 25 parameters to be estimated

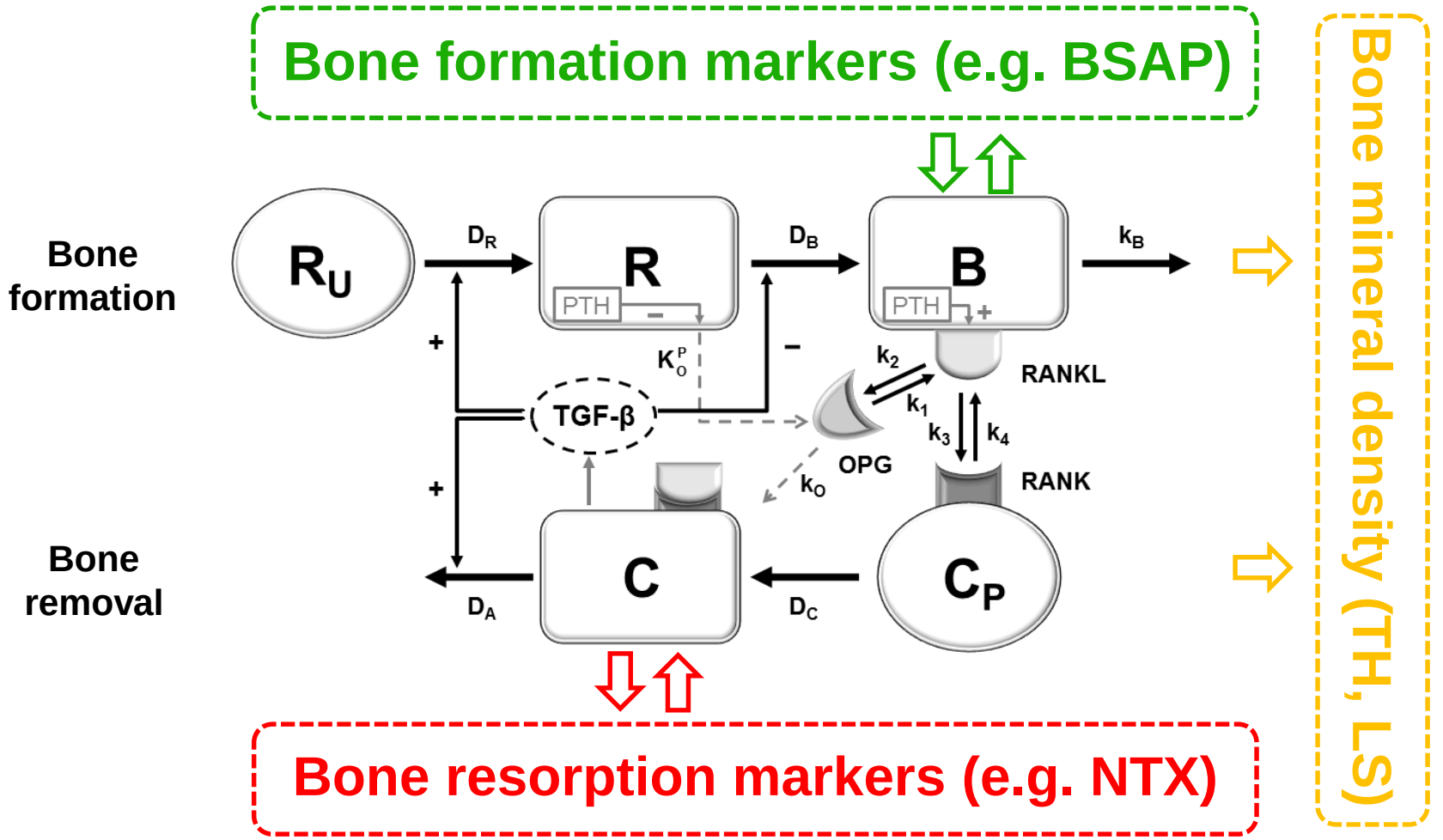
⇨

Reduced system

- ✓ 2 differential equations
- ✓ 5 parameters to be estimated

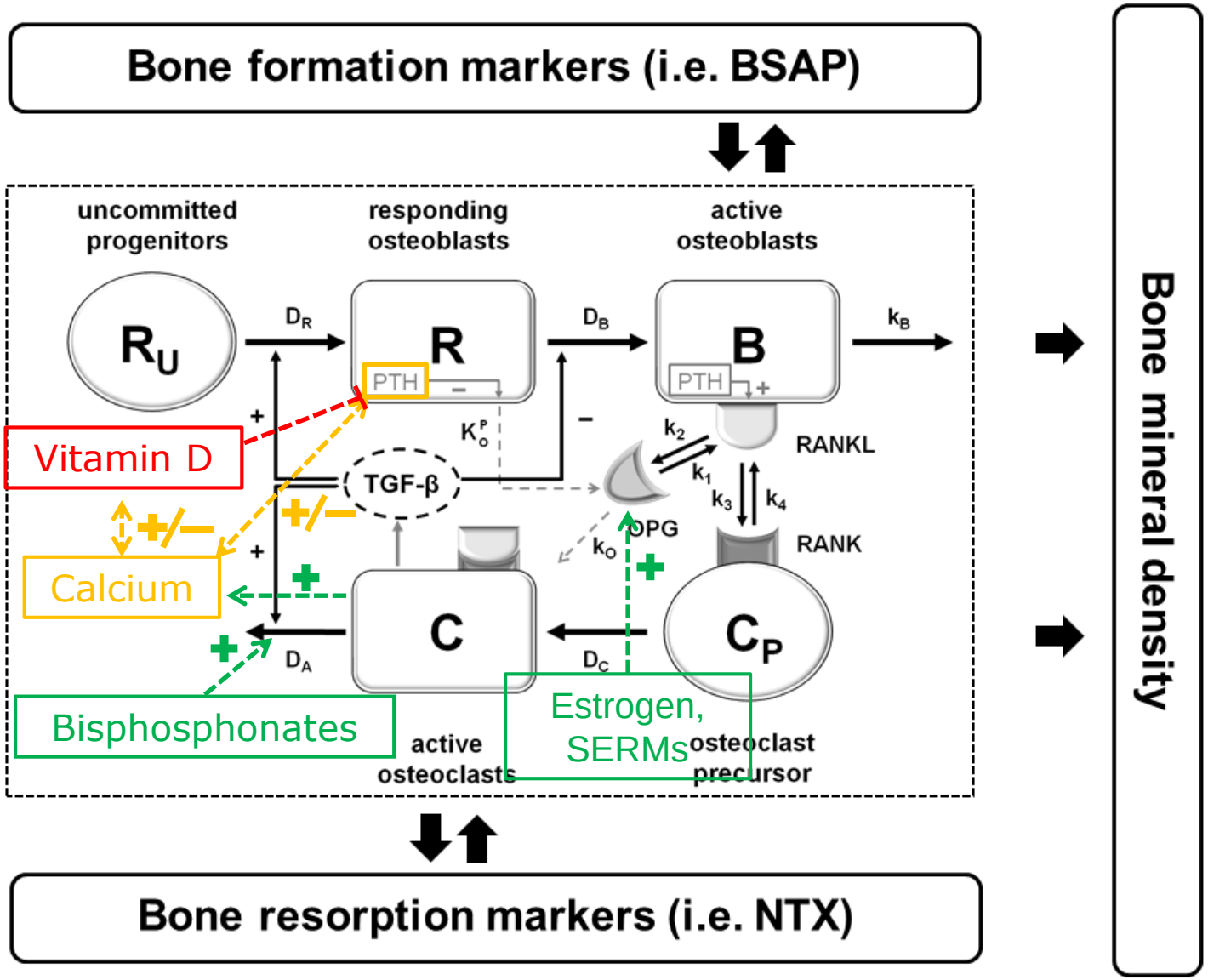
→ Enabled fitting to clinical data

Link to Clinical Biomarkers



*Schmidt et al. (2011) J Pharmacokinet Pharmacodyn **38**: 873-900*

*Post et al. (2013) J Pharmacokinet Pharmacodyn **40**: 143-56*

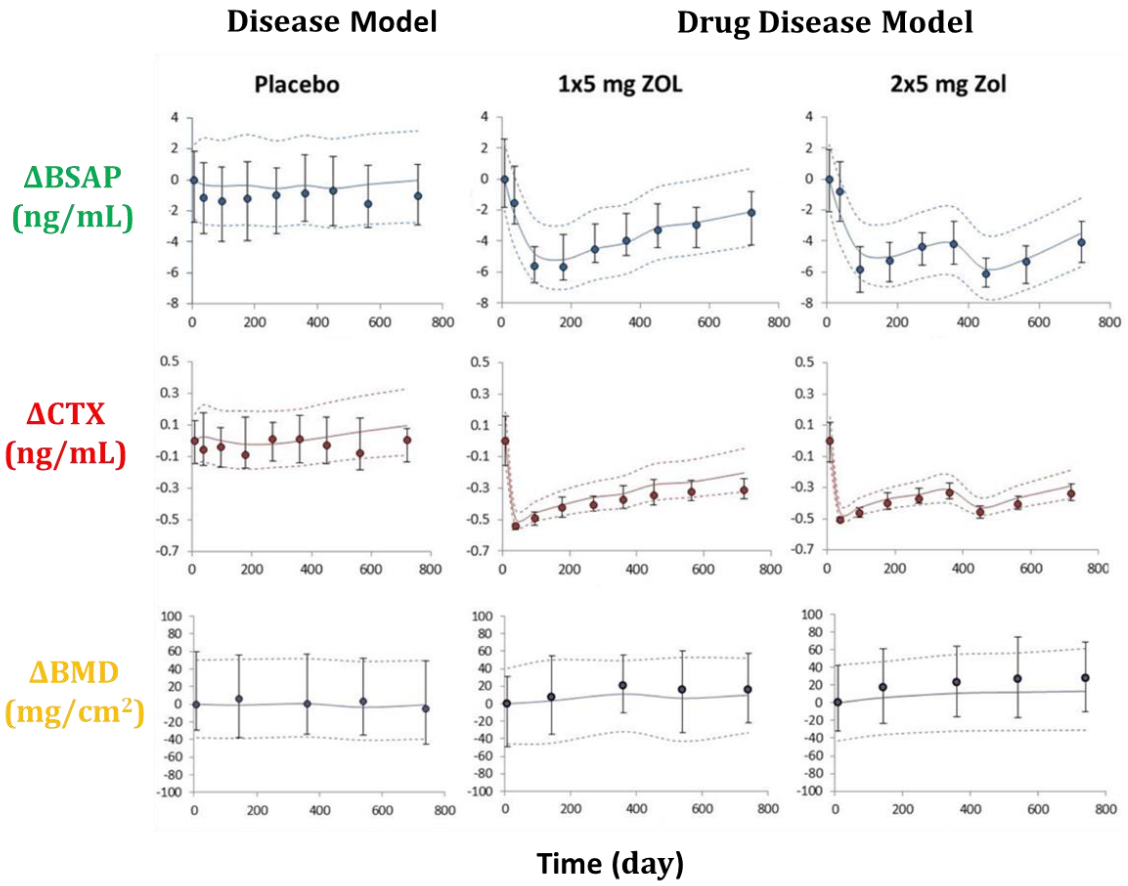


*Schmidt et al. (2011) J Pharmacokinet Pharmacodyn **38**: 873-900.*

*Post et al. (2013) J Pharmacokinet Pharmacodyn **40**: 143-56.*

Berkhout et al. (2015) CPT-PSP: 516-526.

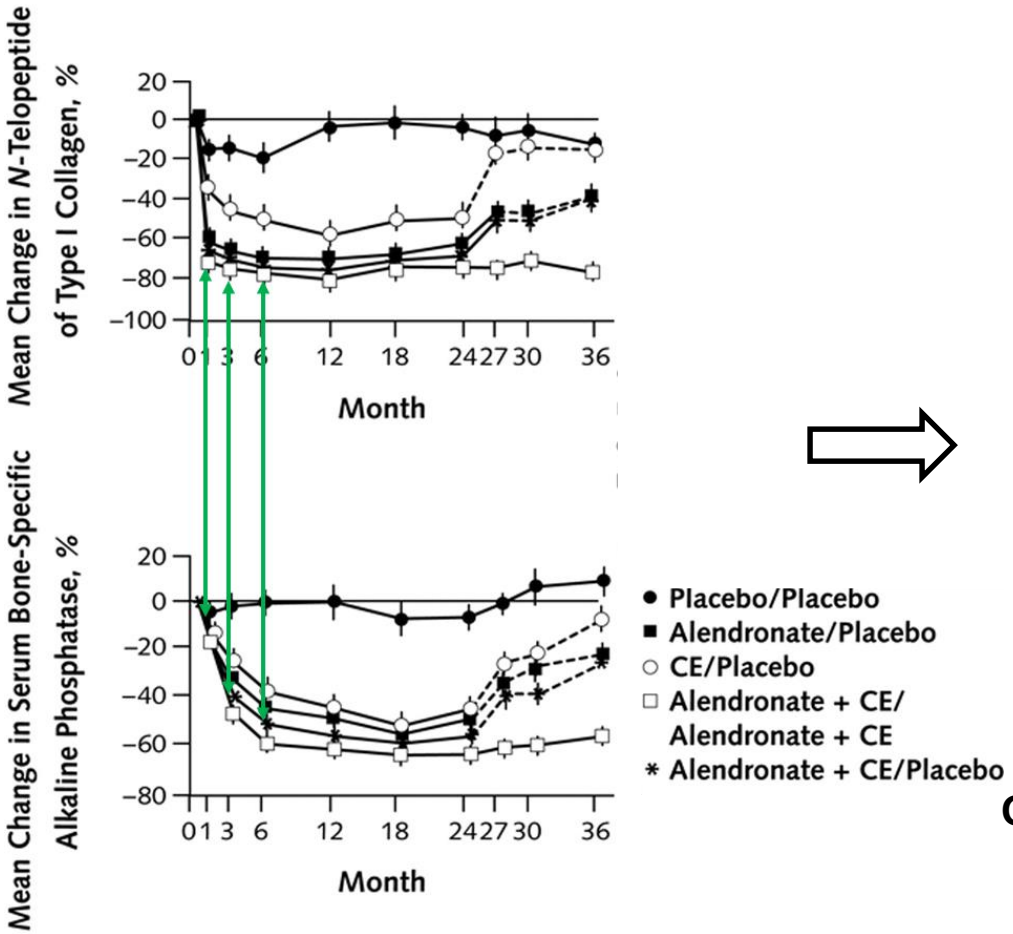
Application to Clinical Zoledronic Acid Data

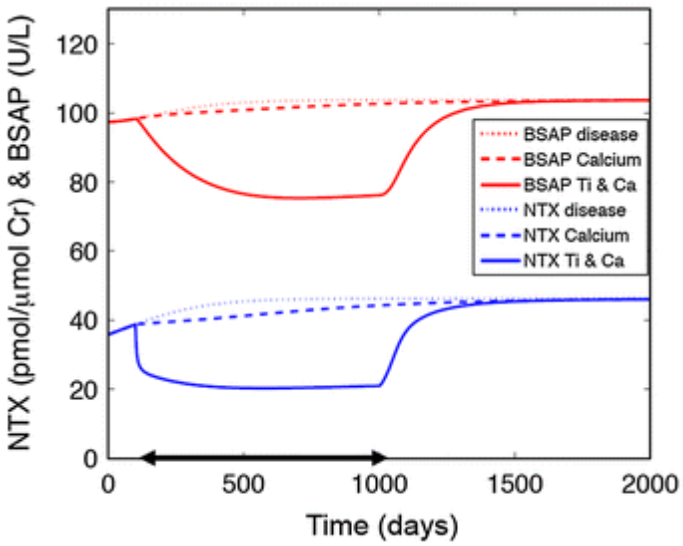


Inter-individual variability	Covariates
Biomarker Baseline	BMI
Drug Clearance	Race
Drug Effects	Age
Years since menopause (YSM)	YSM

Model showed reasonably accurate prediction on clinically relevant biomarkers.

Simple Correlation Analysis May Neglect Biomarker Dynamics



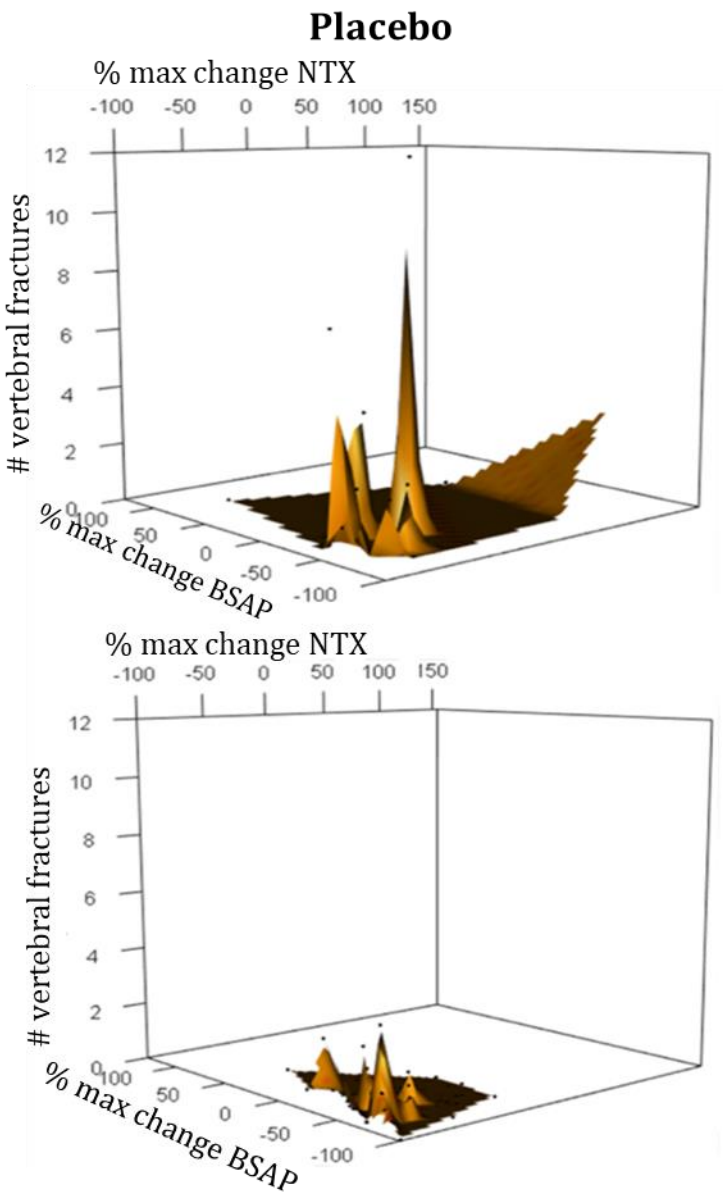


Opportunity: Use of time-dependent Hazard functions using bone cell dynamics as a driver

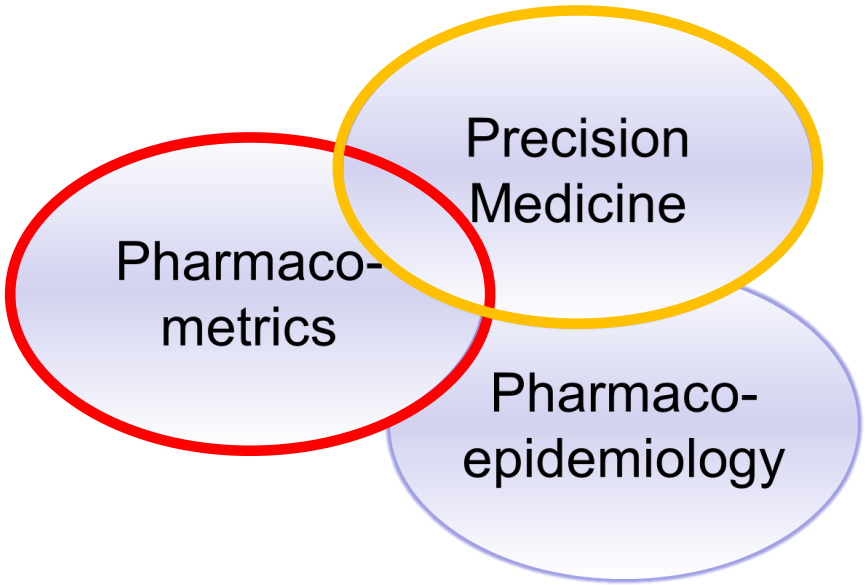
1. Greenspan, S. L. *et al.* Significant differential effects of alendronate, estrogen, or combination therapy on the rate of bone loss after discontinuation of treatment of postmenopausal osteoporosis. A randomized, double-blind, placebo-controlled trial. *Annals of internal medicine* **137**, 875-883 (2002).
2. Post, T. M. *et al.* Application of a mechanism-based disease systems model for osteoporosis to clinical data. *J Pharmacokinet Pharmacodyn* **40**, 143-156, doi:10.1007/s10928-012-9294-9 (2013).

Prior fractures

No prior fractures



Creating Synergy



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Optimization of Voriconazole Therapy for Treatment of Invasive Fungal Infections

Background:

- Invasive fungal infections (IFIs) caused by e.g. ***Candida spp.*** or ***Aspergillus spp.*** are common in immunocompromised patients (e.g. transplant patients)
- **Voriconazole** is frequently used in IFI patients
- **Non-linear** and highly **variable** pharmacokinetics → **TDM**
- 98% of dose is metabolized by **CYP2C19** (polymorphic)
- It takes **5-7** days to reach **steady-state** (2-6mg/L)

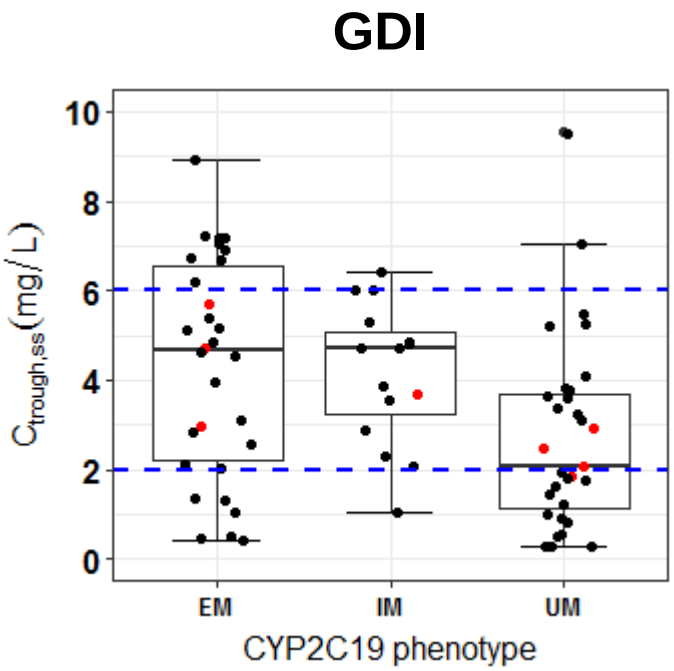
Research Questions:

1) What are clinically-relevant **sources of variability**?
2) Is **dose adjustment** needed?
3) If so, what is the **optimal dose**?

Hamadeh et al. Pharmacogenet Genomics. 2017 May;27(5):190-196.
Mangal et al. Clin Pharmacol Ther. 2018 Jan 9. doi: 10.1002/cpt.1012. [Epub ahead of print]
UL1 TR000064, UL1 TR001427, NIH/NHGRI U01007269.
Collaboration with Drs. Bulitta (CPSP), Cavallari (COP-PTR), Arwood (COP-PTR), Klinker (COP-PTR), Hamadeh (COP-PTR)

Challenge: Large Variability in PK & PD

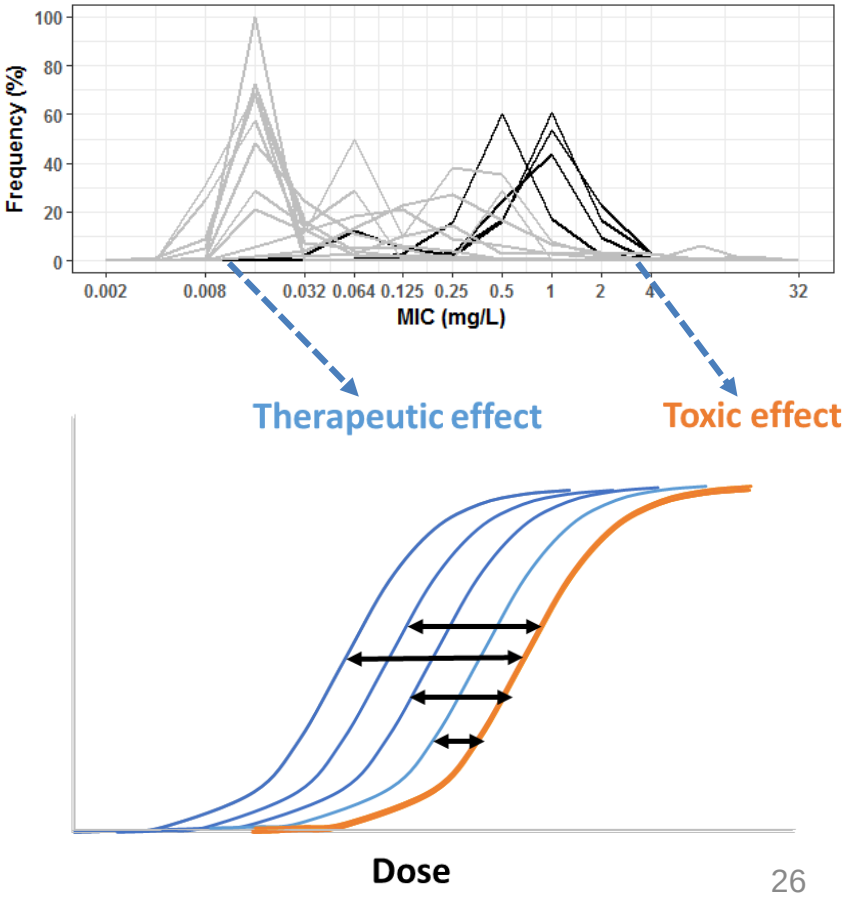
In Pharmacokinetics



LD: 6 mg/kg BID
MD: 4 mg/kg BID

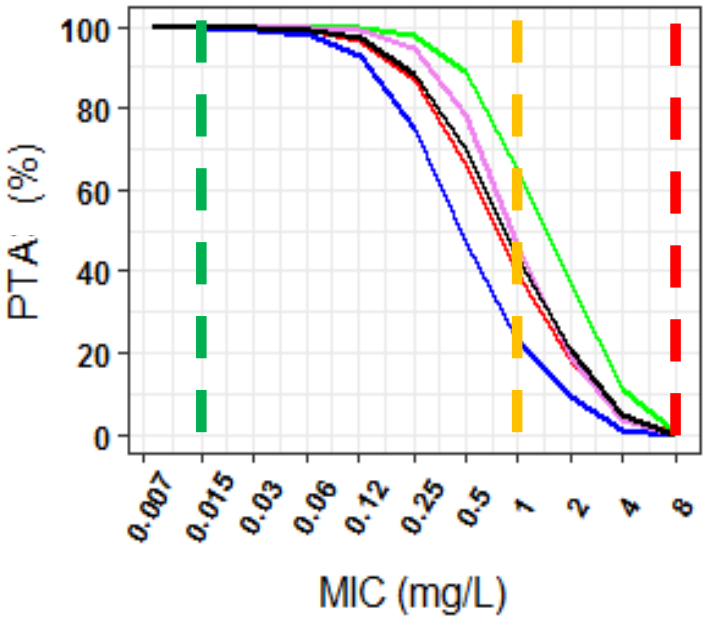
● Before dose adjustment
● After dose adjustment

In Pharmacodynamics



Hamadeh et al. Pharmacogenet Genomics. 2017 May;27(5):190-196.
Mangal et al. Clin Pharmacol Ther. 2018 Jan 9. doi: 10.1002/cpt.1012. [Epub ahead of print]

Probability of Achieving $C_{trough,ss}$/MIC > 2 Following Administration of 200 mg MD



Low susceptibility, MIC = 8 mg/L

Phenotype	PTA (%)
UM non-pantoprazole	<5
EM/IM non-pantoprazole	<5
UM pantoprazole	<5
EM/IM pantoprazole	<5
Overall	<5

Intermediate susceptibility, MIC = 1 mg/L

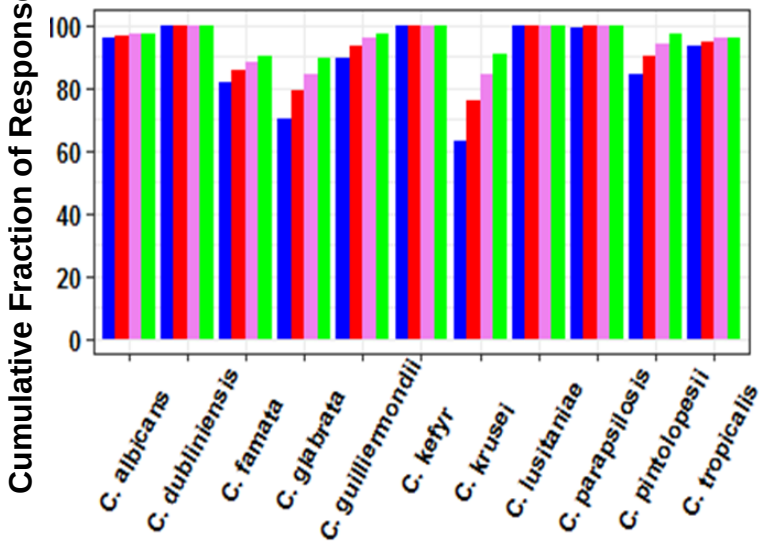
Phenotype	PTA (%)
UM non-pantoprazole	23.2
EM/IM non-pantoprazole	39.9
UM pantoprazole	46.5
EM/IM pantoprazole	64.9
Overall	43.6

High susceptibility, MIC = 0.015 mg/L

Phenotype	PTA (%)
UM non-pantoprazole	~ 100
EM/IM non-pantoprazole	~ 100
UM pantoprazole	~ 100
EM/IM pantoprazole	~ 100
Overall	~ 100

What Does This Mean For Clinical *Candida* & *Aspergillus* Strains?

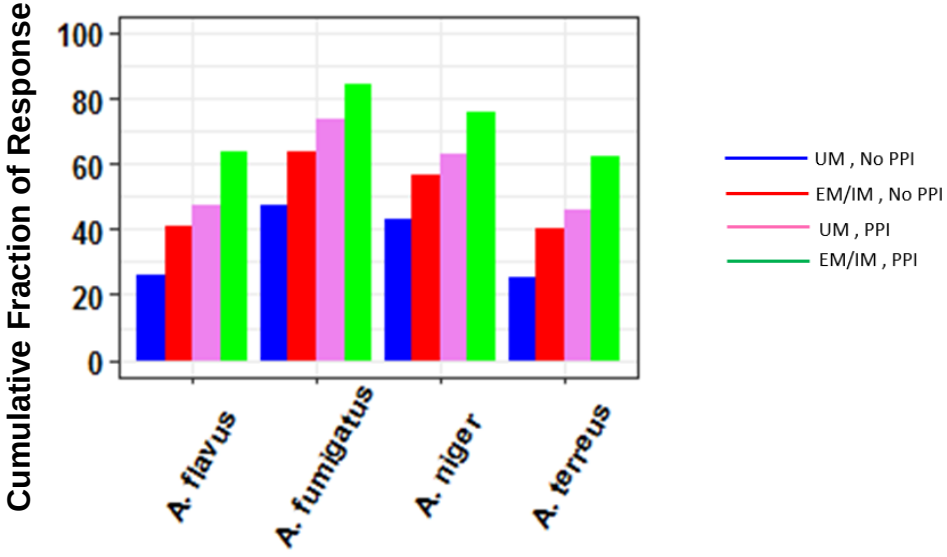
Candida spp.



MIC<0.016 mg/L

Standard MD of **200mg** voriconazole is **sufficient** for most ***Candida spp.*** infections in patients with different clinical phenotypes

Aspergillus spp.



MIC>=1 mg/L

For ***Aspergillus spp***. infections, MD **>200mg** are **needed** in patients with different clinical phenotypes

Mangal et al. Clin Pharmacol Ther. 2018 Jan 9. doi: 10.1002/cpt.1012. [Epub ahead of print]
UL1 TR000064, UL1 TR001427, NIH/NHGRI U01007269.
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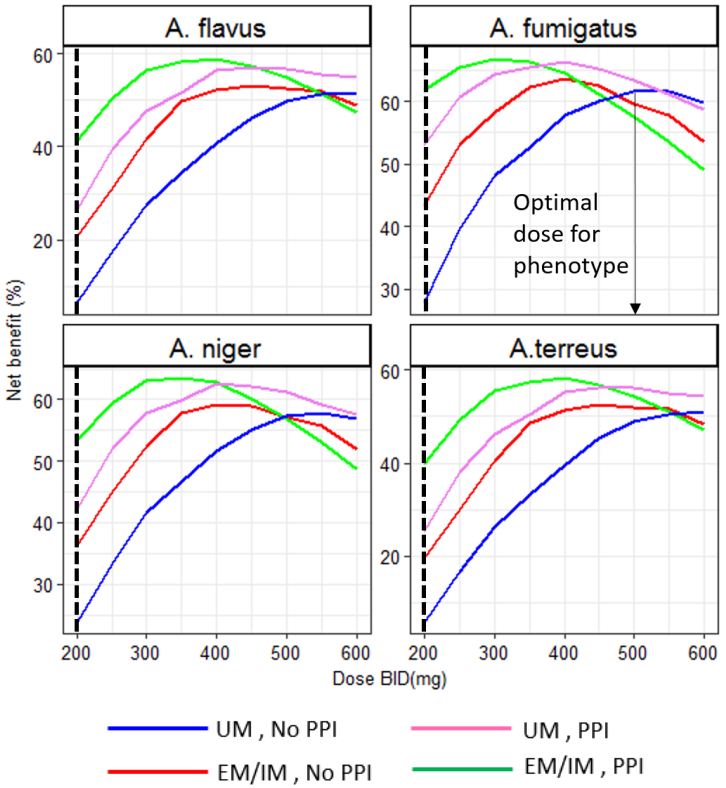
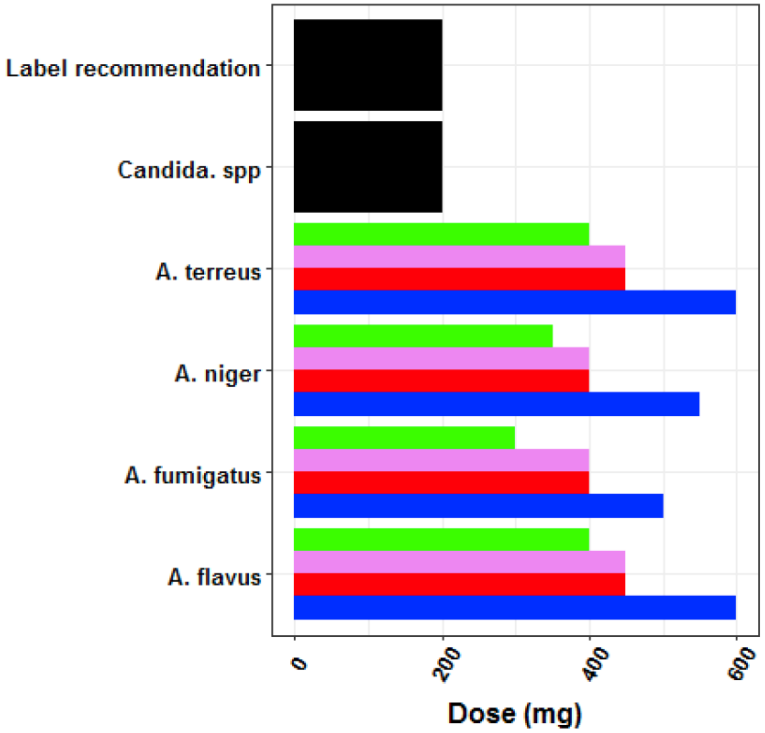
What About Drug-Induced Toxicity?

Dosing Recommendation





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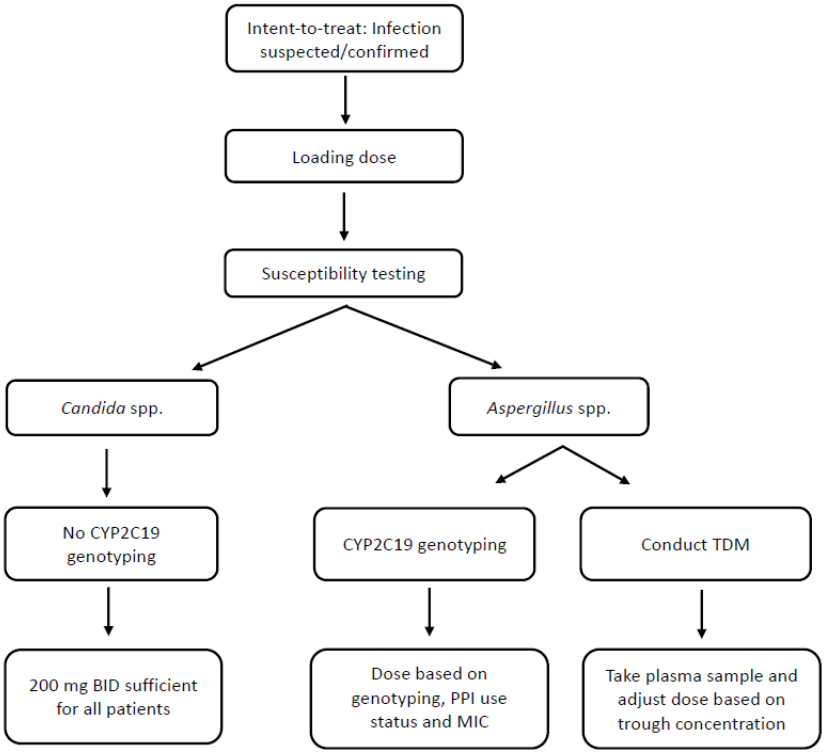
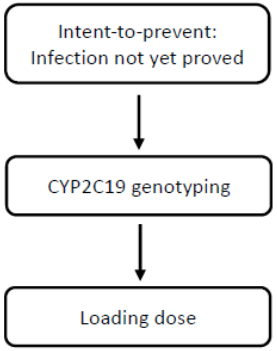
Clinical Opportunity

Intent-to-treat



Intent-to-prevent



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Study Highlights

What is already known?

Voriconazole shows significant **interindividual variability** in clinical response. **TDM** is used to ensure therapeutic concentrations in the clinic.

What this research adds?

- Guide **optimal dosing/treatment selection** for a particular patient based on clinical phenotype and type of infection
- Label-recommended **200mg** voriconazole doses are sufficient for treating ***Candida spp.*** IFIs.
- However, voriconazole doses ranging from **300-600mg** are needed to successfully treat ***Aspergillus spp.*** IFIs, depending on the clinical phenotype of the patient and type of Aspergillus infection.

Mangal et al. Clin Pharmacol Ther. 2018 Jan 9. doi: 10.1002/cpt.1012. [Epub ahead of print]
UL1 TR000064, UL1 TR001427, NIH/NHGRI U01007269.
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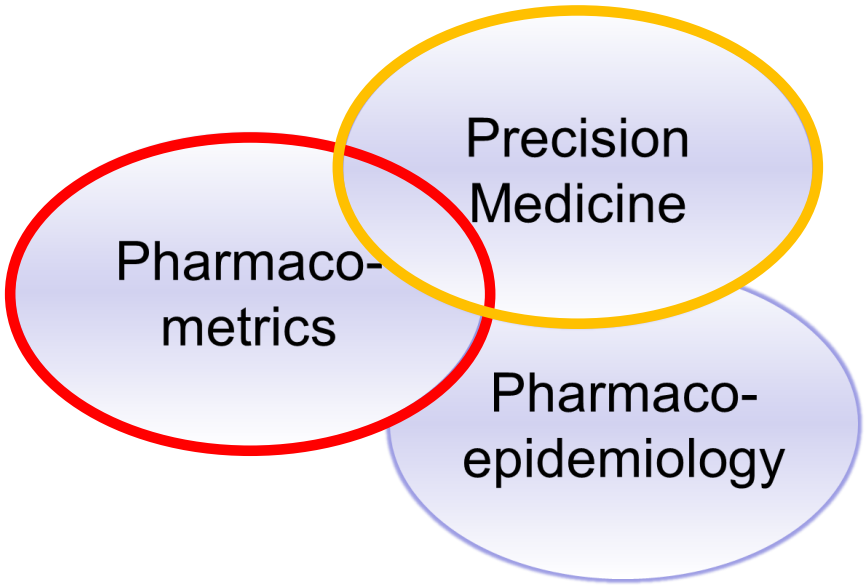

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How Informative Are DDIs of GDIs?

Background:

Regulatory agencies (FDA, EMA, PMDA) expect that clinical pharmacokinetic interactions between an investigational new drug and other drugs should be conducted as part of an adequate assessment of the drug's safety and efficacy.

Cost: ~$1.5M per study

Research Question:

Can DDIs be used to reliably **predict GDIs for CYP2D6, CYP2C9 and CYP2C19** using prototypical victim drugs?

Research Approach:

Determine the overlap in exposure between DDIs and GDIs using: a **Descriptive** and a **PBPK-based** convergence analysis

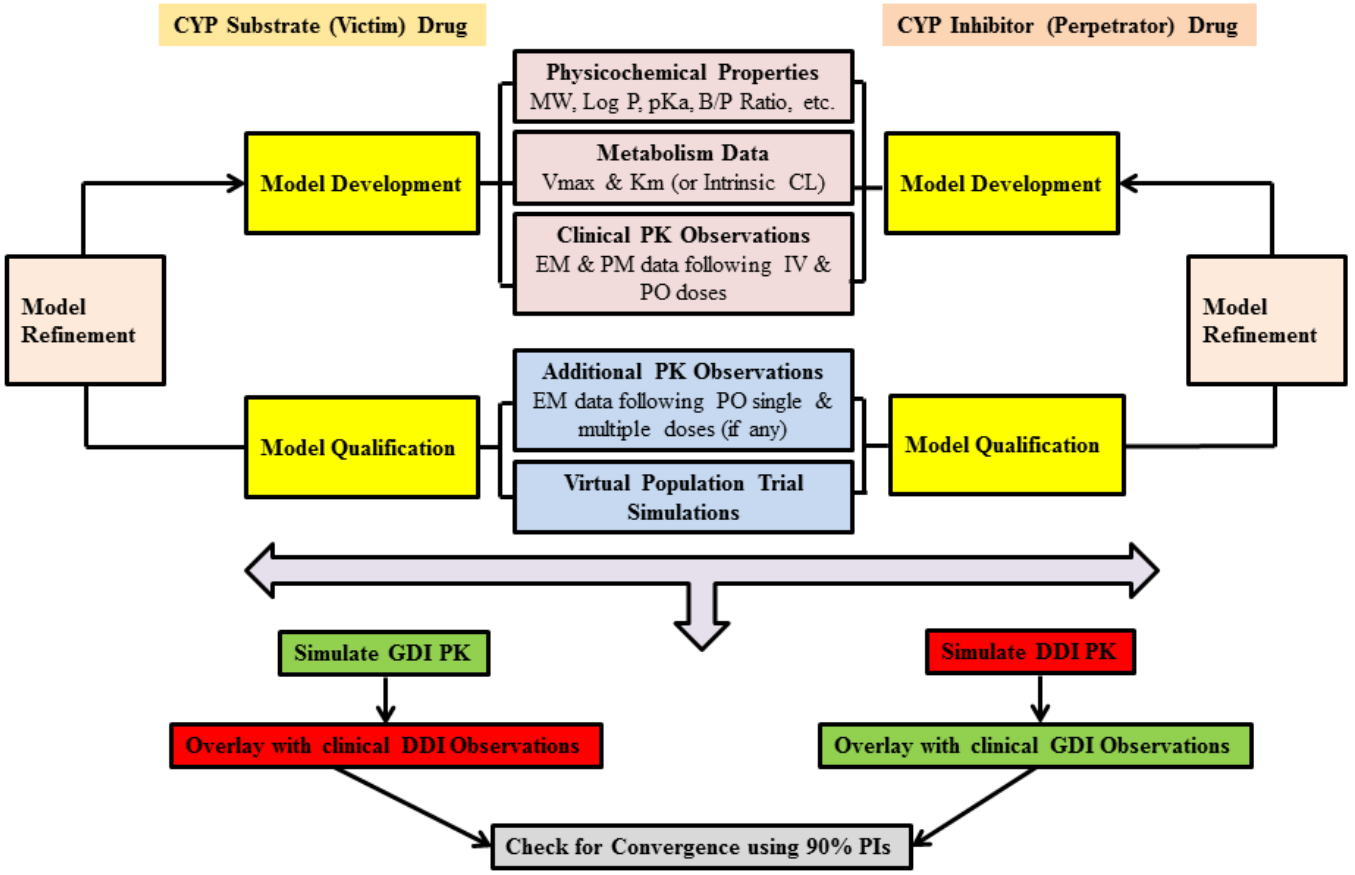
Conrado et al. Pharmacogenomics. 2013 Jan;14(2):215-23.
Lagishetty et al. (2016) J Clin Pharmacol. 2016; 56: 1221-31
Sponsored by FDA's ORISE program
Collaboration with Drs. Lesko (CPSP), Pacanowski (FDA), and Rogers (FDA)

Selection of Enzymes, Substrates & Inhibitors

- ***Polymorphic pathways with clinically different phenotypes:*** ***CYP2D6***, ***CYP2C9***, and ***CYP2C19***
- ***Prototypical substrate drugs*** (preferably f_m > 0.8 via single CYP pathway) for:
  - ***CYP2D6*** *(metoprolol, dextromethorphan, atomoxetine, vortioxetine)*
  - ***CYP2C9*** *(warfarin, flurbiprofen, celecoxib)*
  - ***CYP2C19*** *(omeprazole, clopidogrel)*
- ***Strong inhibitors*** (preferably selective) for single CYP pathways for:
  - ***CYP2D6*** *(paroxetine, fluoxetine, quinidine, buproprion)*
  - ***CYP2C9*** *(fluconazole)*
  - ***CYP2C19*** *(fluconazole, fluoxetine, omeprazole)*
- **PK exposure (AUC)** data was collected from the literature for **poor metabolizers** (PM's) for GDIs and for **strong inhibitor** studies for DDIs
- Substrate **AUC ratios** were calculated in the presence of: *i)* DDIs and *ii)* GDIs using EM's as reference point
- **DDI-GDI convergence** was declared if the computed AUC ratio was within 90% CI (80-125%)

Lagishetty et al. (2016) J Clin Pharmacol. 2016; 56: 1221-31
Sponsored by FDA's ORISE program
Collaboration with Drs. Lesko (CPSP), Pacanowski (FDA), and Rogers (FDA)

PBPK Analysis Workflow



Lagishetty et al. (2016) J Clin Pharmacol. 2016; 56: 1221-31

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Convergence Existed For All Evaluated CYP2D6 Examples

Polymorphic Pathway	*Candidate Drug*	*Statistical DDI-GDI Convergence (Inhibitor Drug)*
CYP2D6	Metoprolol	**Yes** (Paroxetine)
	Dextromethorphan	**Yes** (Quinidine)
	Atomoxetine	**Yes** (Paroxetine & Fluoxetine)
	Vortioxetine	**Yes** (Bupropion)
CYP2C9	Warfarin	**No** (Fluconazole)
	Flurbiprofen	**No** (Fluconazole - ***Low Dose***) **Yes** (Fluconazole - ***High Dose***)
	Celecoxib	**No** (Fluconazole - ***Low Dose***)
CYP2C19	Omeprazole	**No** (Fluconazole)
	Clopidogrel	**Yes** (Omeprazole) **No** (Other proton pump inhibitors – lansoprazole, pantoprazole, dexlansporazole)

Lagishetty et al. (2016) J Clin Pharmacol. 2016; 56: 1221-31

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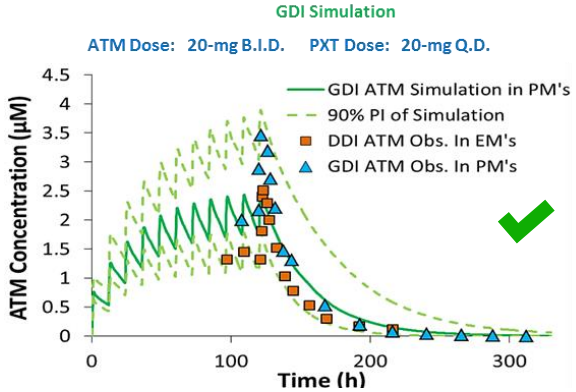
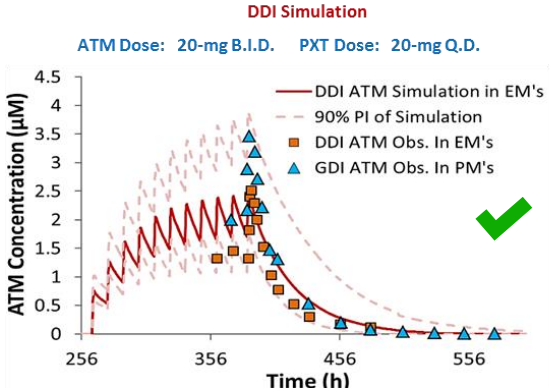
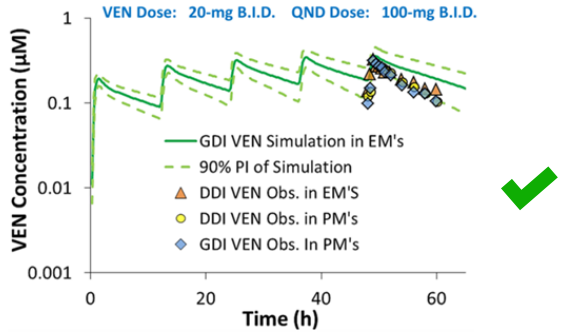
Results Confirmed via PBPK

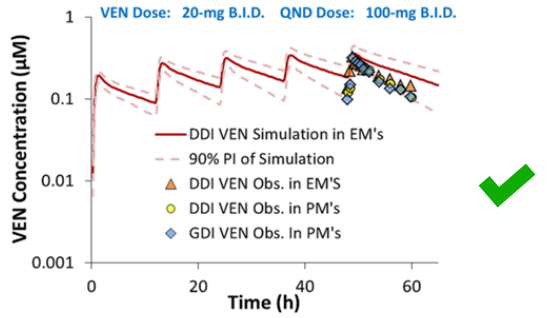
CYP2D6: Atomoxetine



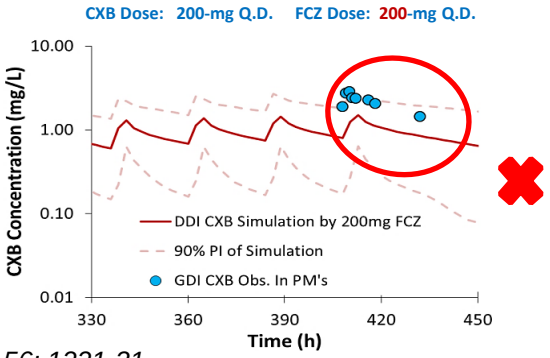


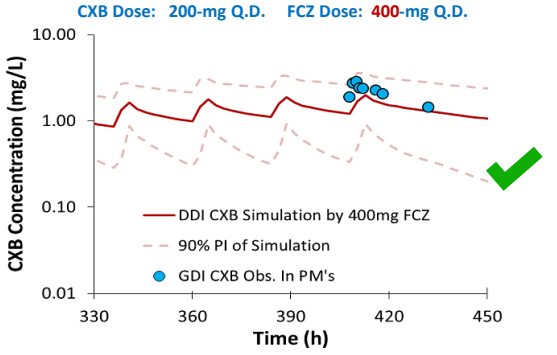
CYP2D6: Venlafaxine





CYP2C9: Celecoxib





Lagishetty et al. (2016) J Clin Pharmacol. 2016; 56: 1221-31

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Study Highlights

What is already known?

Clinical studies of **DDIs** and **GDIs** are **interrelated for polymorphic cytochrome P450 (CYP) enzymes** because both change the intrinsic clearance of an enzyme substrate.

What this research adds?

- DDI studies using strong inhibitors can be used for CYP2D6 substrates to inform respective GDIs.
- The situation is more complex for CYP2C9 and CYP2C19 substrates, where **potency** and **dose** of the **inhibitor** for DDIs as well as **remaining enzyme activity** for loss-of-function allele carriers for **GDIs** need to be considered.
- The approach presents a valuable alternative for: 1) studying **both** DDIs and GDIs **clinically** and 2) **saving time** and development **costs**.

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Regulatory Impact

Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications

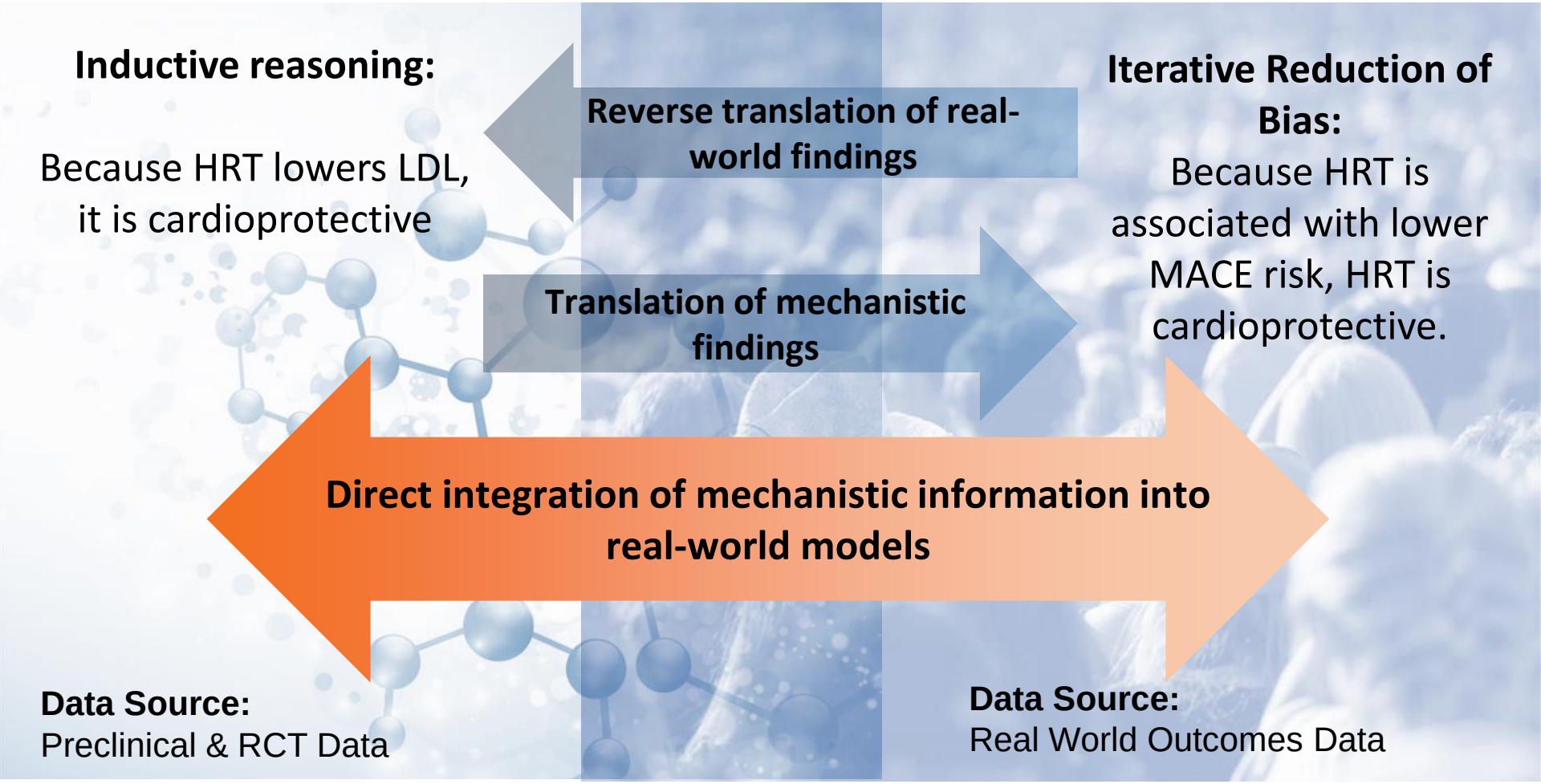
Guidance for Industry

DRAFT GUIDANCE

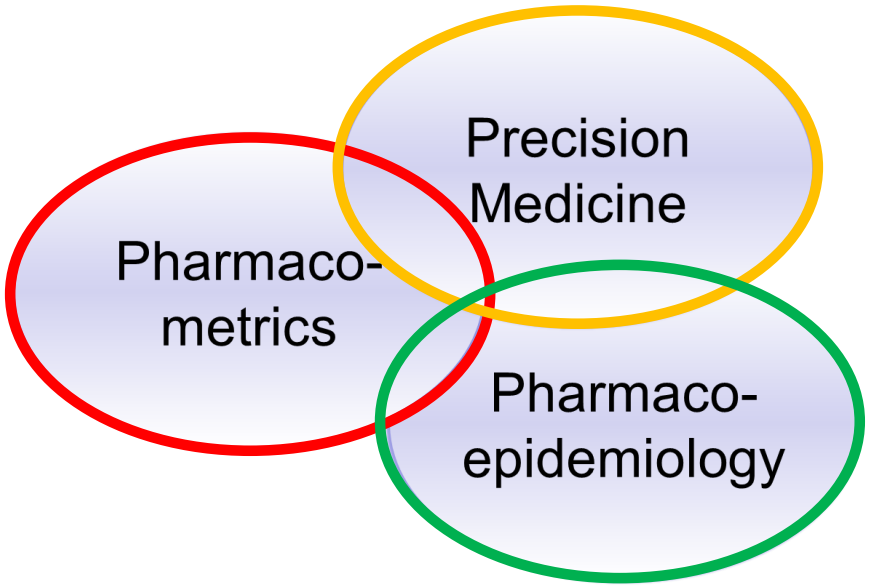
In some instances, a gene-drug interaction study may substitute for a prospective DDI study and vice versa. Suitable substrates for these studies have a high fraction of metabolism ($f_m > 80\%$) by a single CYP enzyme that has loss-of-function alleles.

https://www.fda.gov/downloads/drugs/guidances/ucm292362.pdf

What I Believe Is Next



Creating Synergy



Selected Case Examples:

- Development of a drug-disease-trial model for postmenopausal osteoporosis
- Optimization of voriconazole therapy for the treatment of invasive fungal infections in adults
- How informative are DDIs of GDIs?
- A model- and systems-based approach to efficacy and safety questions related to generic substitution

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

Background:

- **~88%** of prescription drugs filled in the U.S. are **generic**
- **~$1.68 Trillion** of estimated cost savings for U.S. health system between 2005 and 2014
- U.S. FDA occasionally receives complaints about purported adverse events due to lack of efficacy or safety after switching from brand to generic
- Assessment of whether or not these complaints are real can be challenging

Research Strategy:

- 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**

Lesko *et al.* accepted for publication in *J Clin Pharmacol.*, 2017
Basu *et al.* accepted for publication in *J Clin Pharmacol.*, 2017

5U01FD005210 – 04
Collaboration with Drs. Lesko (CPSP), Trame (CPSP), Vozmediano (CPSP), Bihorel (CPSP), Brown (COP-POP), Fang (FDA), Lionberger (FDA)

Analysis Workflow

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

1

Signal Detection

- Formulation problems were reported within the first use of metoprolol XL and were public knowledge within 1-year of launch
- 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
- To provide an active comparison:
  - **Amlodipine/Benazepril** was approved on same date and launched at about the same with **no known formulation issues**

Clinical Event Rates

Rate Ratio Generic vs. Trade (METO)								
		MI	HF	Hypertension	Hypotension	Syncope	Angina	Tachycardia
ER Visits	Primary	2.06	1.31	1.18	1.33	1.43	1.50	1.29
	Secondary	2.42	1.20	1.31	1.22	1.39	1.49	1.21
Hospitalizations	Primary	1.00	1.00	1.08	0.92	0.99	1.22	1.12
	Secondary	1.11	1.08	1.44	1.25	0.95	1.39	1.12
Rate Ratio Generic vs. Trade (AMLO)								
		MI	HF	Hypertension	Hypotension	Syncope	Angina	Tachycardia
ER Visits	Primary	0.86	0.77	0.68	0.84	0.85	1.07	0.91
	Secondary	0.95	0.83	0.82	0.82	0.86	0.95	0.88
Hospitalizations	Primary	0.98	0.78	0.56	1.11	1.03	0.52	0.98
	Secondary	0.95	0.90	0.93	1.02	1.09	0.89	0.93

2

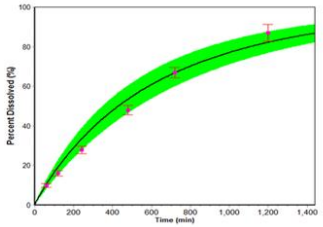
Physiologically-Based Absorption Modeling

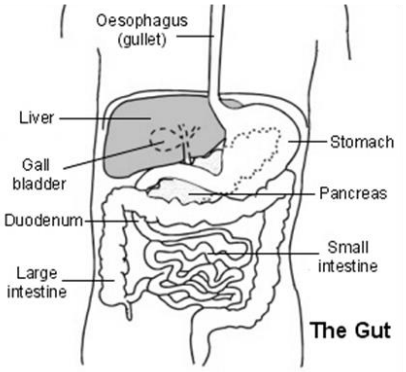
Formulation

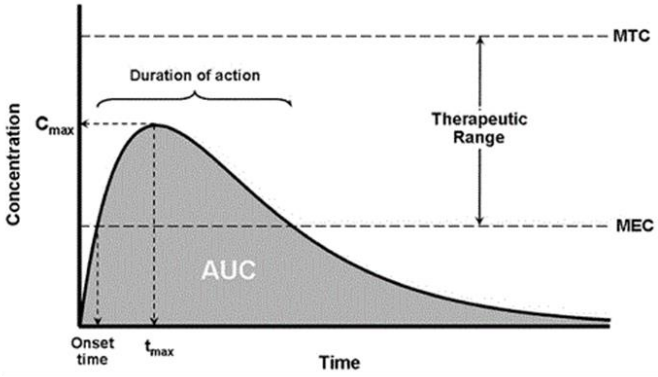
***In vitro* and *in silico* dissolution testing**

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

***In silico* bioequivalence testing**







DDDPlus™

Advanced Compartment and Transit (ACAT) module in GastroPlus™

Lesko *et al.* accepted for publication in *J Clin Pharmacol.*, 2017

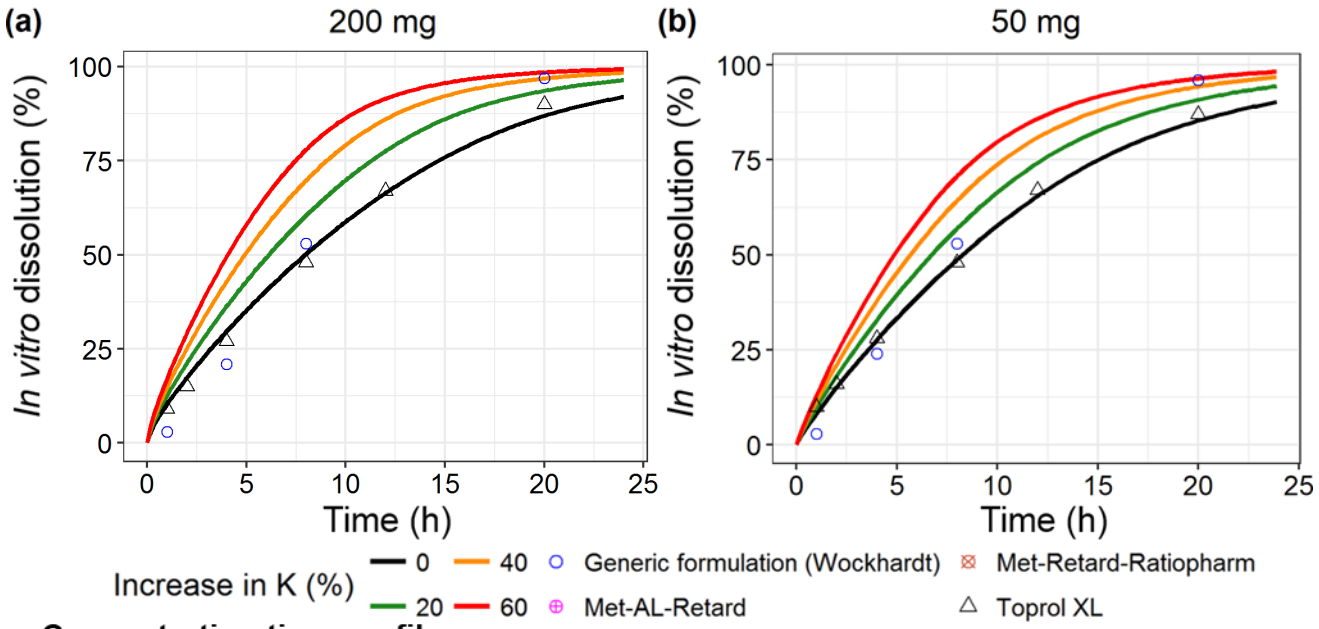
Basu *et al.* accepted for publication in *J Clin Pharmacol.*, 2017

5U01FD005210 – 04

Collaboration with Drs. Lesko (CPSP), Trame (CPSP), Vozmediano (CPSP), Bihorel (CPSP), Brown (COP-POP), Fang (FDA), Lionberger (FDA)

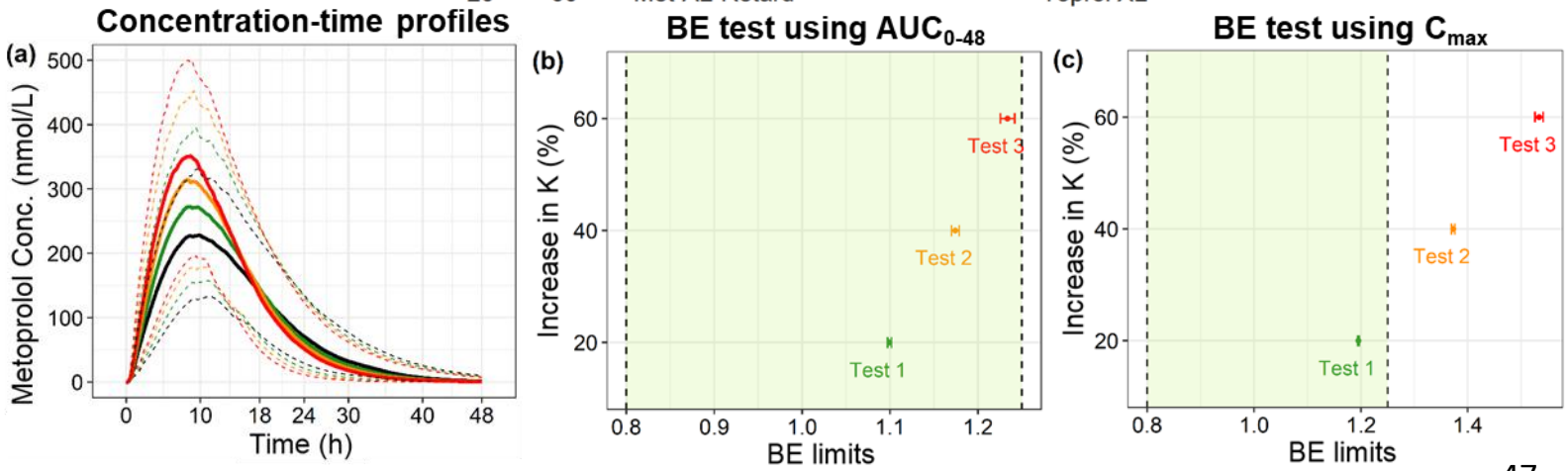
Impact of Formulation Differences on:

In vitro
Dissolution



In vivo
PK

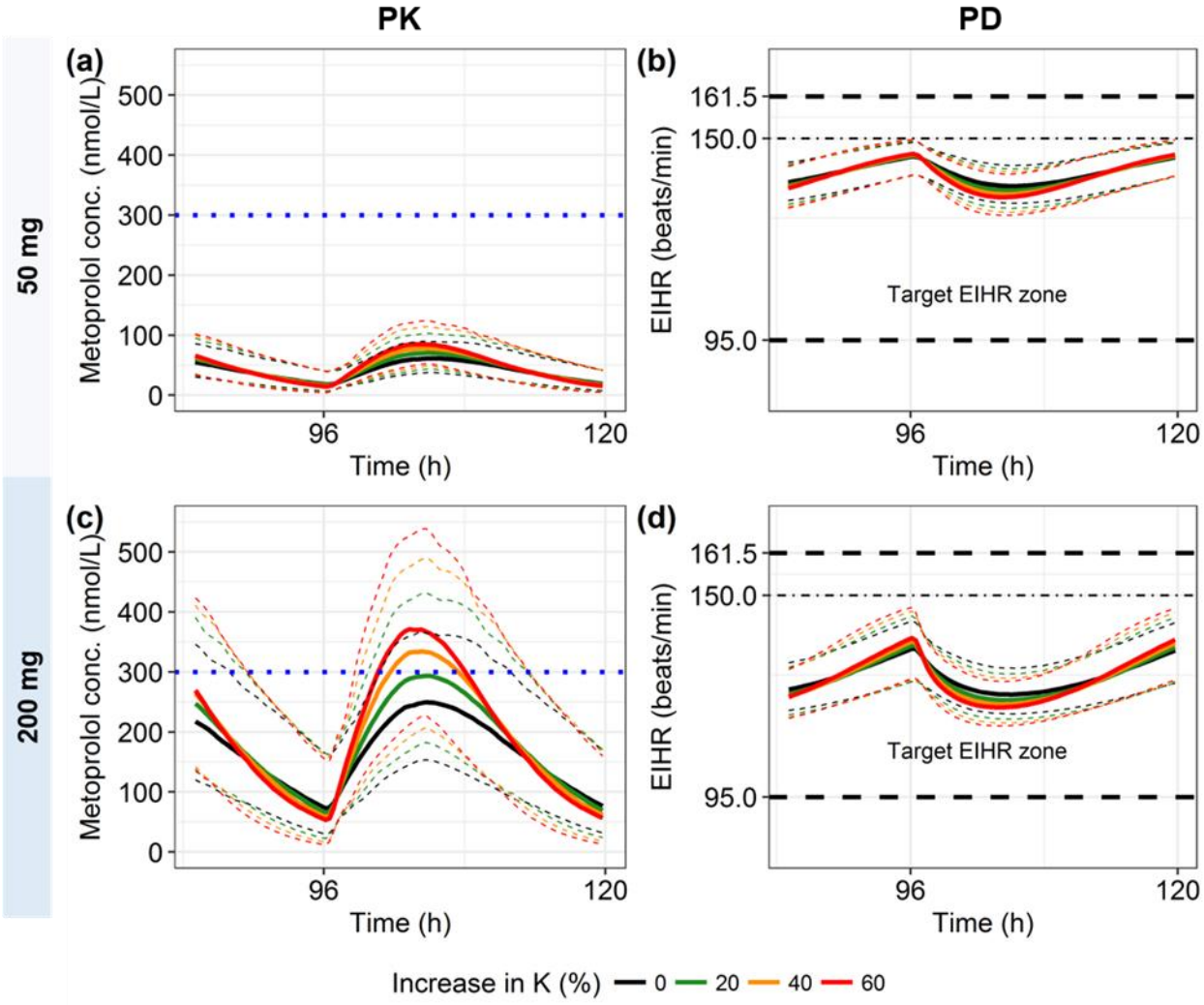
200 mg



Toprol XL: Metoprolol succinate
Met-AL-Retard & Met-Retard-Ratiopharm: Metoprolol tartare

Effect of Drug Release on PD & Therapeutic Equivalence

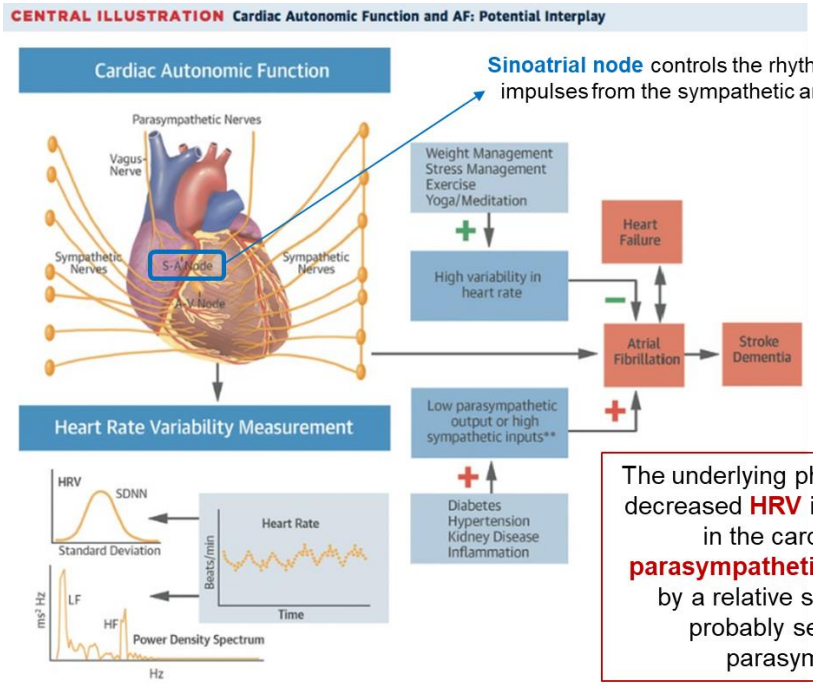
3



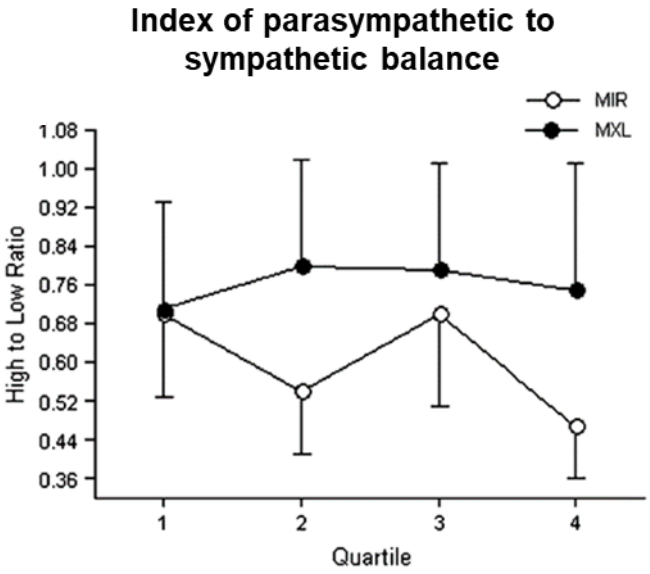
Kim *et al.* manuscript in preparation

Reference for the target EHR zone: https://www.cdc.gov/physicalactivity/basics/measuring/heartrate.htm

Considering Anatomy & Physiology of the Heart



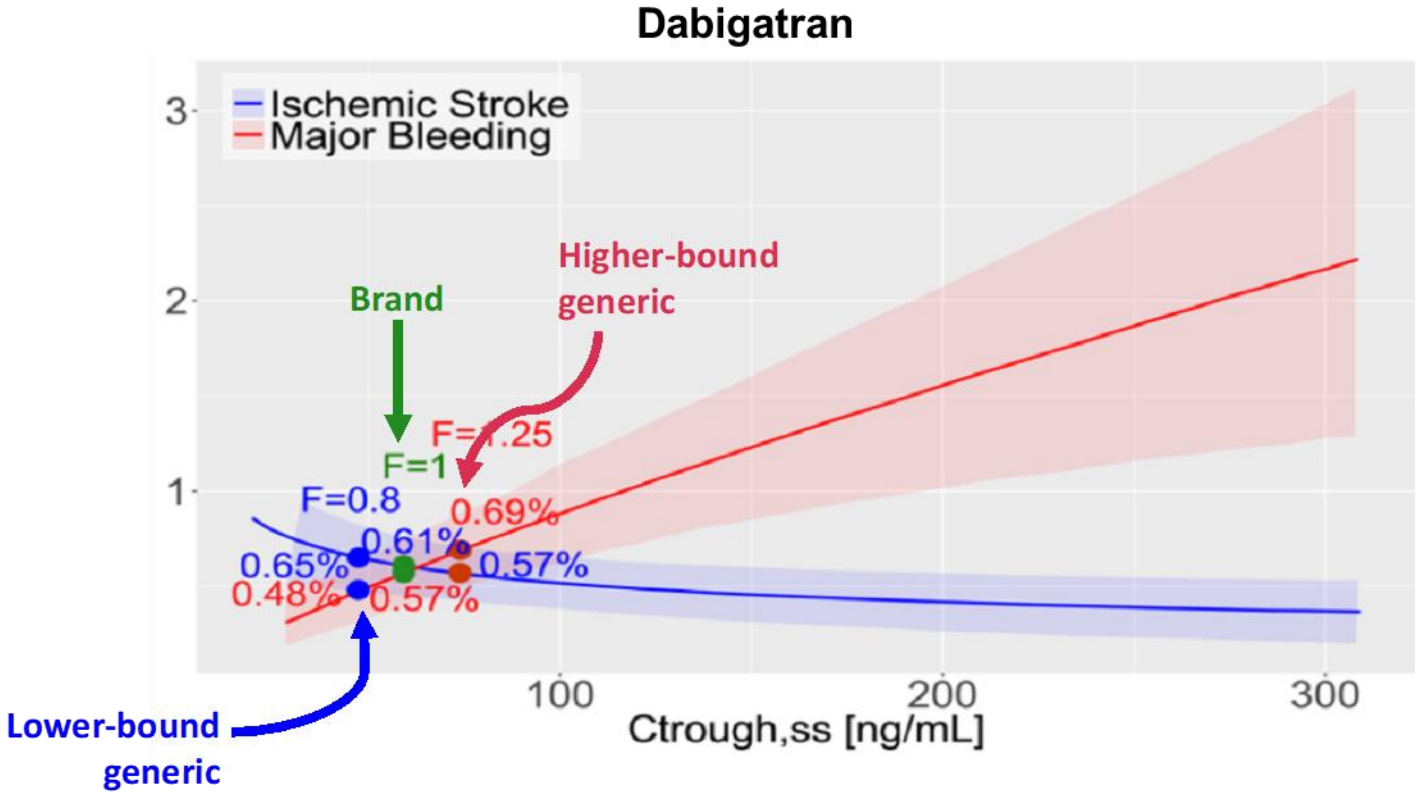
The underlying physiological mechanism of decreased **HRV** is likely to be an alteration in the cardiac **sympathetic–parasympathetic balance**, characterized by a relative sympathetic dominance probably secondary to reduced parasympathetic activity.



Aquilante *et al*, (2006) Journal of Cardiac Failure 12(3): 171-176.

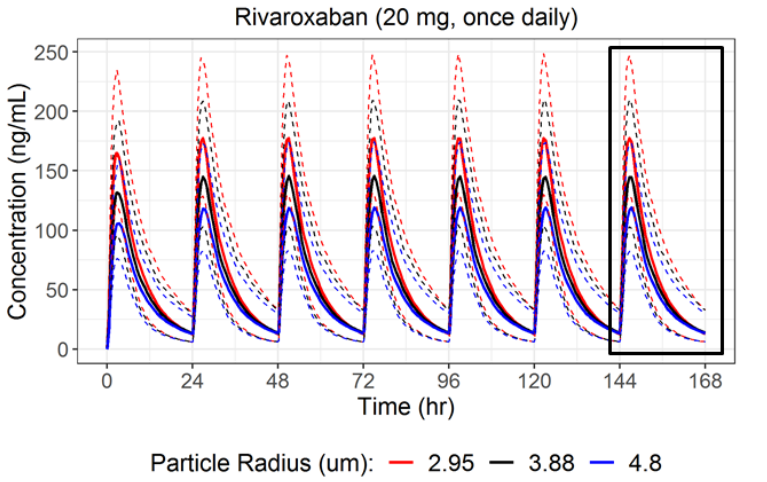
Currently Ongoing: Prospective Method Qualification

Using general BE criteria:



Currently Ongoing: Prospective Method Qualification

Using critical formulation properties:



Solid curve: median
Dashed curves: 5th percentile (lower), and 95th percentile (upper)

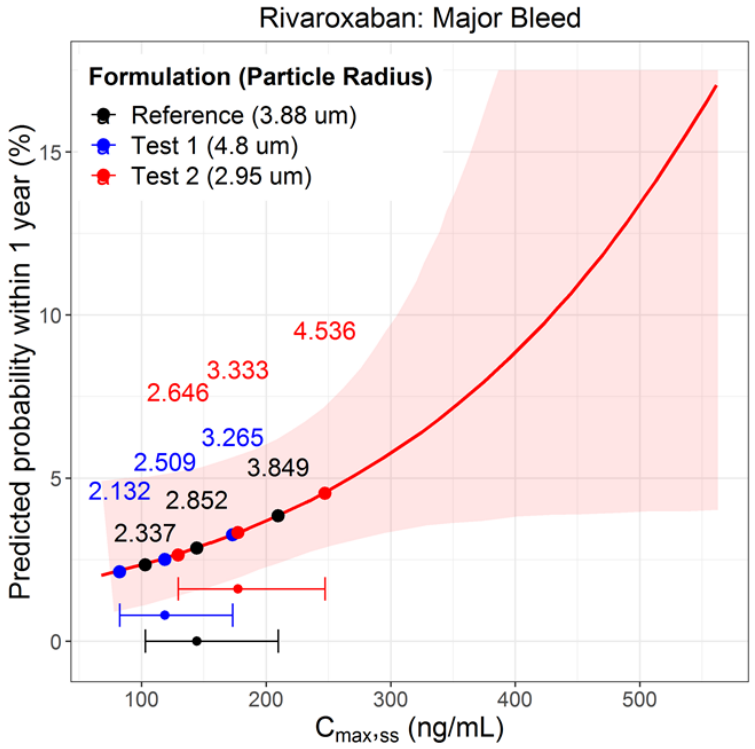


Figure adapted from NDA 22-406.
Solid curve: mean, shaded area: 95% confidence interval, bars on the bottom: 5th to 95th percentiles of rivaroxaban $C_{max,ss}$ by formulation subgroup, and dots on the bars: medians of rivaroxaban $C_{max,ss}$.

Same Concept Applies: Evaluating the Impact of DDIs on the Efficacy and Safety of HCAs

Citation: CPT Pharmacometrics Syst. Pharmacol. (2018) XX, 1–3; doi:10.1002/psp4.12357

COMMENTARY

Establishing a Multidisciplinary Framework to Study Drug-Drug Interactions of Hormonal Contraceptives: An Invitation to Collaborate

Lawrence J. Lesko[1], Valvanera Vozmediano[1], Joshua D. Brown[2], Almut Winterstein[2], Ping Zhao[3], Jörg Lippert[4], Joachim Höchel[5], Ayyappa Chaturvedula[6], Annesha White[6] and Stephan Schmidt[1,*]

Hormonal contraceptive agents (HCAs) are widely used throughout the world, and women taking HCAs are likely to take other medications. However, little is known about the clinical effect of most drug-drug interactions (DDIs) associated with HCAs. A team of interdisciplinary outcomes and pharmacometric researchers from academia and industry jointly engage in a research project to (i) quantitatively elucidate DDI impacts on unintended pregnancies and breakthrough bleeding, and (ii) establish a DDI-prediction framework to inform optimal use of HCAs.

CPT Pharmacometrics Syst. Pharmacol. (2018) 0, 1–3; doi:10.1002/psp4.12357; published online xx xxx xxxx.

It's a Team Effort – So, Thank You!

UF Colleagues

- ✓ Lawrence J Lesko
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- ✓ Almut Winterstein
- ✓ Josh Brown
- ✓ Mirjam N Trame
- ✓ Valvanera Vozmediano
- ✓ Sarah Kim
- ✓ Rodrigo Cristofoletti
- ✓ Julie Johnson
- ✓ Chakradhar Lagishetty (GSK)
- ✓ Kumpal Madrasi (Applied Biomath)
- ✓ Sumit Basu (Merck)
- ✓ Haitao Yang (FDA)
- ✓ Vishnu Dutt Sharma (EMD Serono)
- ✓ Nashid Farhan
- ✓ Snehal Samant (FDA)
- ✓ Jiexin Deng (Pfizer)
- ✓ Naveen Mangal (EMD Serono)
- ✓ Sibo Jiang
- ✓ Yi-Ting Lien
- ✓ Karthik Lingineni
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- ✓ Fang Li, Ph.D.
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- ✓ Theresa Kehoe, M.D

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