

Population-Based Pharmacokinetic Modelling and Simulation.

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Have you designed your clinical PK studies with adequate power?

What we do

The Simcyp Population-based ADME Simulator

Simcyp provides a platform for modelling and simulation of drug absorption, distribution, metabolism and excretion (ADME) in virtual populations. The Simulator is licensed to our Consortium member clients for use in drug discovery and development.

Currently, 9 of the top 10 pharmaceutical companies worldwide have access to Simcyp expertise through Consortium membership. The Consortium helps guide scientific development at Simcyp, ensuring that our products continue to meet, and exceed, industry needs.

Simcyp maintains strong academic links and our science team conducts internationally recognised cutting-edge research and development. We also offer consultancy services and run education programmes around the world.

[see more](#)

Latest News



Workshops



New study investigates covariates influencing the amount of human microsomal protein per gram of liver

03 Nov 2008

[more](#)

Medical Products Agency, Sweden, renews Simcyp licenses

30 Oct 2008

Simcyp confirms additional speaker for Tokyo seminar day

29 Oct 2008

Wyeth joins the Simcyp Consortium

23 Oct 2008

[all news](#)

Consortium members and associates include:



Commercial Organisations:

Amgen	F Hoffmann-La Roche	Novartis	Sanofi-Aventis
AstraZeneca	GlaxoSmithKline	Novo Nordisk	Servier
Biovitrum	Lundbeck	Nycomed(Altana)	Takeda
Daiichi-Sankyo	Neurocrine	Pfizer	UCB

Regulatory/Governmental Organisations:

MPA - Medical Product Agency (Sweden)

NAM - National Agency for Medicines (Finland)

ECVAM - EU Centre for Validation of Alternative Methods (Italy)

FDA (USA) [negotiations in final stages for renewal of their License]

MEB - Medicines Evaluation Board (Holland) [under negotiations]

etc.

Universities:

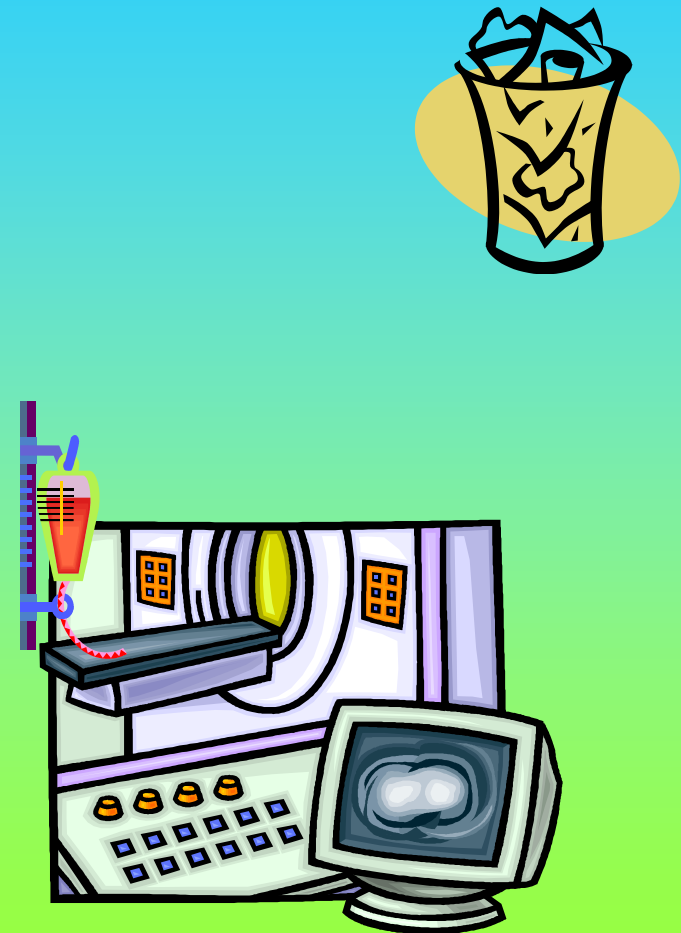
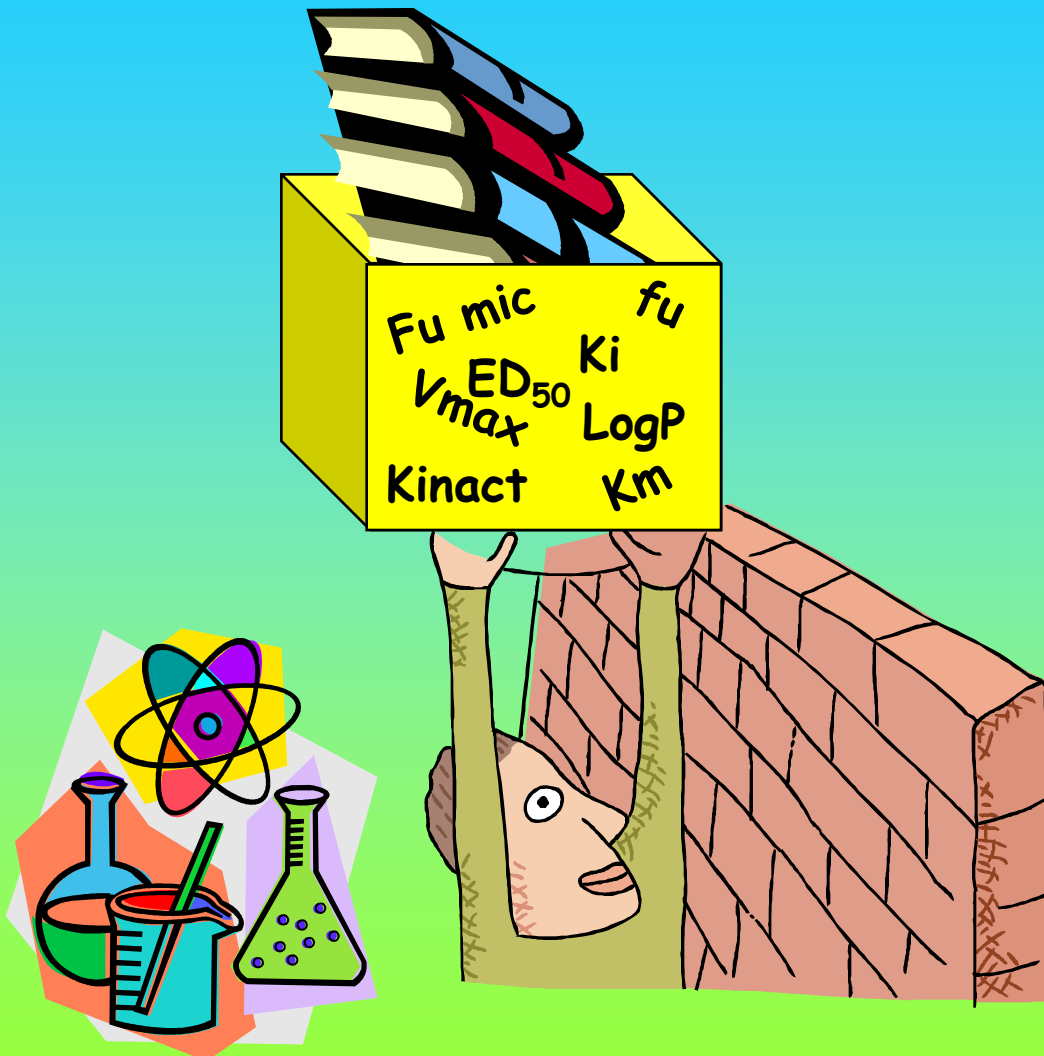
e.g. Manchester (UK); Uppsala (Sweden); Aberdeen (UK); Lisbon (Portugal); Showa (Japan); Buffalo (USA); Göteborg (Sweden); China Pharmaceutical (China); Missouri (USA); Méditerranée (France), Groningen (Holland), Malta University,

Primary aims included:

- Integrate new science in IVIVE area into the regulatory process of assessing mDDI
- Focus on “toolkit” development rather than being product-specific
- Provide opportunity to work in a consortia involving industry, academia, and government agencies

PRE-CLINICAL

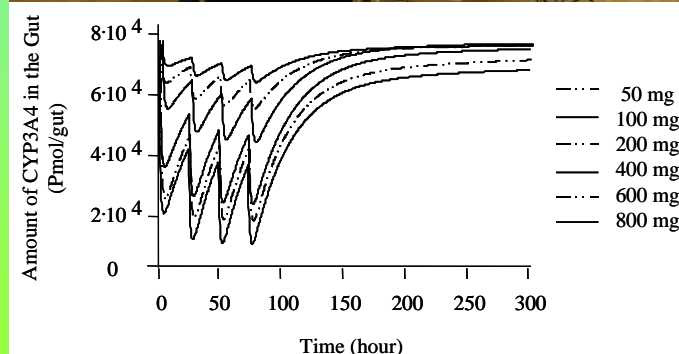
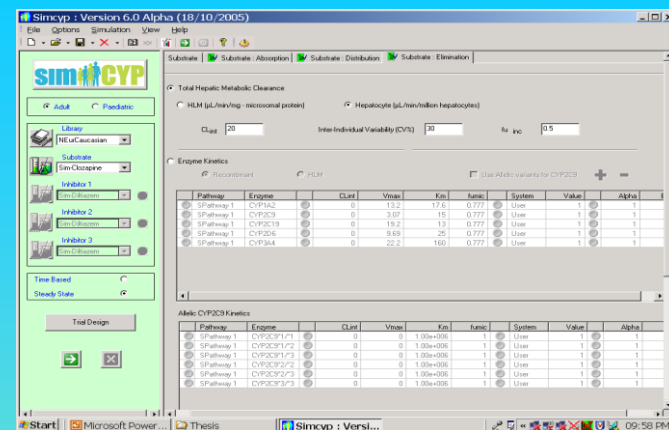
CLINICAL



Continual Development and Update of a User Friendly, Comprehensive, Mechanistic Platform for Integration of ADME Models & Databases
(simulation of candidate drugs in virtual populations)

Regular Worldwide Workshops and Seminars on PK & IVIVE for Key Players on the Drug Development Scene
(e.g. scientists in regulatory agencies and different sections of industry - as internal or open meeting)

Gathering Advice / Reaching Consensus on Common IVIVE & ADME Issues / Identifying Areas of Further Research
(defining common or specific projects in the form of focus groups)



Activities: Hands-On IVIVE Workshops (2005 - 2006)

A unique hands-on experience, illustrated with **practical examples** of *in vitro* - *in vivo* extrapolation (IVIVE), & designed for those who are interested in optimal use of *in vitro* data to improve the design and the outcome clinical studies in drug development.



Nashville



A unique hands-on workshop, illustrated with practical examples of *in vitro* - *in vivo* extrapolation (IVIVE), & designed for those who are interested in optimal use of *in vitro* data to improve the design and the outcome clinical studies in drug development.

Register before February 27th & SAVE 33%

HANDS-ON WORKSHOP ON "APPLICATIONS" (11th & 12th APRIL 2006)

Hands-on Course in Population based In Vitro Extrapolation

2 Day Course

Professo

Gaylord O Nashf 5th & 6th N

EXPIRED

Philadelphia

HANDS-ON WORKSHOPS ON "CONCEPTS" (MAY 30th & 31st 2006) & "APPLICATIONS" (2nd JUNE 2006)

EXPIRED

HANDS-ON WORKSHOPS ON "CONCEPTS" (JULY 25th & 26th 2006) & "APPLICATIONS" (28th JULY 2006)

EXPIRED

Sheffield

The 7th Simcyp Consortium Meeting
Wednesday 4th & Thursday 5th October 2006



The Sheffield Marriott Hotel
Kenwood Road, Sheffield S7 1NQ, UK



Evening welcome reception on Tuesday 3rd October at Chatsworth House

Pre- and Post-Consortium Hands-On Courses:
(I) Concepts and (II) Applications of Physiologically Based Pharmacokinetics and In Vitro In Vivo Extrapolation of ADME Properties

(see inside for further details)

Participating companies include:

- Alana Pharma
- Amgen
- AstraZeneca
- Biovitrum
- Daiichi Sankyo
- GSK
- Hoffmann-La Roche
- Neurocrine
- Novartis
- NovoNordisk A/S
- Pfizer Inc
- Sanofi-aventis
- Servier
- Takeda



Hands-on
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Dr Ami
Dr Karen
Dr Mas
Dr Jian
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Hands-on IV

A 2 Day Comp

Professo

Gaylord O

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Preceding the "AAPS 2005

Nov

More workshops will be l

For more information on the [linkinse](#)

Tokyo

Professor Geoff Tucker, B. Pharm, PhD, FRCA, F1 of Sheffield, & chairman of Simcyp Limited

Professor Hitoshi Sato, Department of Pharmacy, Dr Anin Rostami, Reader in Clinical Pharmacology

Dr Shin-ichi Inoue, Associate Chief Researcher, Dns Sankyo Co., Ltd, Japan

Steve Marciniak, Systems Analyst, Simcyp Limited,

Dr Karen Rowland-Yee, Senior Scientific Manager, I

Dr Yuko Tsukamoto, Assistant Manager, Drug Meta

Dr Masayuki Yamaguchi, Assistant Manager, Expert Global Bridging Department, Daiichi Pharmaceutical C

Professor Geoff Tucker (Sheff Sheffield, UK)
Prediction of drug clearance and metabolic drug-drug

Dr Bob Ings (Vice President, Roche, Palo Alto)
New era for drug development: Implications of be routinely measured in vivo data into the pipeline

Dr Jenny Chan (Principal Research Scientist, Eli Lilly, In Situ-dependent and question-driven simulations: c

Professor Mary Payne (Chapel Hill, North Carolina)
Assessment of inter-individual variability in gut wall & first-pass effect and associated MDD

Dr Wei Tang (Director of DMPP, Merck Research Lab, B
Dealing with differences in ICYP systems when pre

Dr Heidi J. Einolf (Senior Fellow, DMPP, Novartis Pharm
Predicting in vivo metabolic drug interactions from in v

Dr Karthik Venkatasubramanian (Associate Director, Cl
In vitro-in vivo extrapolation of CYP mechanism-based

Dennis Smith (Vice-President of Pharmacokinetics, Dynamics and Metabolism at Pfizer Global Research & Development, Sandwich, UK)
New Roles for M&S in Drug Development

Thierry Lavoie (Head of Pharmacokinetic Modelling and Simulation, Hoffmann-La Roche Ltd, Switzerland)
M&S as a Vehicle for Data Integration

Hans Lennernäs (Professor in Biopharmaceutics, Uppsala University, Sweden)
Requirements for M&S of Absorption from GI Tract

Panos Moschonas (Professor in Biopharmaceutics & Pharmacokinetics, University of Athens, Greece)
M&S of Absorption from GI in the Case of Solid Dosage For

Olavi Pelkonen (Professor of Pharmacology, Oulu University Finland)
Requirements for M&S of Hepatic Clearance

Basel

Baltimore - April



A Simcyp Sponsored Seminar
Wednesday 4th April 2007

Register before
February 15th &
SAVE 33%/

ADME in Drug Development: Bridging DM-PK-PD Using Modelling and Simulation

Register free as part of attendance at our

**Hands-on Workshops on "Concepts" and "Applications" of
Population based *In Vitro* - *In Vivo* Extrapolation of ADME Properties**

VISIT: www.simcyp.com for details

2nd - 3rd April 2007
Concepts Workshop

5th - 6th April 2007
Applications Workshop

Baltimore Marriott Waterfront Hotel, Baltimore, USA

The workshops will centre around practical examples demonstrating how data generated during drug discovery and pre-clinical drug development can be used to predict:

- Metabolic drug clearance (CL)
- Metabolic drug-drug interactions (DDIs)
- Gut first-pass metabolism
- Oral drug absorption including the effect of efflux transporters
- Drug distribution to different organs
- Plasma drug concentration-time profiles
- Metabolic CL and DDIs in specific populations (*pediatric, ethnic groups, disease groups*)

The main emphasis will be on assessing population variability and optimizing the design of clinical studies within the framework of whole body physiologically-based pharmacokinetics (WB PBPK).

Speakers in the Seminar include:

David J Greenblatt, Professor & Chairman,
Dept. of Pharmacology & Experimental
Therapeutics, Tufts University

Micaela Reddy, Research Scientist, Roche,
Palo Alto

Amin Rostami, Reader in Clinical
Pharmacology and Drug Metabolism, Univ
Sheffield and Director of Scientific R&D,
Simcyp Limited

Ed LeCluyse, Chief Scientific Officer,
Celzdirect

David Plowchalk, Associate Research
Fellow, Pfizer, Groton

Steve Toon, Executive Director, Simcyp
Limited, Sheffield

Sean Ekins, Senior Vice President, Arnold
Consulting Technologies LL

Alex Avdeef, Co-founder and President,
pION INC., Woburn

Joseph Polli, Section Manager, DMPK,
GlaxoSmithKline, RTP

Rajesh Krishna, Head, Quantitative Clinical
Pharmacology, Merck, Rahway



Prague - May



A Simcyp Sponsored Seminar
Wednesday 16th May 2007

Register before
14th March 2007
SAVE 33%/

ADME in Drug Development: Bridging DM-PK-PD Using Modelling and Simulation

Register free as part of attendance at our

**Hands-on Workshops on "Concepts" and "Applications" of
Population based *In Vitro* - *In Vivo* Extrapolation of ADME Properties**

www.simcyp.com

14th - 15th May 2007
Concepts Workshop

17th - 18th May 2007
Applications Workshop

Courtyard Marriott, Prague, Czech Republic

The workshops will centre around practical examples demonstrating how data generated during drug discovery and pre-clinical drug development can be used to predict:

- Metabolic drug clearance (CL)
- Metabolic drug-drug interactions (DDIs)
- Gut first-pass metabolism
- Oral drug absorption including the effect of efflux transporters
- Drug distribution to different organs
- Plasma drug concentration-time profiles
- Metabolic CL and DDIs in specific populations (*pediatric, ethnic groups, disease groups*)

The main emphasis will be on assessing population variability and optimizing the design of clinical studies within the framework of whole body physiologically-based pharmacokinetics (WB PBPK).

Speakers in the Seminar include:

Geoff Tucker, Professor and Head, Unit of Clinical
Pharmacology, University of Sheffield

Gabriele Cruciani, Professor, Laboratory for
Chromometrics and Cheminformatics, University
of Perugia

Ken Korzekwa, Director, Preclinical Drug
Metabolism, DMPK, Merck, West Point

Steven Clarke, Director, Pre-clinical Development
DMPK, GlaxoSmithKline, The Frythe

Richard J. Weaver, Head of Drug Metabolism,
Division of DMPK, Servier R&D

Piet H. van der Graaf, Head of Preclinical PK
and PKPD, Pfizer Global Research &
Development

Phill Jeffery, Head of Drug Metabolism and
Pharmacokinetics, GlaxoSmithKline, Harlow

Leon Aarons, Professor, Pharmacokinetics
Group, University of Manchester

Heyo Kroemer, Professor, Ernst Moritz
Arndt Universität Greifswald

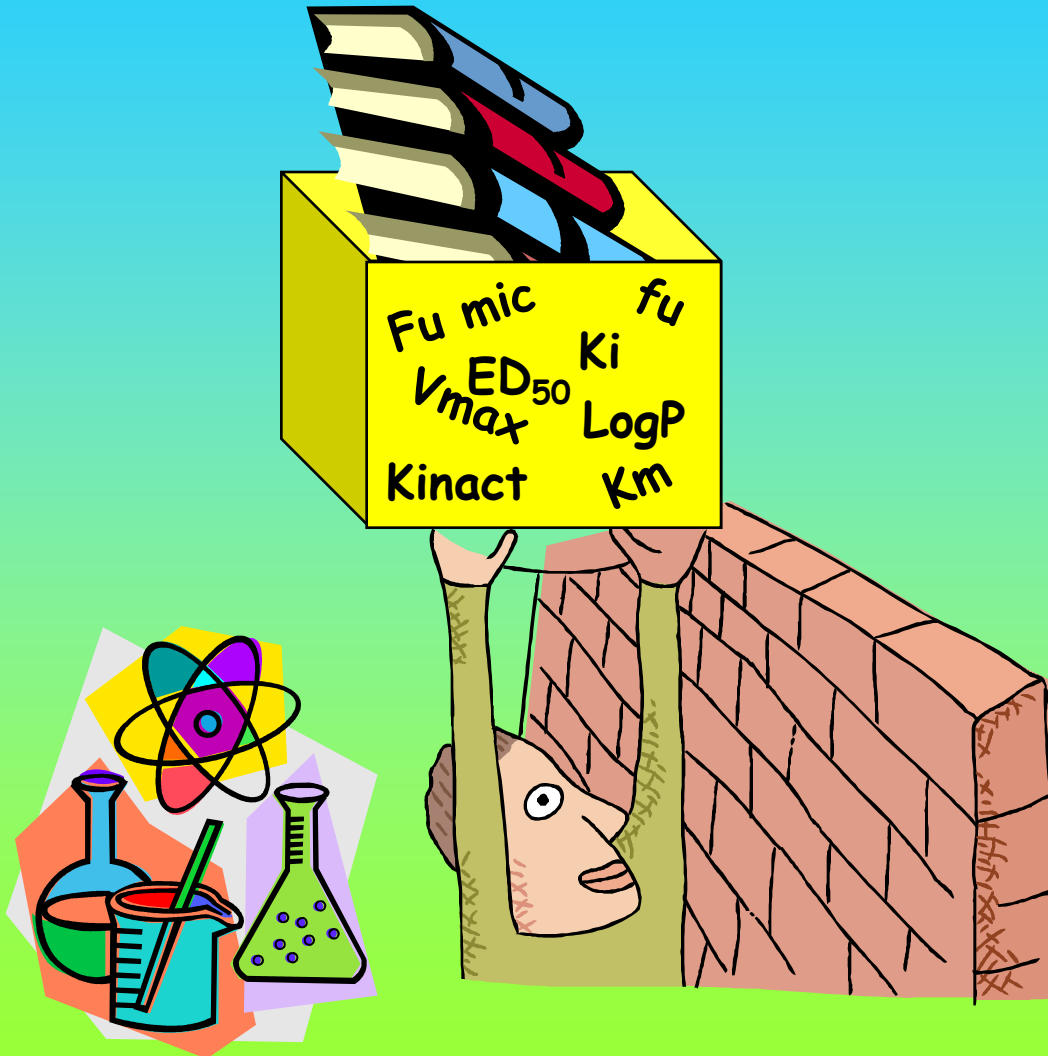
Gery Groothuis, Professor, University of
Groningen



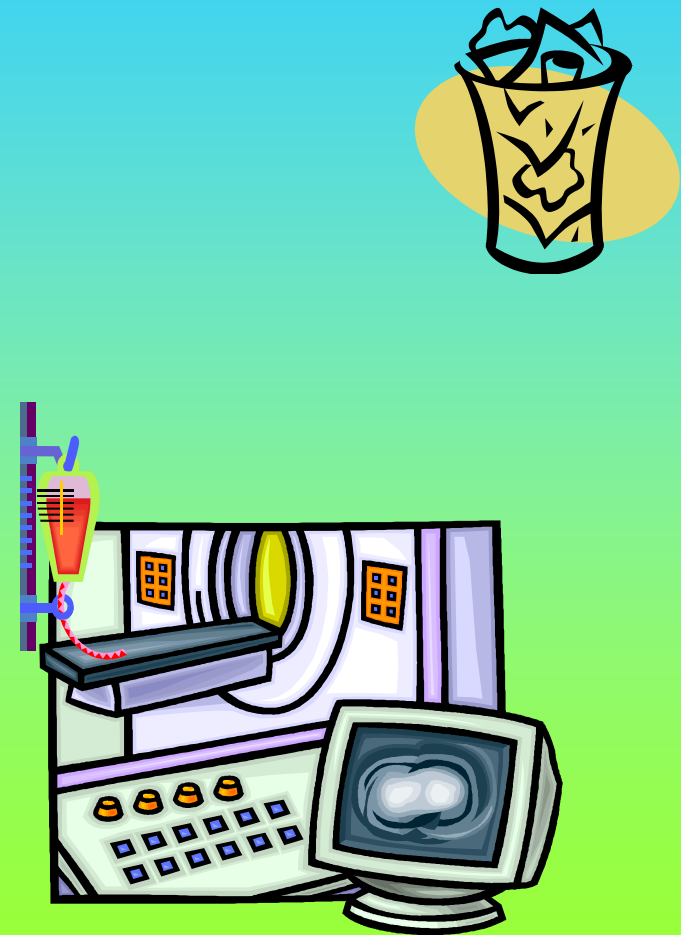
- Introduction to Simcyp IVIVE Course
- IVIVE - Prediction of Clearance & Issues related to Quality Assurance
- Hands on Workshop - Prediction of Clearance

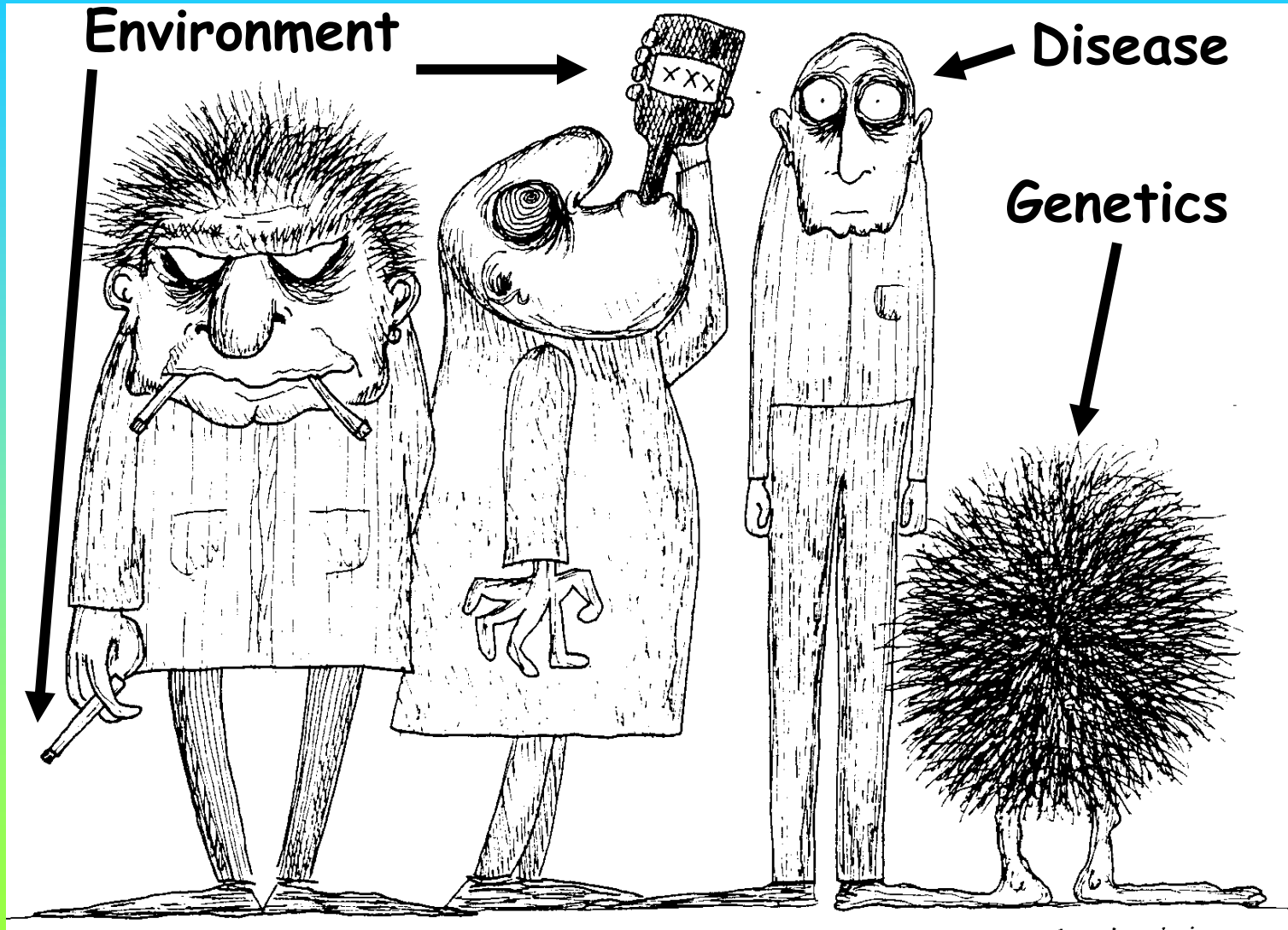
- IVIVE - Prediction of Gut First-Pass
- Hands on Workshop - Gut First-Pass
- IVIVE - Incorporating Biological Variability
- Hands on Workshop - Incorporating Interindividual Variability
- IVIVE - Prediction of Age & Ethnicity Related Changes
- Hands on Workshop - Predicting Clearance in Neonates & Japanese
- IVIVE - Prediction of Metabolic Drug-Drug Interactions
- Hands on Workshop - Metabolic Drug-Drug Interactions
- Liver Models & the Case for Sensitivity Analysis
- Hands on Workshop- Sensitivity Analysis

PRE-CLINICAL

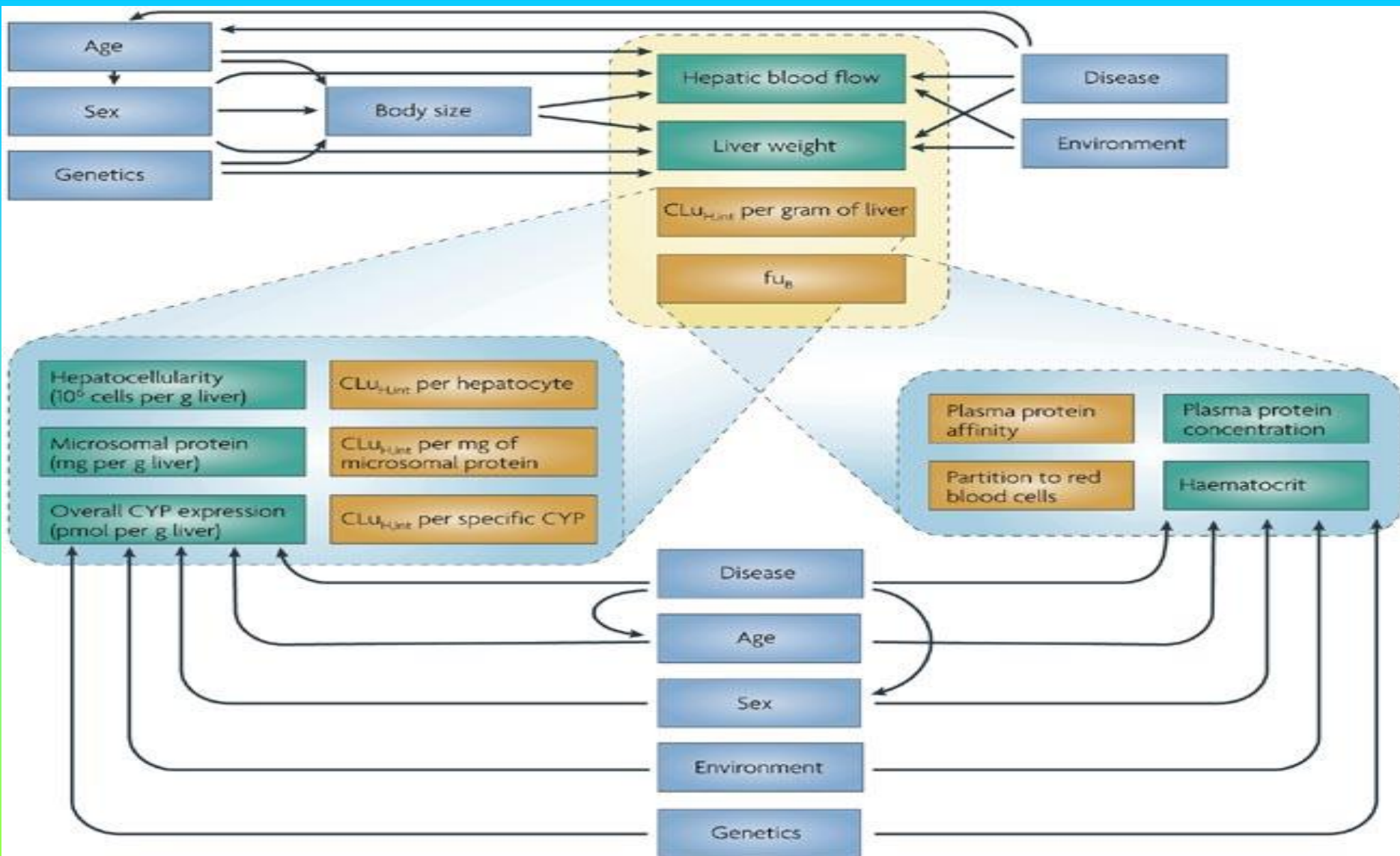


CLINICAL



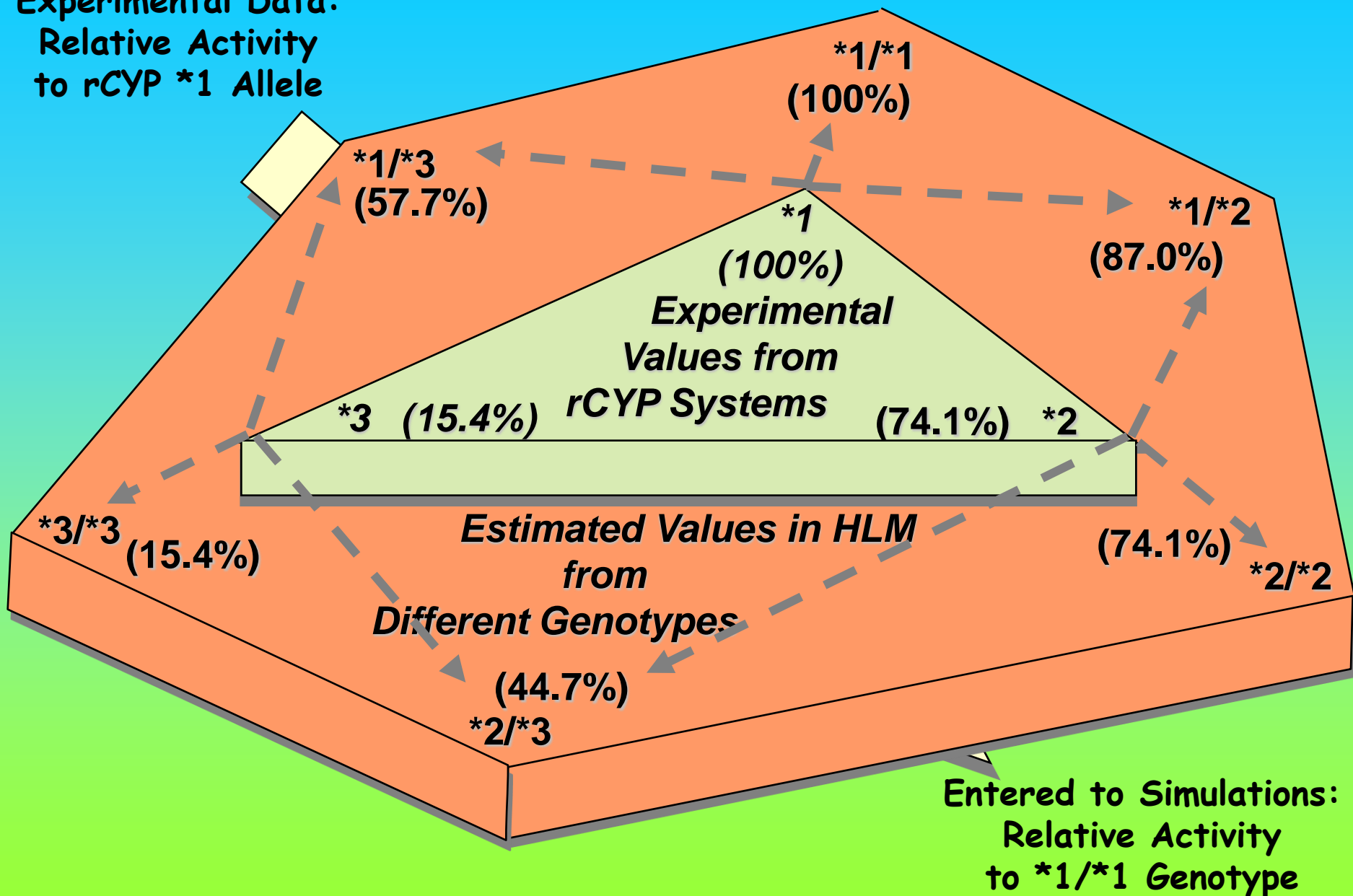


The Complexity of Covariate Effects

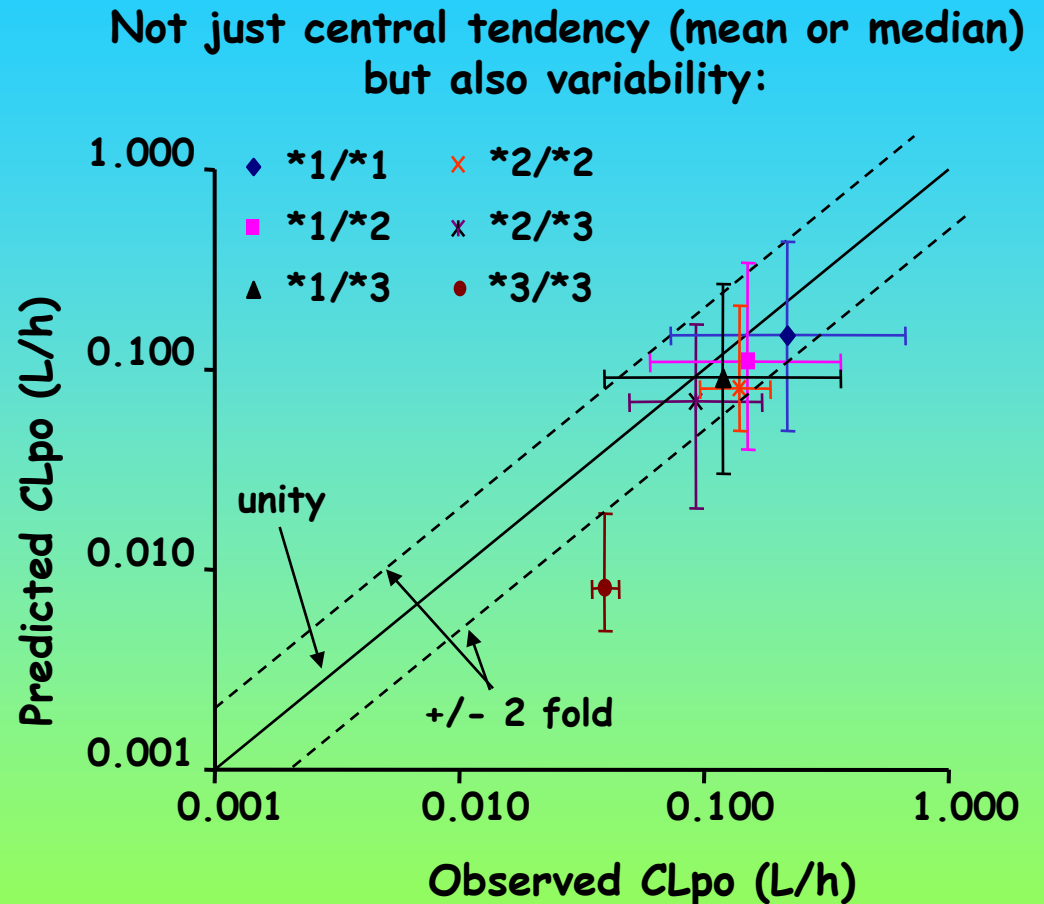
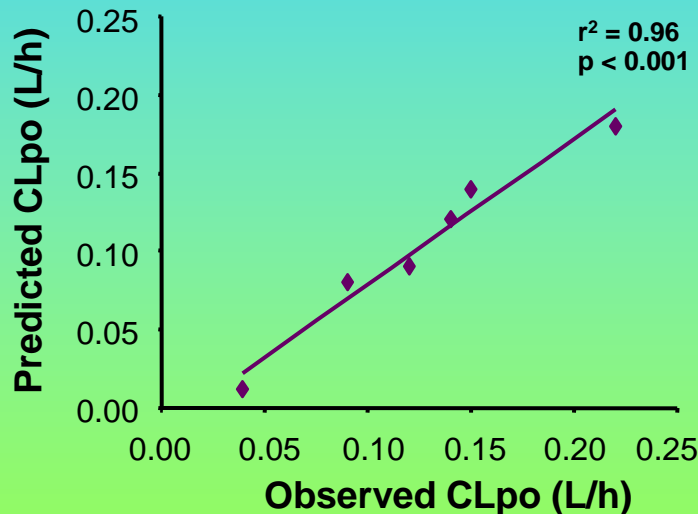
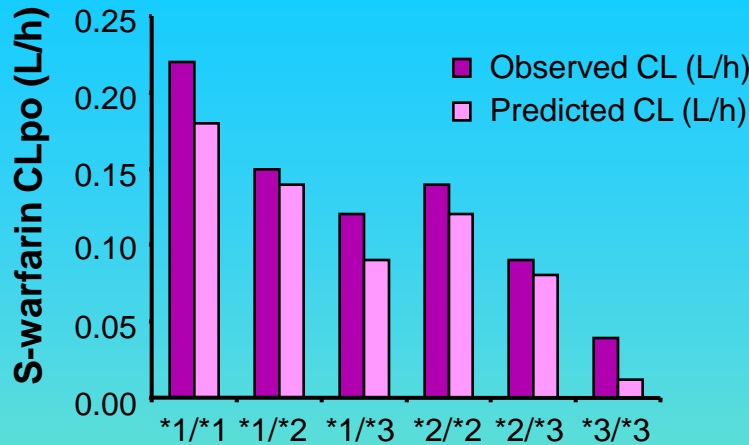


Use of rCYP to Assess Effects of Genetics

**Experimental Data:
Relative Activity
to rCYP *1 Allele**



S-Warfarin - Lisa Almond (ISSX Manchester 2006)



The Propagation of Genetic Polymorphism in CYP2C9 into Tolbutamide Pharmacokinetics: Assessment Using an Integrated Model

Difficulties with Retrospective Studies

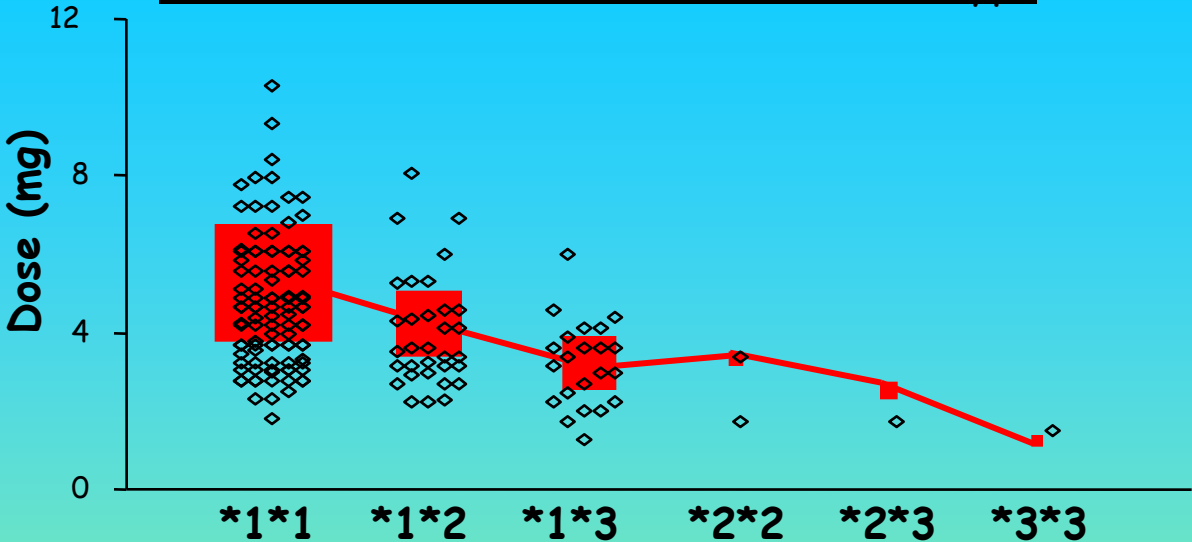
Warfarin Dose in Clinic vs CYP2C9 Genotype

■ = Meta-analysis (literature)

- Siguret et al, 2004; n = 126 -
- Kamali et al, 2004; n = 121
- King et al, 2004; n = 159
- Aithal et al, 1999; n = 52
- Taube et al, 2000; n = 561
- Hillman et al, 2004; n = 453
- Scordo et al, 2002; n = 93
- Loebstein et al, 2001; n = 156
- Higashi et al, 2002; n = 185
- Margaglione et al, 2000; n = 180

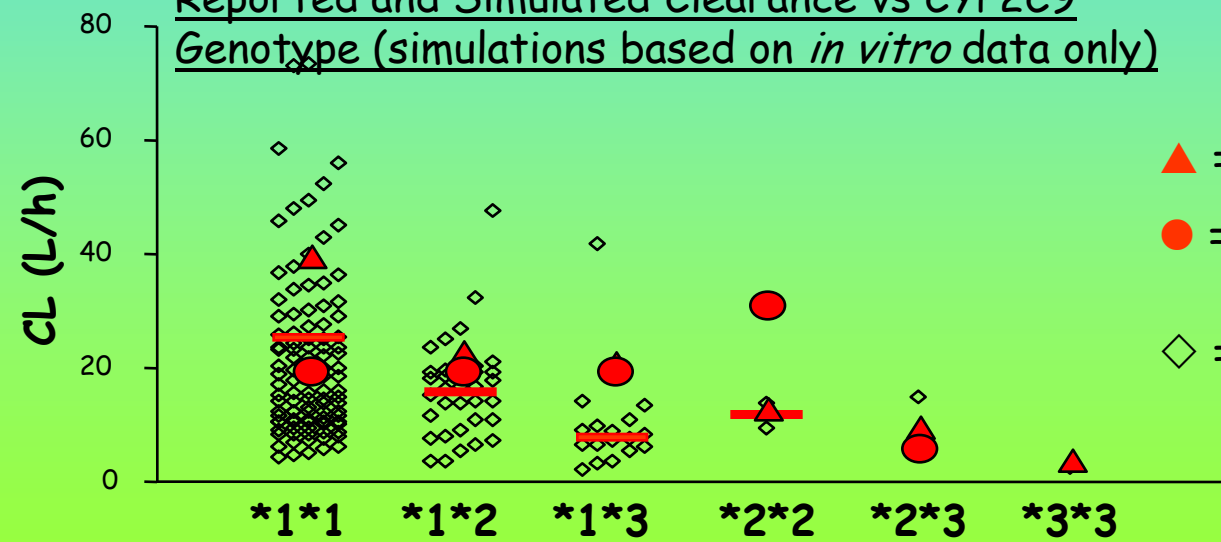
◇ = Individual data

Daly et al, 2005 (n = 159)



Reported and Simulated Clearance vs CYP2C9 Genotype (simulations based on *in vitro* data only)

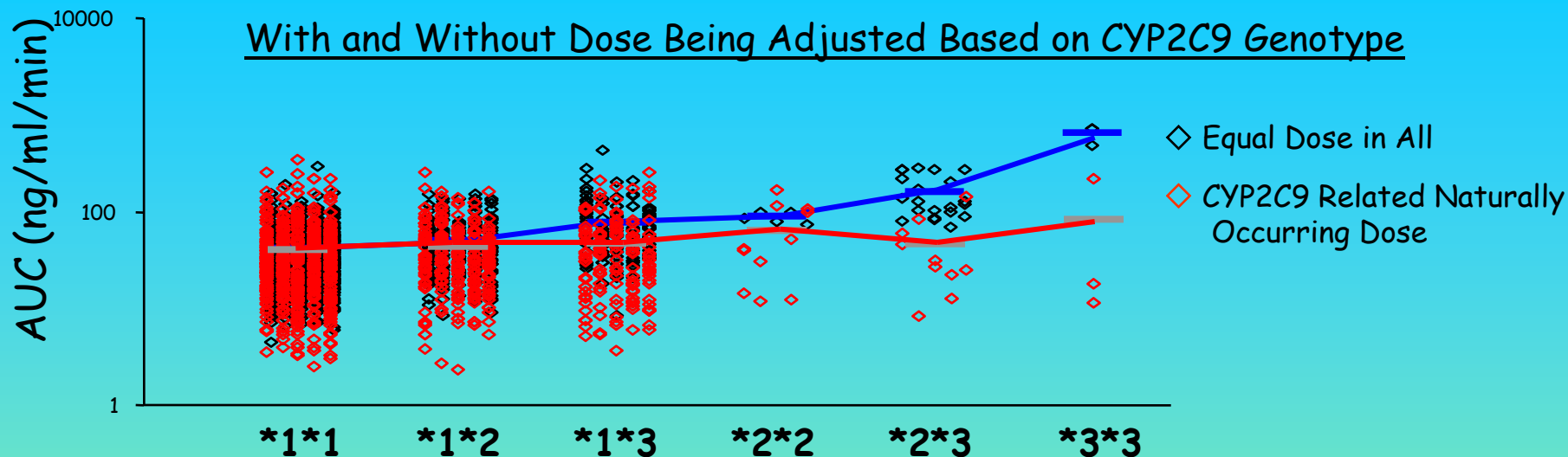
- ▲ = Scordo et al, 2002; n=93
- = Takahashi et al, 2003; n = 47
- ◇ = Simulated CL Values (n = 159)



Propagation of CYP2C9 Effects on PK/PD

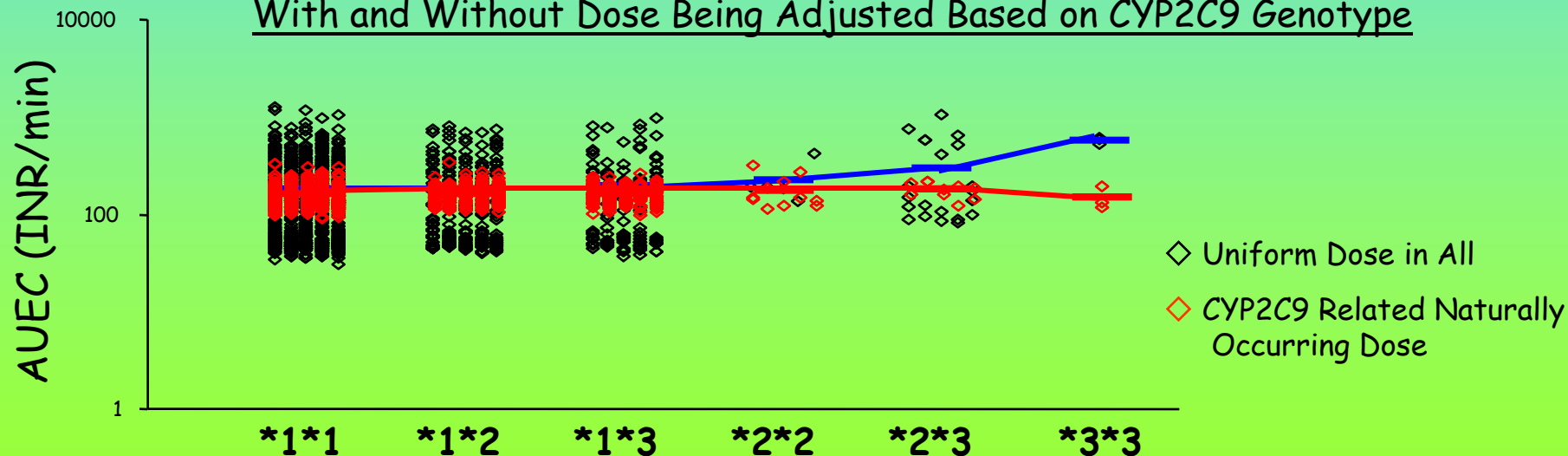
Simulated Exposure (AUC ; n = 1000)

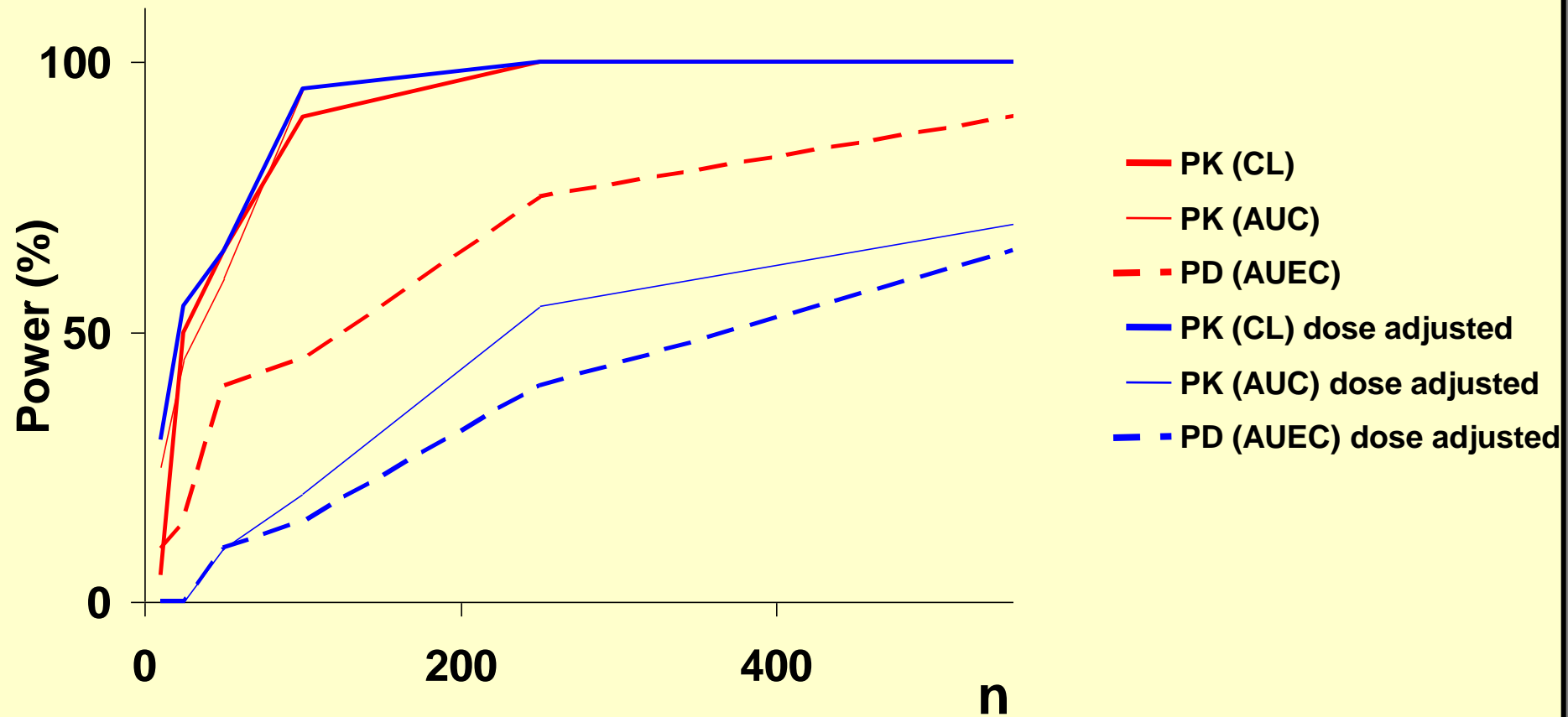
With and Without Dose Being Adjusted Based on CYP2C9 Genotype



Simulated Effects (AUEC of INR ; n = 1000)

With and Without Dose Being Adjusted Based on CYP2C9 Genotype





Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling



II. BACKGROUND

Identifying metabolic differences in patient groups based on **genetic polymorphism, or on other readily identifiable factors, such as age, race, and gender**, can aid in interpreting results. **The extent of interactions may be defined by these variables (e.g., CYP2D6 genotypes)**. Further, in subjects who lack the major clearance pathway, remaining pathways become important and should be understood and examined.

III. GENERAL STRATEGIES

To the extent possible, drug development should follow a sequence in which **early *in vitro* and *in vivo* investigations can either fully address a question of interest or provide information to guide further studies.**

III. GENERAL STRATEGIES

(A) *IN VITRO* STUDIES

In vitro studies can frequently serve as a screening mechanism to rule out the importance of a metabolic pathway and the drug-drug interactions that occur through this pathway so that subsequent *in vivo* testing is unnecessary.

SECTION IV. DESIGN OF *IN VIVO* DRUG-DRUG INTERACTION STUDIES

(A) STUDY POPULATION

Performance of **phenotype or genotype determinations to identify genetically determined metabolic polymorphisms** is important in evaluating effects on enzymes with polymorphisms, notably CYP2D6, CYP2C19, and CYP2C9. Subjects lacking the major clearance pathway, for example, cannot show metabolism and **remaining pathways can become important and should be understood and examined.**



SECTION III - GENERAL STRATEGIES

(A) *IN VITRO* STUDIES

(B) SPECIFIC *IN VIVO* CLINICAL INVESTIGATIONS

(C) POPULATION PHARMACOKINETIC SCREENS

*The results from such analyses can be informative and **sometimes conclusive** when the clinical studies are adequately designed to detect significant changes in drug exposure due to drug-drug interactions. Simulations can provide valuable insights into optimizing the study design.*

SECTION IV. DESIGN OF *IN VIVO* DRUG-DRUG INTERACTION STUDIES

(A) STUDY DESIGN

The inhibiting/inducing drugs and the substrates should be dosed so that the exposures of both drugs are relevant to their clinical use, including the highest doses likely to be used. **Simulations can be helpful in selecting an appropriate study design.** The following considerations may be useful: [1] - attainment of steady state (SUB/INHIB); [2] - time to achieve maximum effect (INDUCERS/MBI/ACCUMULATION OF METABOLITES); [3] -

SECTION IV. DESIGN OF *IN VIVO* DRUG-DRUG INTERACTION STUDIES

(C) CHOICE OF SUBSTRATE AND INTERACTING DRUGS (NID as Substrate of CYPs)

Evaluation of multiple CYP inhibitors if: (1) the drug exhibits blood concentration-dependent safety concerns; (2) multiple CYP enzymes are responsible for the metabolic clearance of the drug; (3) the residual or non-inhibitable drug clearance is low.

Before investigating the impact of multiple inhibitors on drug exposure, it is important to first characterize the individual effects of the CYP inhibitors and to estimate the combined effect of the inhibitors based on computer simulation.

General Aim of DDI Studies



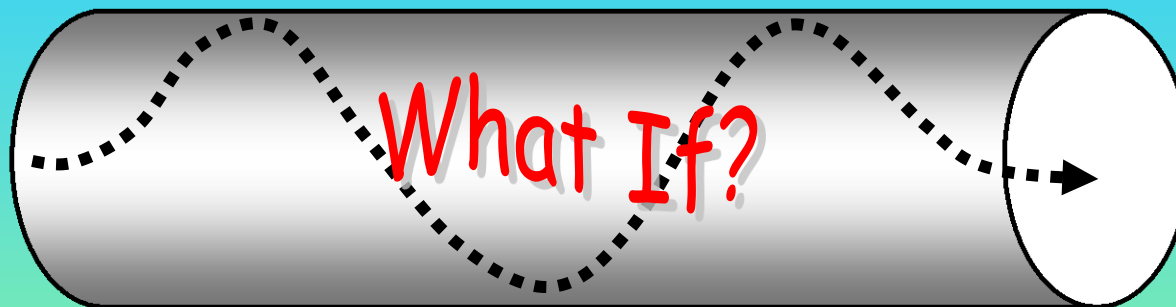
In some instances, understanding **how to adjust dose or dosage regimen** in the presence of an interacting drug, or how to avoid interactions, **may allow marketing of a drug that would otherwise have been associated with an unacceptable level of toxicity.**

When a drug-drug interaction of potential importance is clearly present, the sponsor should provide specific **recommendations regarding the clinical significance of the interaction based on what is known about the dose-response and/or PK/PD relationship** for either the investigational agent or the approved drugs used in the study. FDA recognizes that dose-response and/or PK/PD information can sometimes be incomplete or unavailable, especially for an older approved drug used as substrate.

Accumulation of Information on Compound (as Substrate)

fm via each route in average subject	→	Population distribution of fm
Estimates of microsomal/plasma binding	→	Actual f_u and $f_{u_{mic}}$
Estimates of gut absorption (e.g. Caco-2)	→	f_a from Phase I
Estimate of CL_R	→	CL_R from mass balance
Estimate of CL_{int}	→	K_m and V_{max}

Simulation



Assumptions for Inputs

Confidence in Outputs

Single concn simulations	→	Full concn profile
Possible effects on transporters	→	Characterised effects on transporters
Likely mechanism of inhibition	→	Confirmed mechanism of inhibition
Estimate of inhibitory potency (IC_{50})	→	K_i

Accumulation of Information on Compound (as Inhibitor)

PRE-CLINICAL



CLINICAL

