Society for Clinical Trials 34th Annual Meeting

Workshop P2
Clinical Pharmacology and Pharmacometrics for Statisticians and Clinical Trialists

Sunday, May 19, 2013
8:00 AM - Noon
Berkeley Room

Principles of Pharmacometrics

Kevin Sweeney

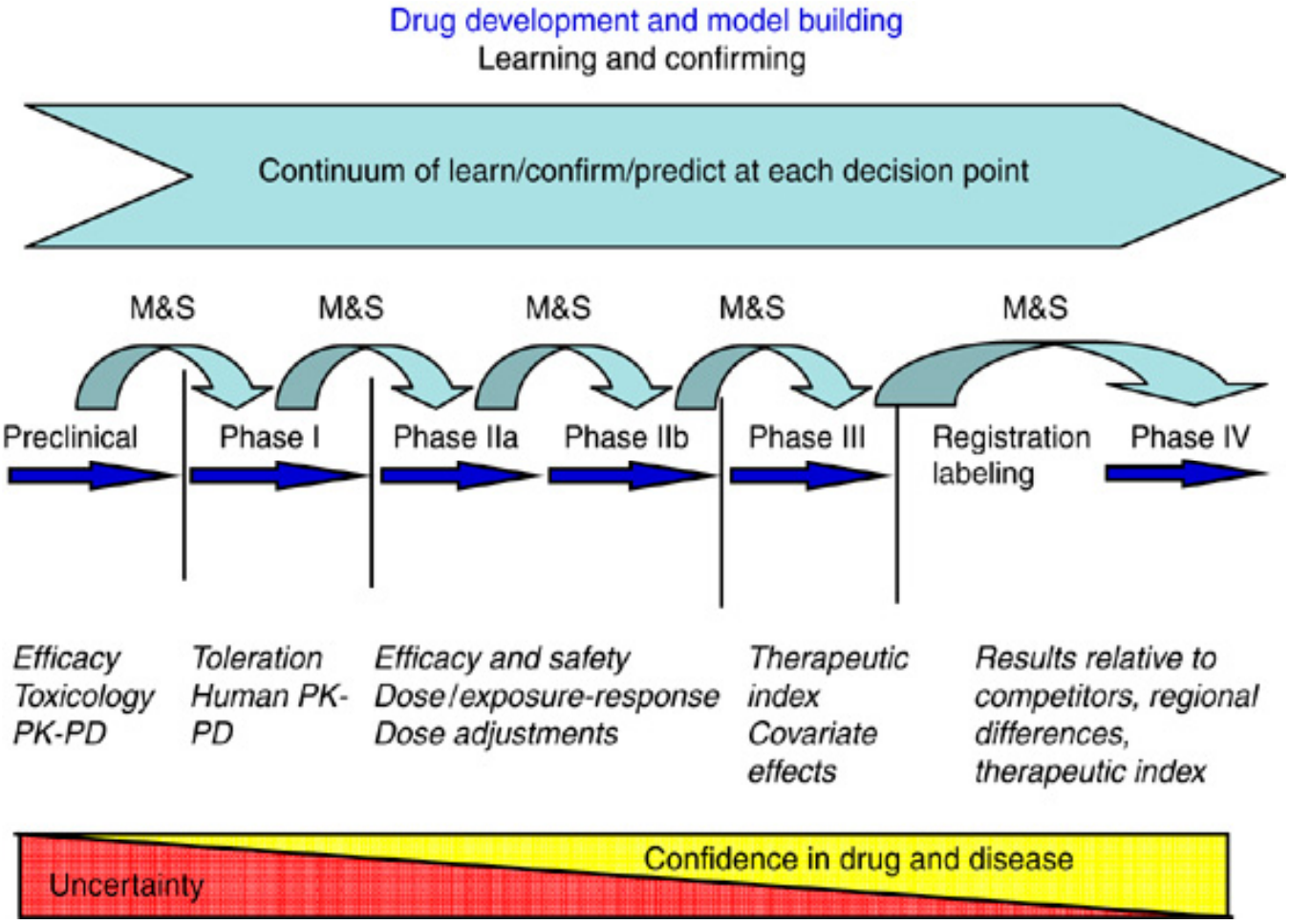
Principles of Pharmacometrics

- George Box wrote that "essentially, all models are wrong, but some are useful" (in *Empirical Model-Building and Response Surfaces*, Wiley, 1987*)*
- Essentially, models account for fixed effects (structural components like drug clearance or ED_{50}) and random effects (between subject variability, residual variability), but biological systems are very complex

Model-Based Drug Development (MBDD)

- **Simply stated, MBDD is the development and application of models that help inform decision making (Lalonde et. al, CPT, 82, 21–32, 2007)**
  - clinical and pre-clinical data
  - all phases of drug development
- **Consistent with "learn and confirm" concepts, as originally stated by Sheiner (CPT, 61:275, 1997)**
  - the "learn" phase occurs during early drug development (Phase 1 and 2), identifying appropriate therapeutic doses
  - the "confirm" phase occurs in later drug development (Phase 3), demonstrating acceptable safety and efficacy
  - MBDD applicable in this cycle, identifying dose-exposure relationship, effect size and uncertainty, shape of dose-response relationship, rational dose for intended use

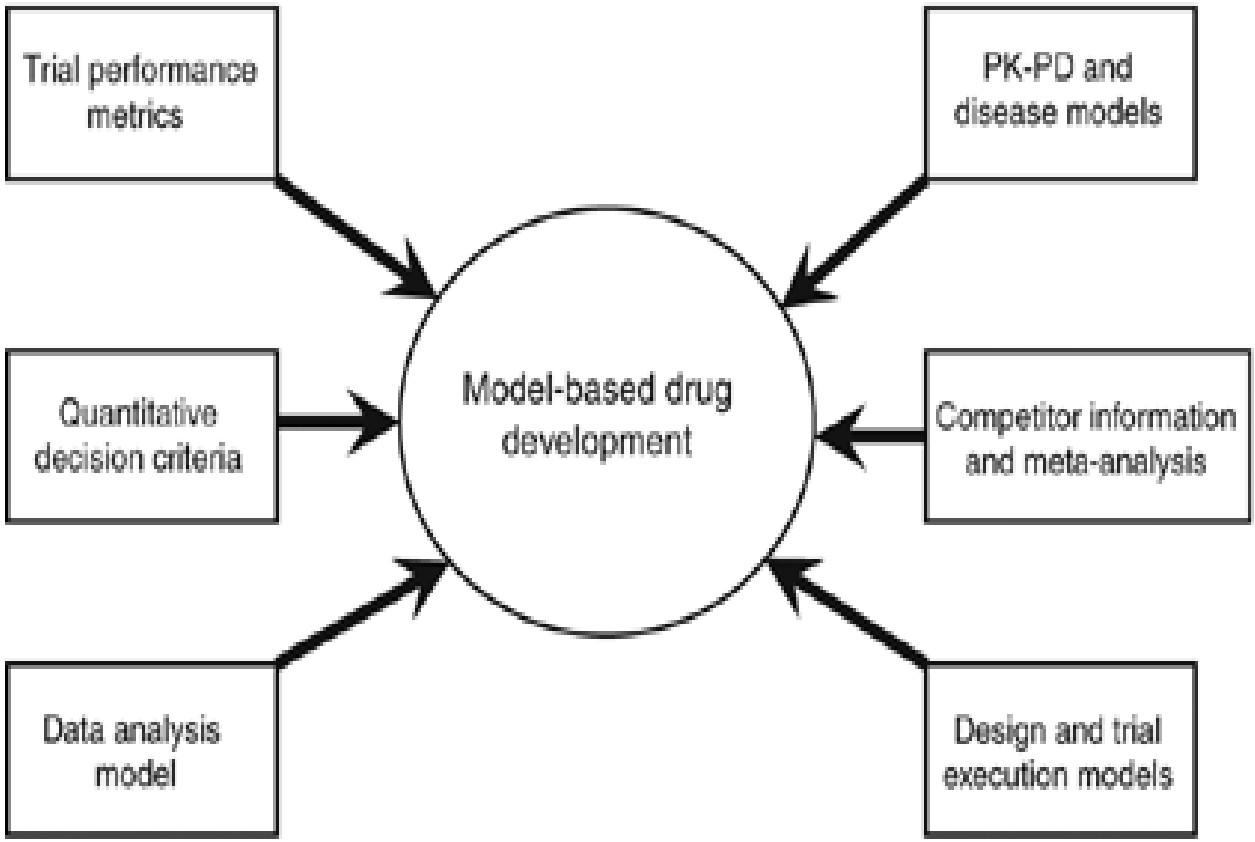
MBDD – "Learn/Confirm" Progression



MBDD - Examples

- **Many applications of MBDD are focused on modeling efforts with population approaches, to include…**
  - pharmacokinetic (PK) analysis to identify relevant patient-specific information (covariates) that also describes between subject variability in parameters of interest
  - pharmacodynamic (PD) analysis that describes relationship between safety/efficacy endpoints and dose or exposure (PKPD)
  - model-based meta analysis (MBMA) of published literature data to help understand relevant effect size, useful for positioning a compound in development into the completive landscape
- **Advantageous to perform longitudinal PD analysis over landmark analysis, as all data over study period contributes to better understanding of disease progression and treatment effects**

MBDD Schematic



MBDD – Core Elements

- **PKPD and Disease Models**
  - describe temporal relationships between dose (exposure) and response
- **Meta Analysis of Competitor Data**
  - estimation of effect size and uncertainty from published aggregate study level) data
- **Design and Trial Execution Models**
  - implementation of adaptive design models for dosing and drop-out/compliance models
- **Data Analysis Models**
  - prospectively defined statistical analysis models
- **Quantitative Decision Criteria**
  - rules applied to distribution of expected treatment effect, i.e., 80% confidence that the true effect > lower confidence value
- **Trial Performance Metrics**
  - probability of making a “correct” decision, irrespective of decision with a “go” or “no go” result

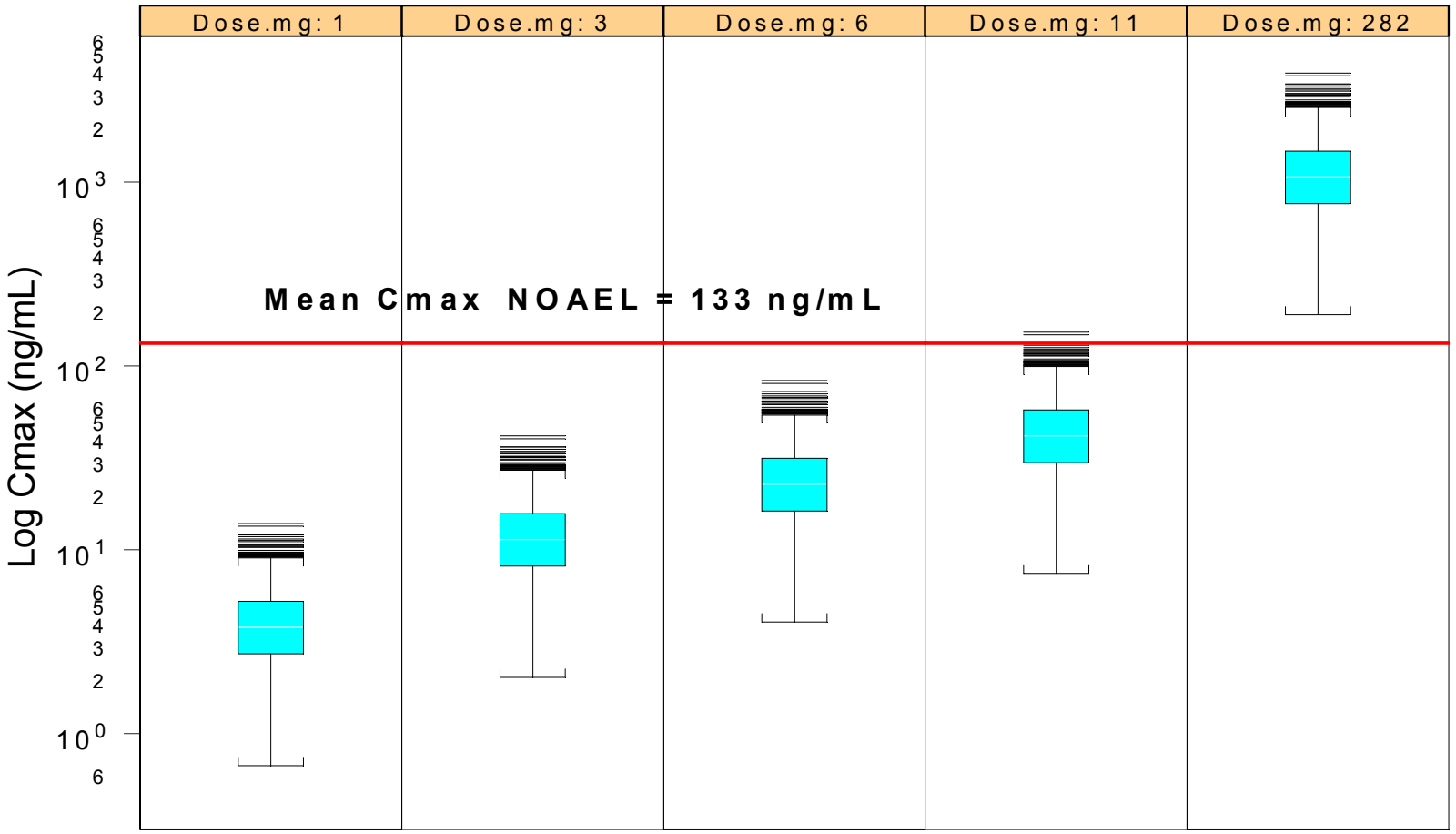
Model Building

- **Let data drive complexity of model**
  - PK: one compartment disposition with linear elimination and input, progress to multi-compartment disposition and complex absorption processes as necessary
  - PD: step change, linear and nonlinear drug effect
- **Fixed effects (CL, E_{MAX}, ED_{50}) and random effects (between subject and residual variability)**
- **At each step, more complex model tested for significant benefit in predictive performance**
- **Test final model performance with visual predictive check (simulation), bootstrap confidence intervals**

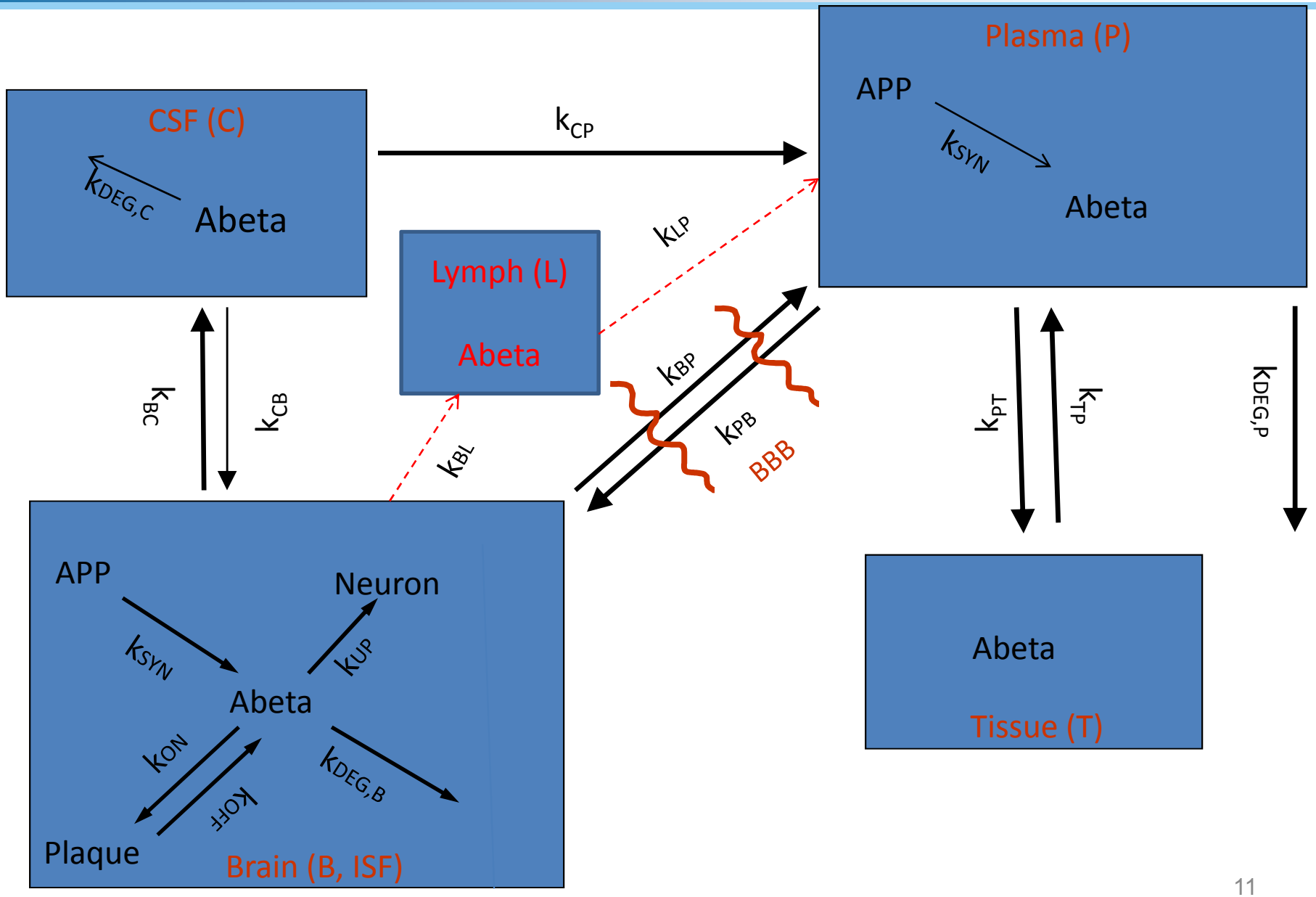
Pharmacometrics Applications

- **Models used can be quite simplistic as in most population PK applications, trending towards quite complex for systems biology/pharmacology applications**
  - Translational model to help understand potential dose limitations in first in human trials
  - Systems model to better understand beta amyeloid (Abeta) trafficking between specific body spaces
  - Logistic regression to understand hypoglycemic adverse event dose response
  - Population pharmacokinetics

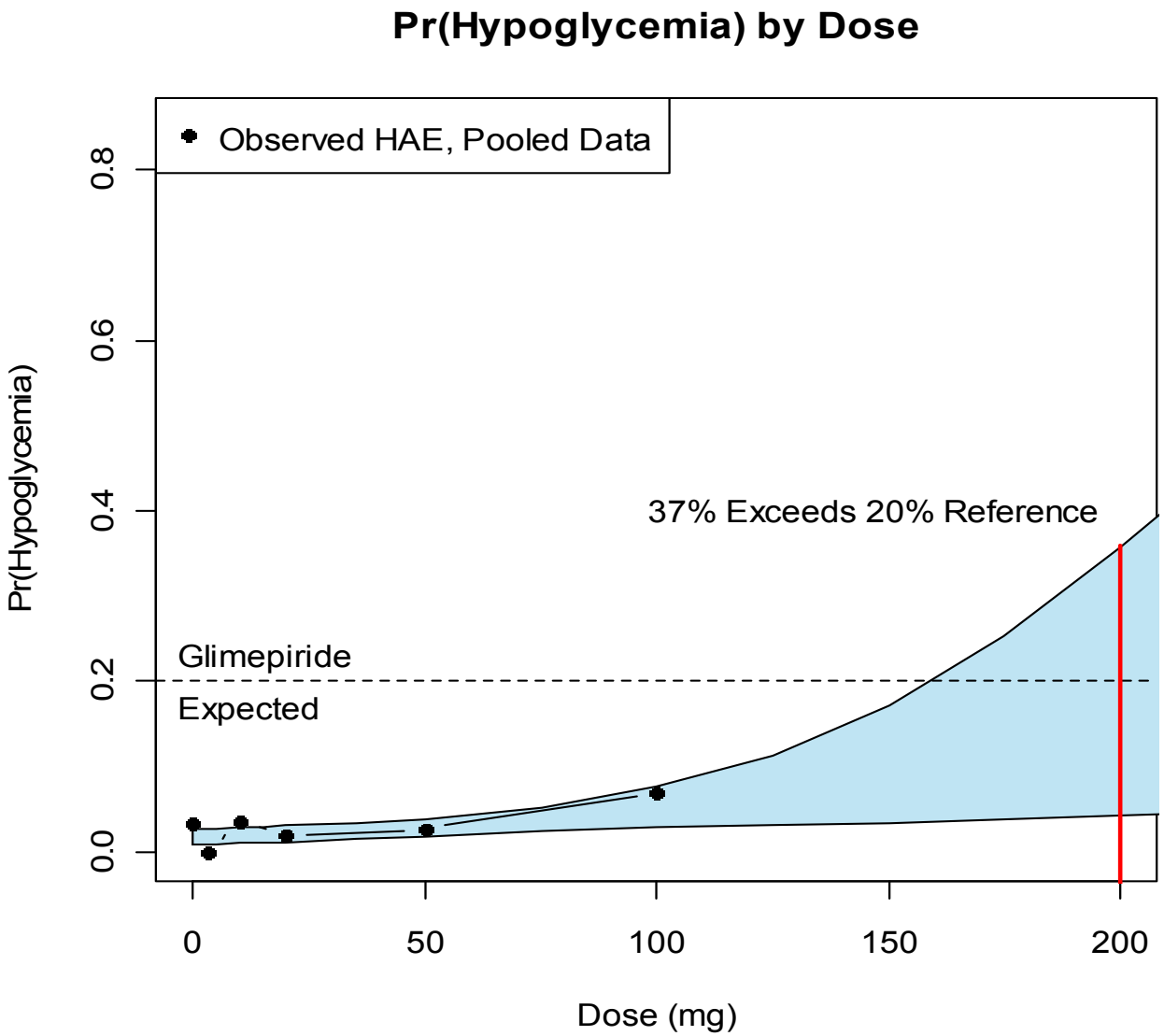
Translational Modeling of Cmax



Systems Biology Model of Abeta



Logistic Regression Model of Hypoglycemia

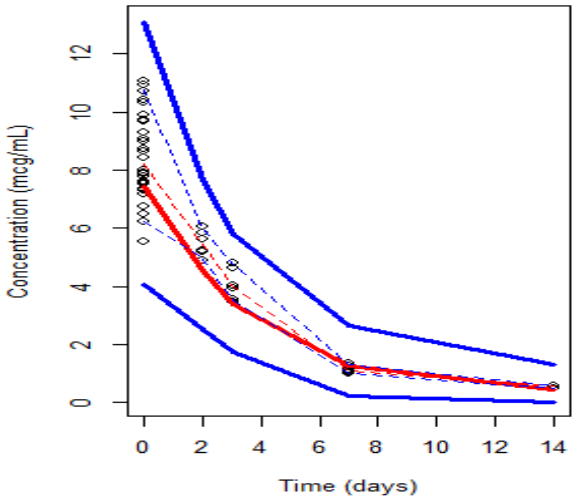


Population Pharmacokinetics Analysis (1)

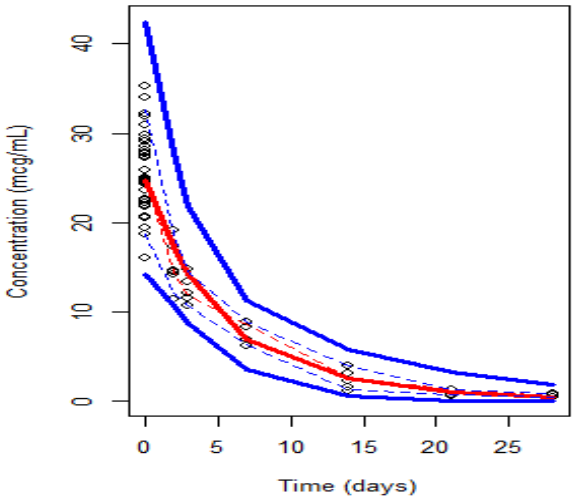
- Identify best “base” model, which captures concentration time profile of subjects, and includes relevant between subject and residual variability
- Identify non-collinear patient-specific covariates based on physiology and/or pharmacology, e.g., creatinine clearance on drug clearance, body size on clearance and volume of distribution, dose on absorption rate constant, concomitant medication on clearance to assess DDIs
- Advocate full model approach, all covariates on base model, estimate and bootstrap, clinical significance of covariate from confidence interval assessment
- Diagnostic plots to evaluate each step
- Perform visual predictive check to assess overall model performance, ability to simulate data from which model was built

Population Pharmacokinetics Analysis (2)

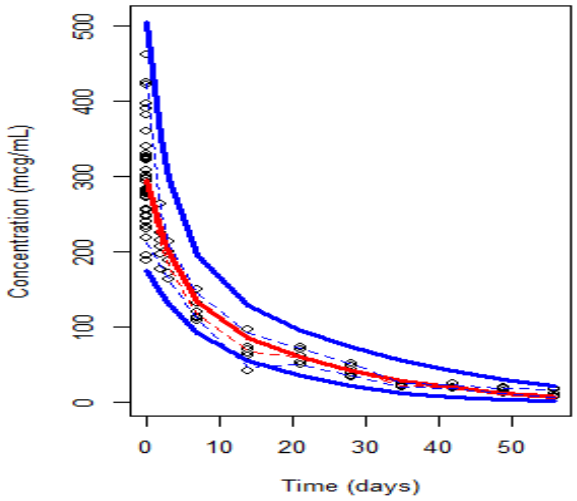
0.3 mg/kg



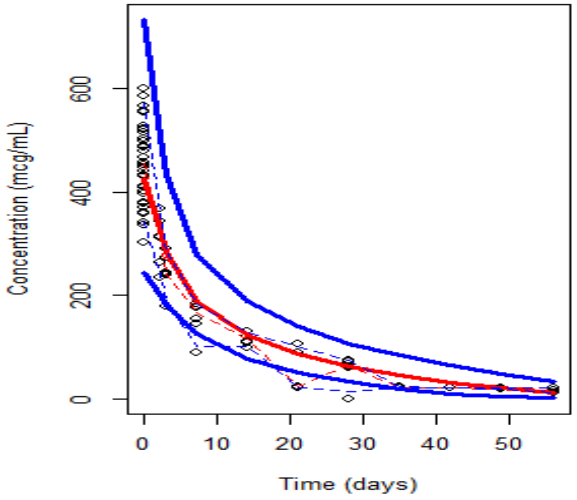
1.0 mg/kg



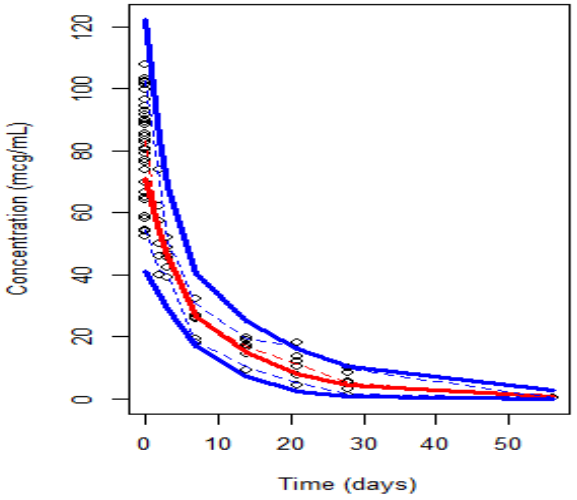
12 mg/kg



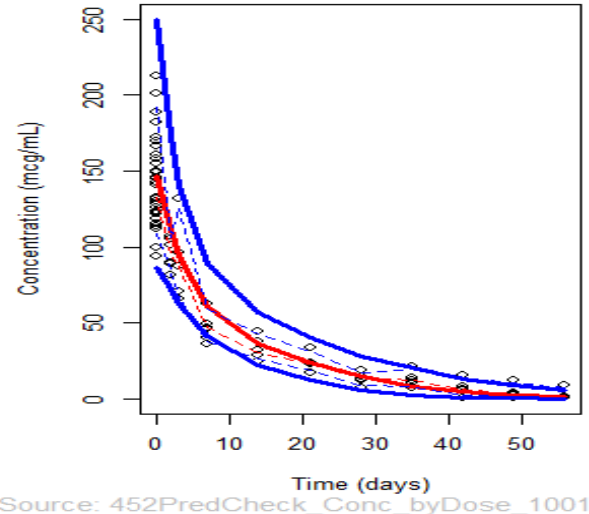
18 mg/kg



3.0 mg/kg



6 mg/kg



Source: 452PredCheck_Conc_byDose_1001.png

Case Study #1:
Estimate Target Performance
Pioglitazone

Background

- **Quantify magnitude (uncertainty) and time frame of HbA1c- and FPG-lowering effects of the TZD (thiazolidinediones) class of diabetic agents**
- **Effect thought to be mediated through activation of the peroxisome proliferator-activated receptor gamma (PPARγ), improving insulin sensitivity**
- **Aggregate data obtained from placebo-controlled trials, including pioglitazone and rosiglitazone**
  - Pioglitazone (Actos): 8 literature sources, 28 active treatment arms with 147 total data points
  - Rosiglitazone (Avandia): 9 literature sources, 25 active treatment arms with 125 total data points

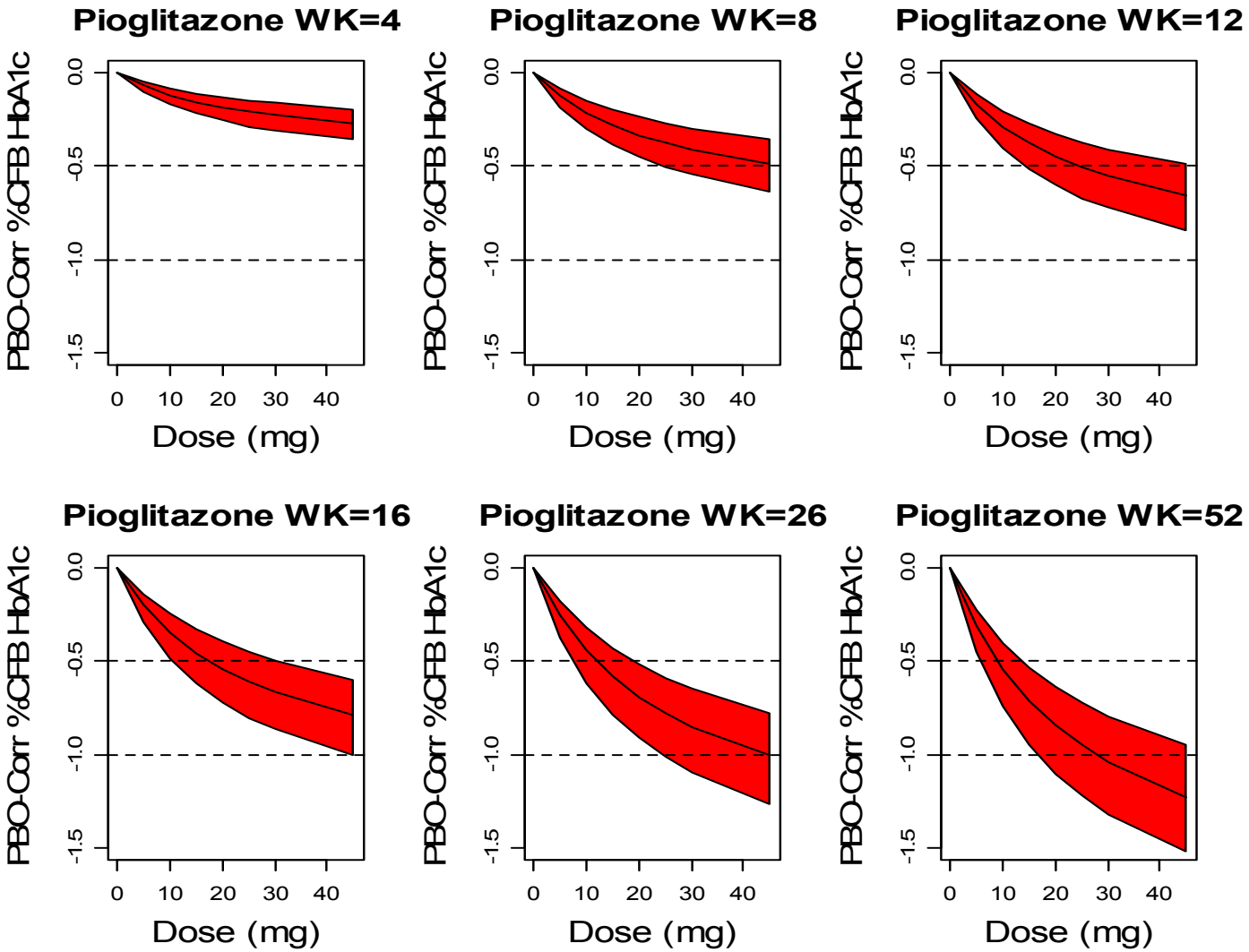
Methods (1)

- Longitudinal modeling of data was implemented to provide information on time-frame of response, E_{MAX} model characterized magnitude of response
- Data observed to 26 weeks, predictions made to 52 weeks using final longitudinal model
- Model accounted for placebo response over time (disease progression) in addition to drug effect (dose) over time
- Results presented are placebo-adjusted change from baseline values

Methods (2)

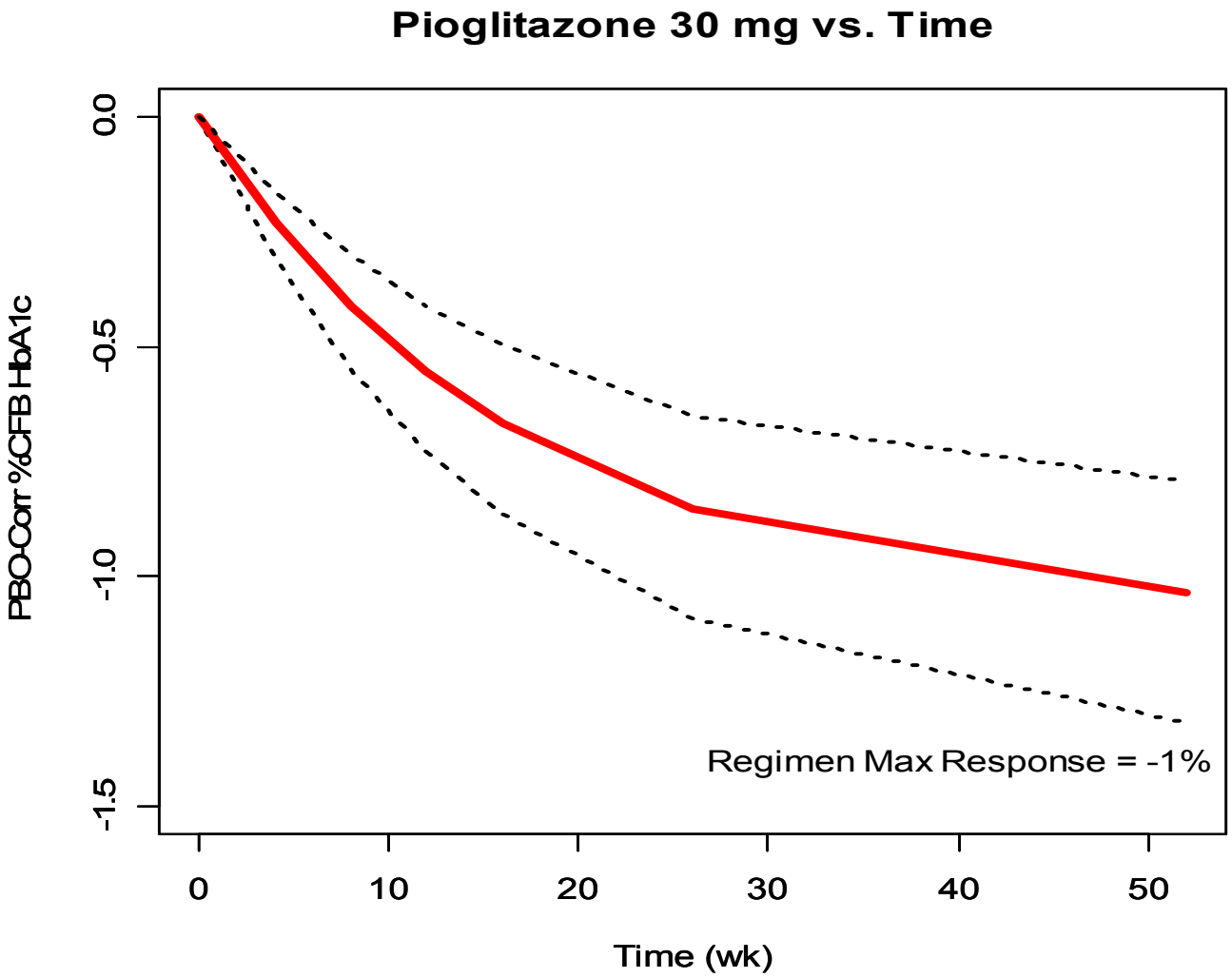
- Intrinsic activity assumed to be similar in class, attempts made to tease out potency differences between pioglitazone and rosiglitazone
- Accomplished by estimating pioglitazone ED_{50} with scale factor characterizing the relative potency of rosiglitazone
- Focus of analysis was pioglitazone (target performance), rosiglitazone data added to improve model stability
- Baseline effect estimated, normalized to a HbA1c value of 8% and FPG value of 120 mg/dL

Results (1): HbA1c Effect by Week



Dashed lines represent -0.5% and -1.0% as reference

Results (2): Temporal Profile of HbA1c

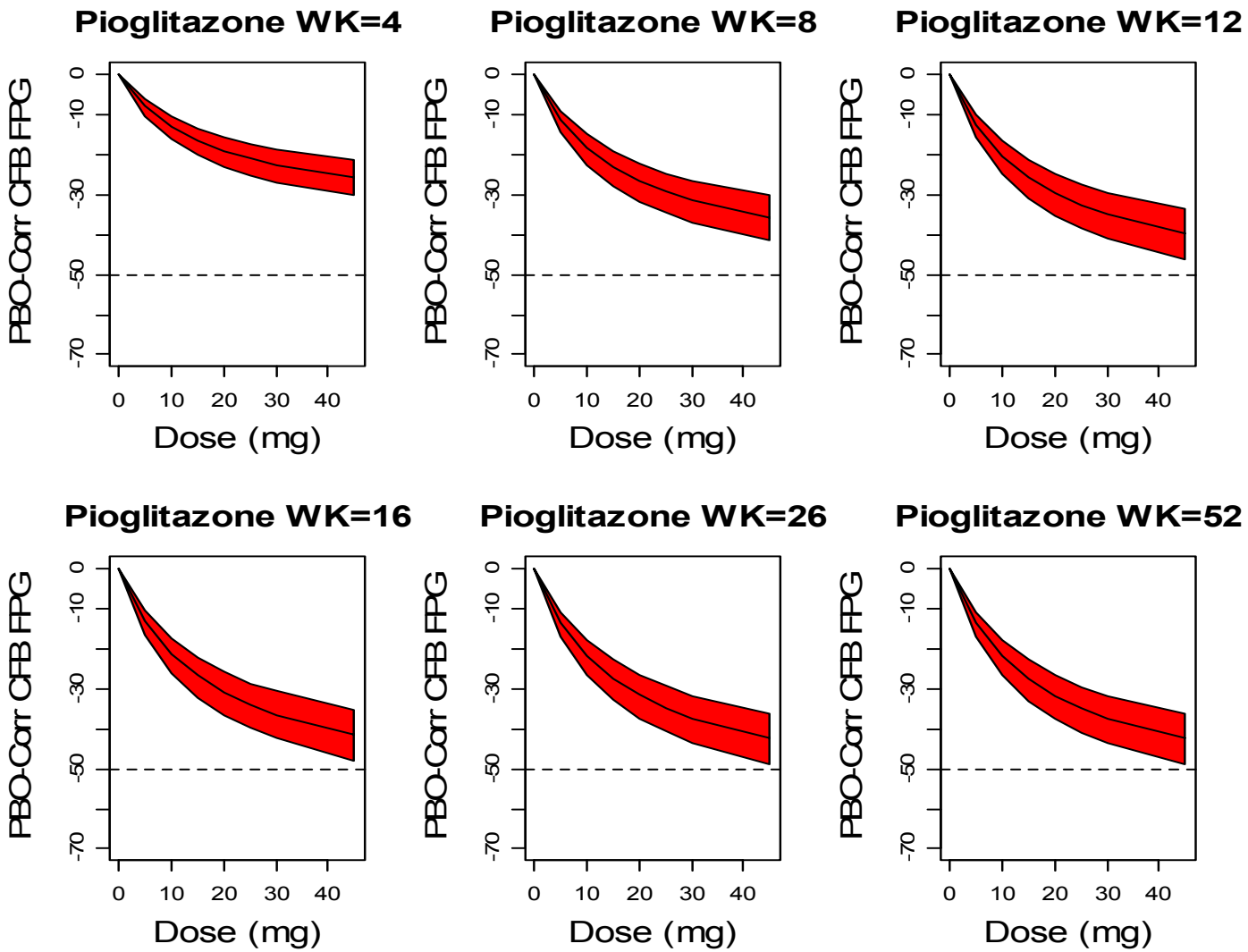


Red line represents expected pioglitazone 30 mg mean (90% CI) HbA1c response

Results (3): HbA1c Lowering

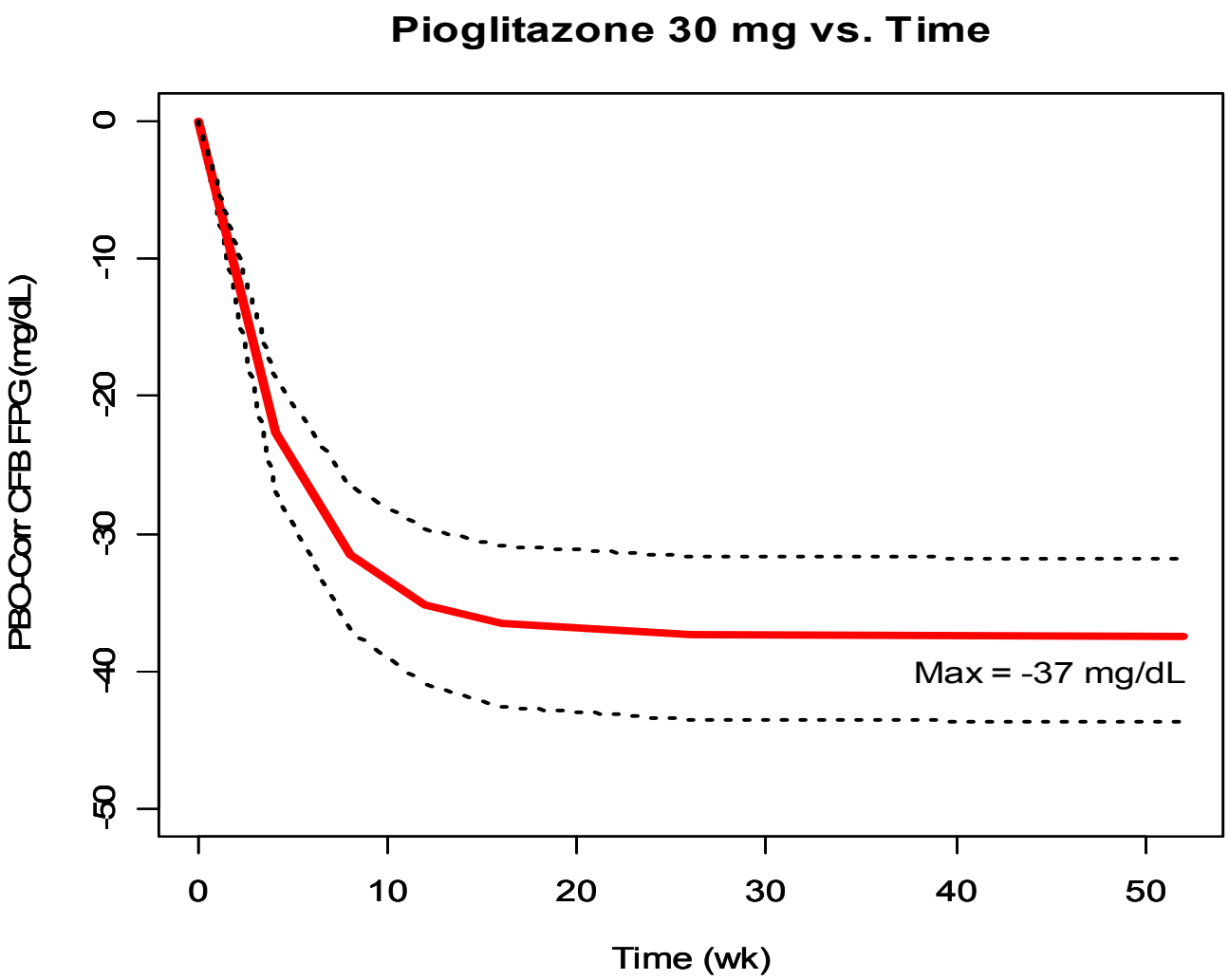
Weeks	LCB	Mean	UCB
4	-0.31	-0.23	-0.16
8	-0.55	-0.41	-0.30
12	-0.73	-0.55	-0.41
16	-0.87	-0.67	-0.50
26	-1.09	-0.85	-0.65
52	-1.32	-1.03	-0.79

Results (4): FPG Effect by Week



Dashed line represents -50 mg/dL as a reference in all panels

Results (5): Temporal Profile of FPG



Red line represents expected pioglitazone 30 mg mean (90% CI) FPG CFB response

Results (6): FPG Lowering

Weeks	LCB	Mean	UCB
4	-27	-23	-19
8	-37	-32	-27
12	-41	-35	-30
16	-43	-37	-31
26	-44	-37	-32
52	-44	-37	-32

Conclusion

- **Longitudinal E_{MAX} model adequately described HbA1c and FPG CFB data**
- **Rosiglitazone estimated to be ~8-fold more potent than pioglitazone in HbA1c/FPG lowering**
- **All placebo-corrected, HbA1c and FPG CFB confidence intervals exclude zero, significant lowering effect**
- **Target profile for TZD-like drug, 1-year**
  - HbA1c: -1.03% (-1.32, -0.79)
  - FPG: -37 mg/dL (-44, -32)

Case Study #2

HbA1c Lowering Performance

Background

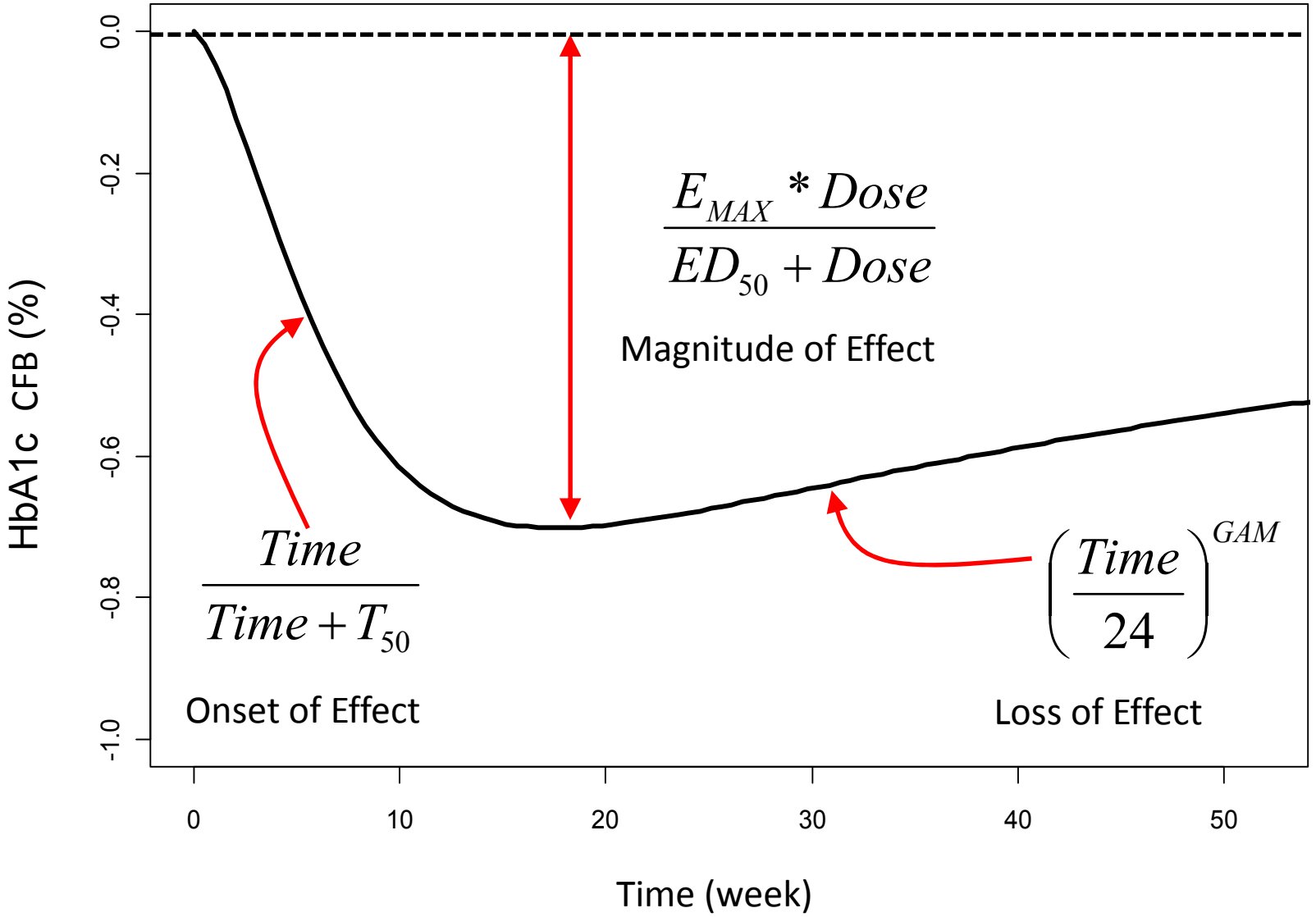
- Study conducted (12-week) testing mechanism of glucose lowering/HbA1c reduction
- Resultant study data modeled, providing estimates of maximal effect, potency, baseline effect on E_{MAX} and temporal profile of efficacy endpoints
- Make a statement regarding expectation of mean response, and uncertainty of that response
- Generate probability of attaining marginal difference of endpoint

Methods (1)

$$Y_{ij} = HbA1c_{Baseline,i} - \left(PBO_i + \frac{E_{MAX} * Dose}{ED_{50} + Dose} \right) * \left(\frac{Time}{T_{50} + Time} \right) * \left(\frac{Time}{24} \right)^{GAM} + \varepsilon_{ij}$$

- Individual longitudinal data, E_{MAX} model was fitted to the data
- Y_{ij} = the observed HbA1c at the j^{th} time in the i^{th} individual
- E_{MAX}= the maximal response
- ED_{50} = the potency, dose required to elicit half of E_{MAX}
- T_{50} = time to 50% steady-state profile
- GAM = durability effect (negative = loss)
- ε_{ij} = the residual variability at the j^{th} time in the i^{th} individual

Methods (2): Model of HbA1c Time Course



Methods (3)

- Longitudinal E_{MAX} dose-response model fitted to observed HbA1c data (observed cases, not LOCF)
- Final model point estimates of relevant model parameters and covariance matrix used to simulate 10,000 vectors of parameter space
- Response for relevant doses generated from simulated parameter vectors
- Confidence intervals generated to characterize uncertainty in response and probability of achieving a clinically relevant reduction in HbA1c also calculated

Methods (4)

- **1,000 clinical trials simulated, difference between test drug and lead competitor generated, varied by number of subjects per trial**
- **For each simulated trial, the 95% CI of the difference between the two treatments was calculated (drug – competitor, negative favors test drug)**
- **The outcome was classified as:**
  - Superior if upper 95%CI < 0 as drug is significantly better than competitor (**green**)
  - Non-inferior if upper 95%CI < 0.3 (**green** + **blue**, anything superior is also non-inferior)
  - Inferior if lower 95% CI > 0 (if significantly worse than competitor but also non-inferior is not classified as inferior) (**red**)
  - Inconclusive is none of the above (**orange**)

Results (1): 12-Week Performance

Dose (mg)	Predicted Mean Response (%)	80% CI
1	-0.49	-0.65, -0.31
5	-0.64	-0.78, -0.50
10	-0.67	-0.81, -0.53
25	-0.70	-0.84, -0.55

- **Longitudinal E_{MAX} dose-response model results used to generate dose-specific mean HbA1c reduction with uncertainty expressed as an 80% CI**
- **Assumes baseline HbA1c of 8% (study entry inclusion criteria)**

Results (2): 12-Week Pr(Target)

Baseline HbA1c	Dose		
	5mg	10mg	25mg
7.75%			
Pr (≤ -0.6%)	0.433	0.557	0.630
Pr (≤ -0.7%)	0.133	0.203	0.271
8%			
Pr (≤ -0.6%)	0.648	0.753	0.807
Pr (≤ -0.7%)	0.291	0.406	0.489

- **Probability of achieving a clinically relevant HbA1c reduction of 0.6% or 0.7%, conditional on baseline HbA1c level**

Results (3): 24-Week Performance

Dose (mg)	Predicted Mean Response (%)	80% CI
1	-0.60	-0.80, -0.38
5	-0.78	-0.96, -0.61
10	-0.82	-1.00, -0.65
25	-0.85	-1.03, -0.67

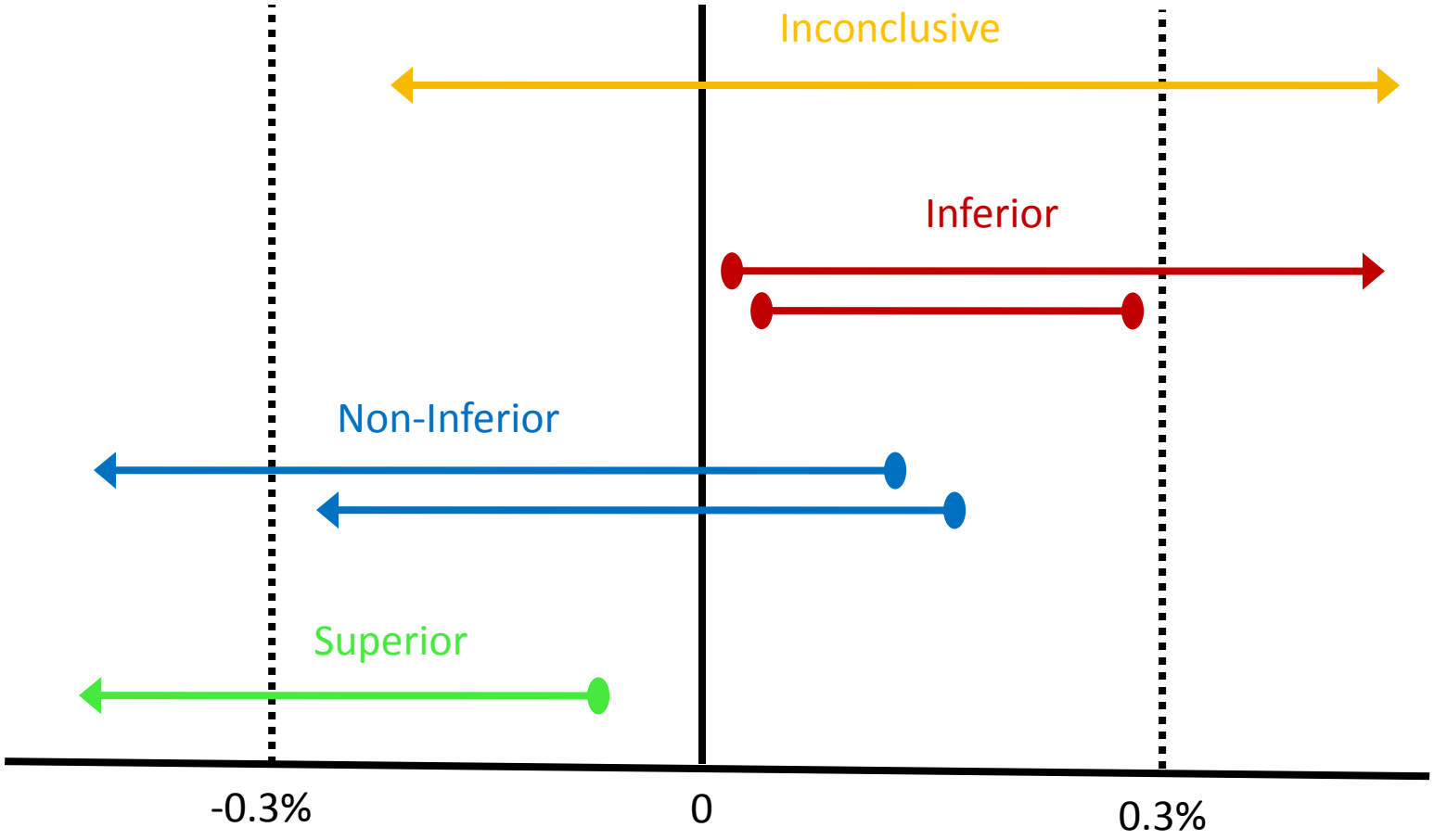
- **Longitudinal E_{MAX} dose-response model results used to predict dose-specific mean HbA1c reduction with uncertainty expressed as an 80% CI**
- **Assumes baseline HbA1c of 8% (study entry inclusion criteria)**

Results (4): 24-Week Pr(Target)

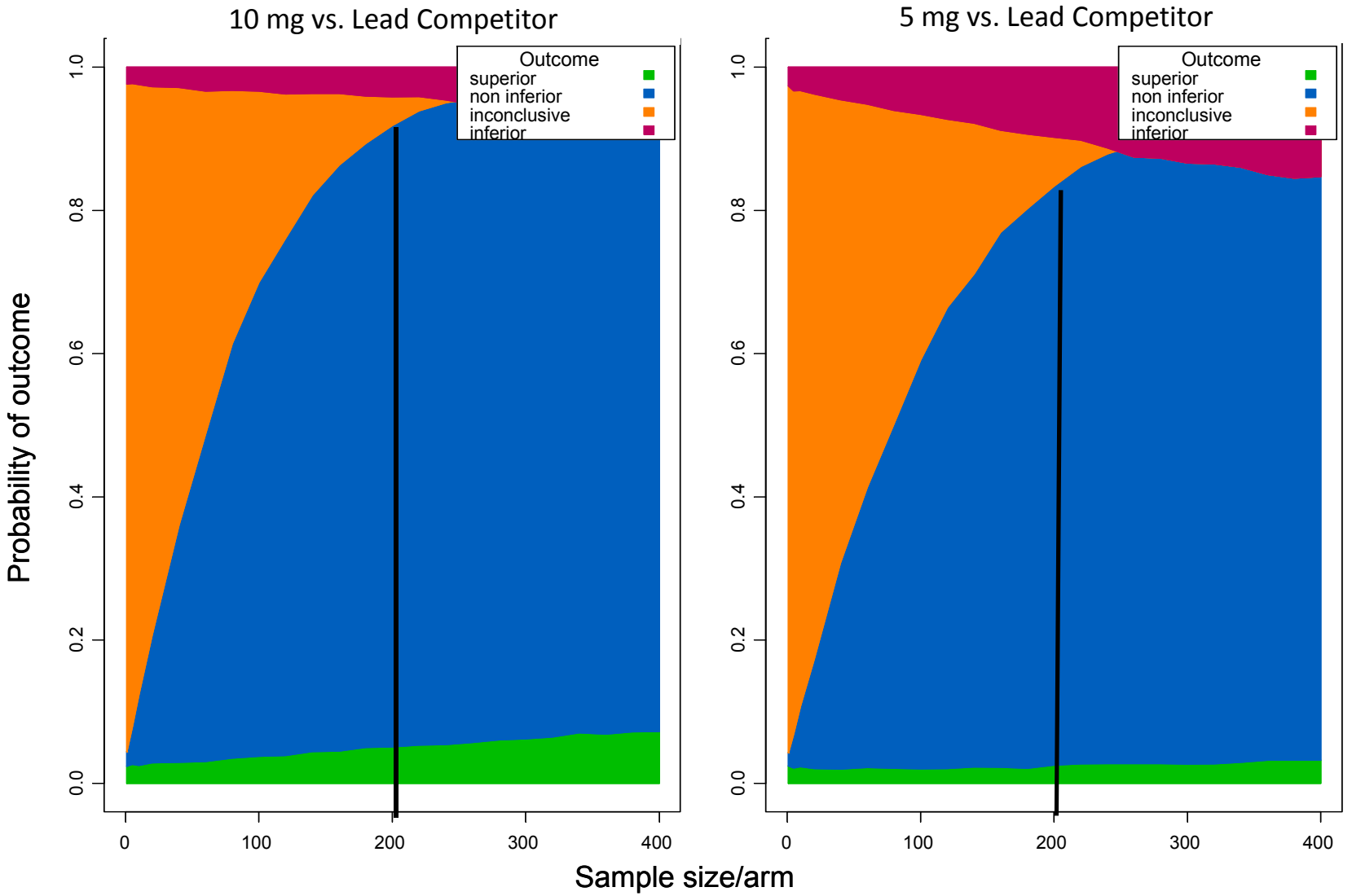
Baseline HbA1c	Dose		
	5mg	10mg	25mg
7.75%			
Pr (≤ -0.6%)	0.815	0.879	0.6906
Pr (≤ -0.7%)	0.540	0.649	0.713
8%			
Pr (≤ -0.6%)	0.907	0.948	0.961
Pr (≤ -0.7%)	0.727	0.813	0.853

- **Probability of achieving a clinically relevant HbA1c reduction of 0.6% or 0.7%, conditional on baseline HbA1c level**

Results (5): Trial Decision Criteria



Results (6): Comparison, Sample Size



Conclusions

- Longitudinal E_{MAX} model adequately described individual %CFB HbA1c
- The 5, 10 and 25 mg doses appear to be similar with respect to HbA1c lowering effect at 12 weeks
- Probability of achieving at least a 0.6% placebo-adjusted CFB reduction in HbA1c at 24 weeks (registration trial length) appears to be >90% for the 5, 10 and 25 mg doses, with a baseline HbA1c of 8%
- If a head-to-head trial were run, with at least 80% probability of showing non-inferiority, need ~200 subjects (100/arm) at 5 or 10 mg

PHARMACOKINETICS

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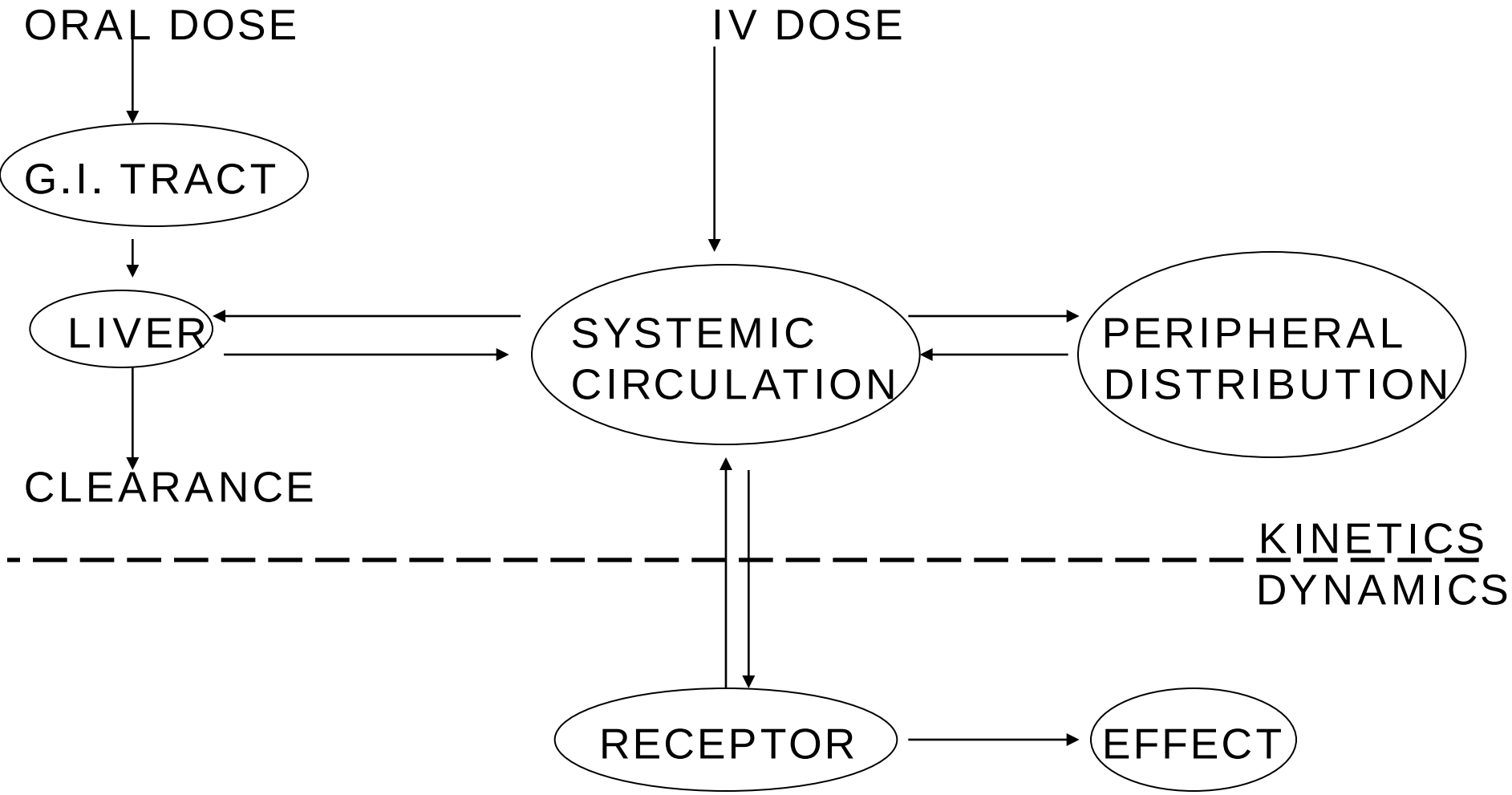
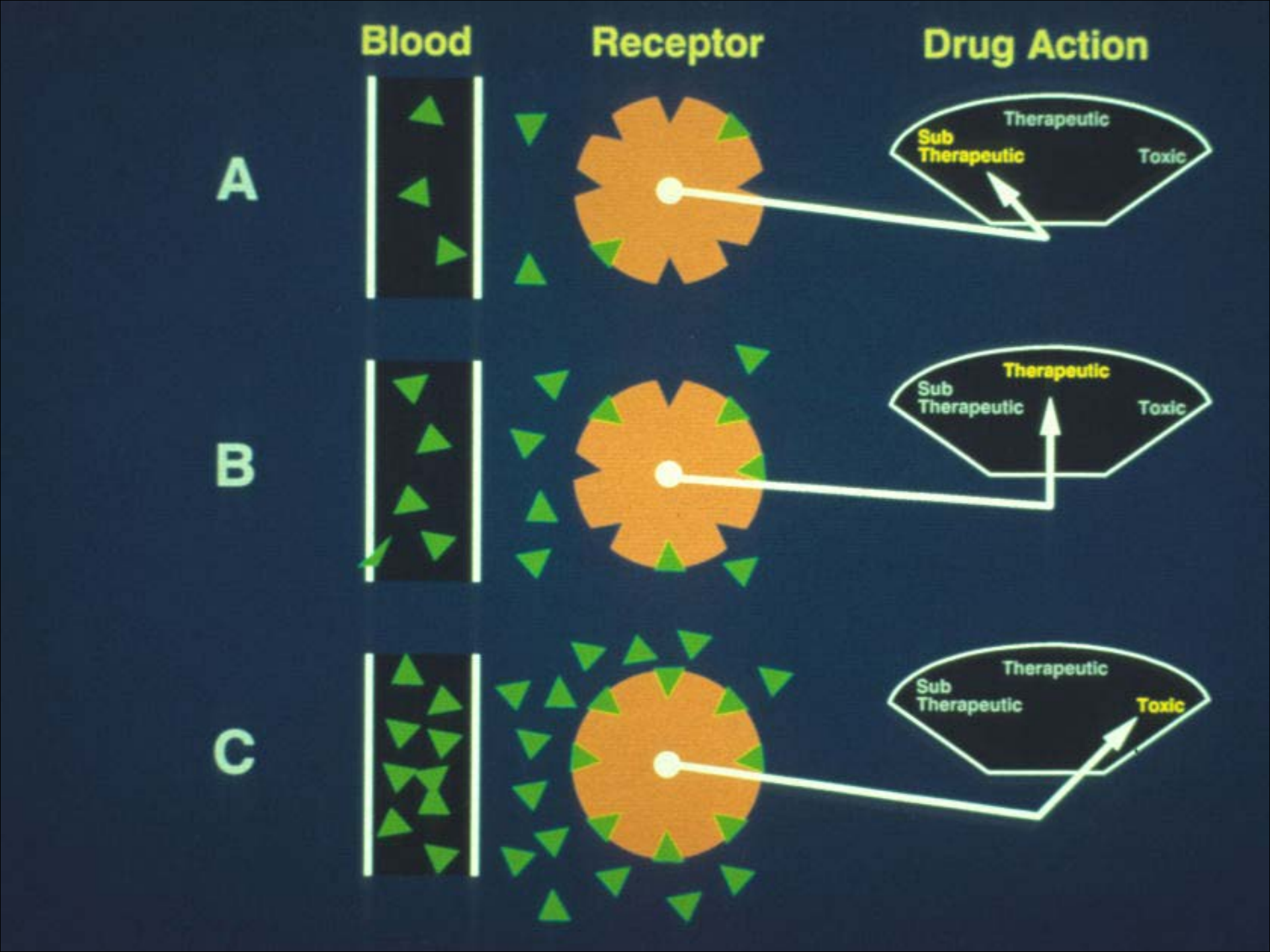
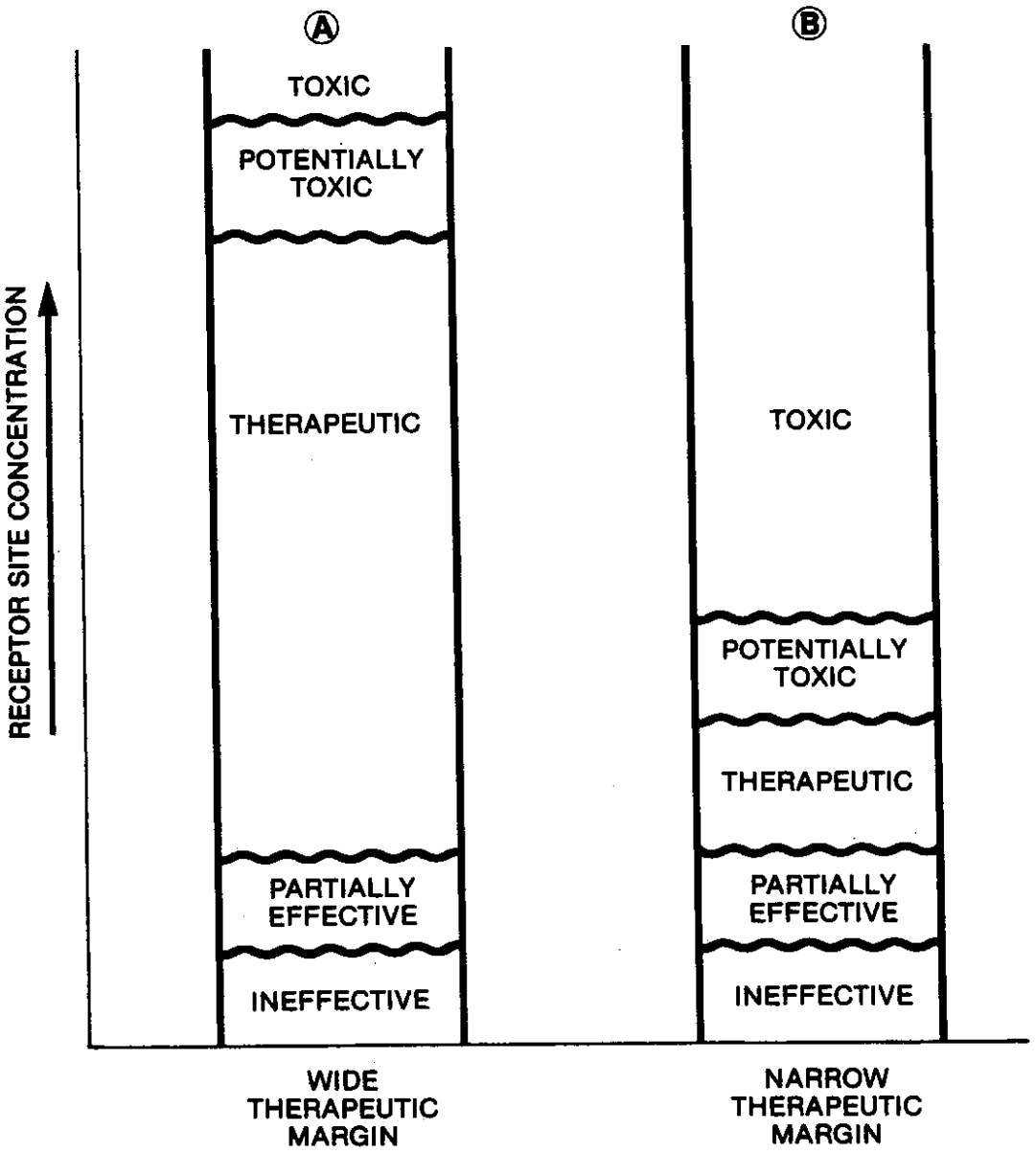
Subject	Independent variable	Dependent variable
Pharmacokinetics	Time	Concentration
Pharmadynamics	Time	Effect
Kinetic-dynamic modeling	Concentration	Effect


ORAL DOSE
IV DOSE
G.I. TRACT
LIVER
SYSTEMIC CIRCULATION
PERIPHERAL DISTRIBUTION
CLEARANCE
KINETICS
DYNAMICS
RECEPTOR
EFFECT


Blood
Receptor
Drug Action
A
Therapeutic
Sub
Therapeutic
Toxic
B
Therapeutic
Sub
Therapeutic
Toxic
C
Therapeutic
Sub
Therapeutic
Toxic

Concentration	Result
Too low	Lack of efficacy
Correct	Desired therapeutic effect
Too high	Toxicity


Ⓐ
Ⓑ
TOXIC
POTENTIALLY TOXIC
THERAPEUTIC
PARTIALLY EFFECTIVE
INEFFECTIVE
TOXIC
POTENTIALLY TOXIC
THERAPEUTIC
PARTIALLY EFFECTIVE
INEFFECTIVE
RECEPTOR SITE CONCENTRATION
WIDE THERAPEUTIC MARGIN
NARROW THERAPEUTIC MARGIN

CORE CONCEPTS

- Volume of distribution
- Elimination half-life
- Clearance

$$\text{CONCENTRATION} = \frac{\text{AMOUNT}}{\text{VOLUME}}$$

$$V_d = \frac{X}{C}$$

VOLUME OF DISTRIBUTION

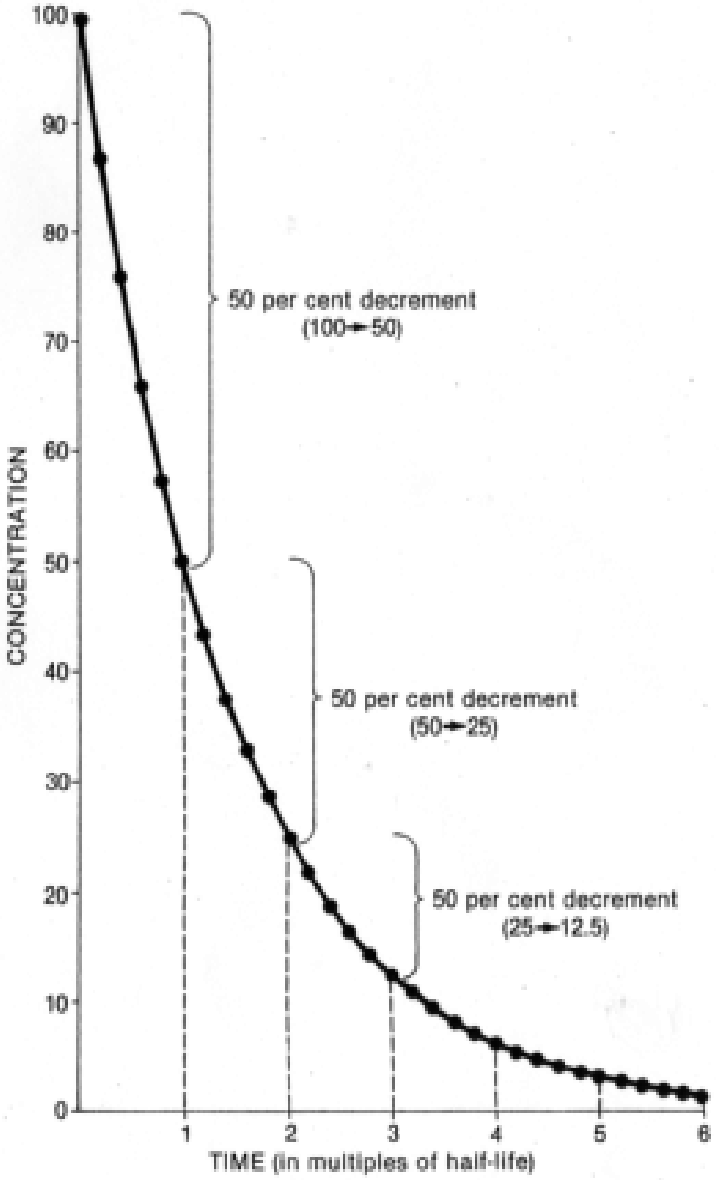
- Is imaginary
- Does not tell you where the drug is
- Is not the sum of anatomic volumes of sites of uptake
- Quantitatively reflects peripheral tissue uptake
- Is related to lipid solubility

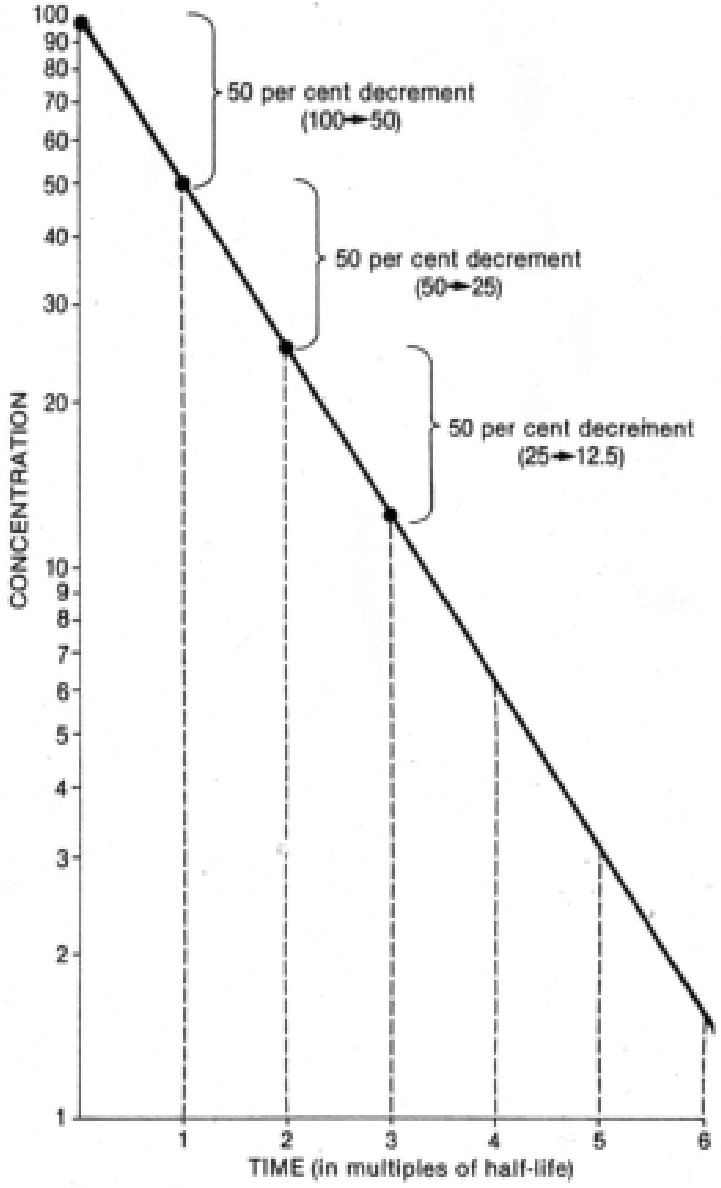
I.V. dose = 2 mg

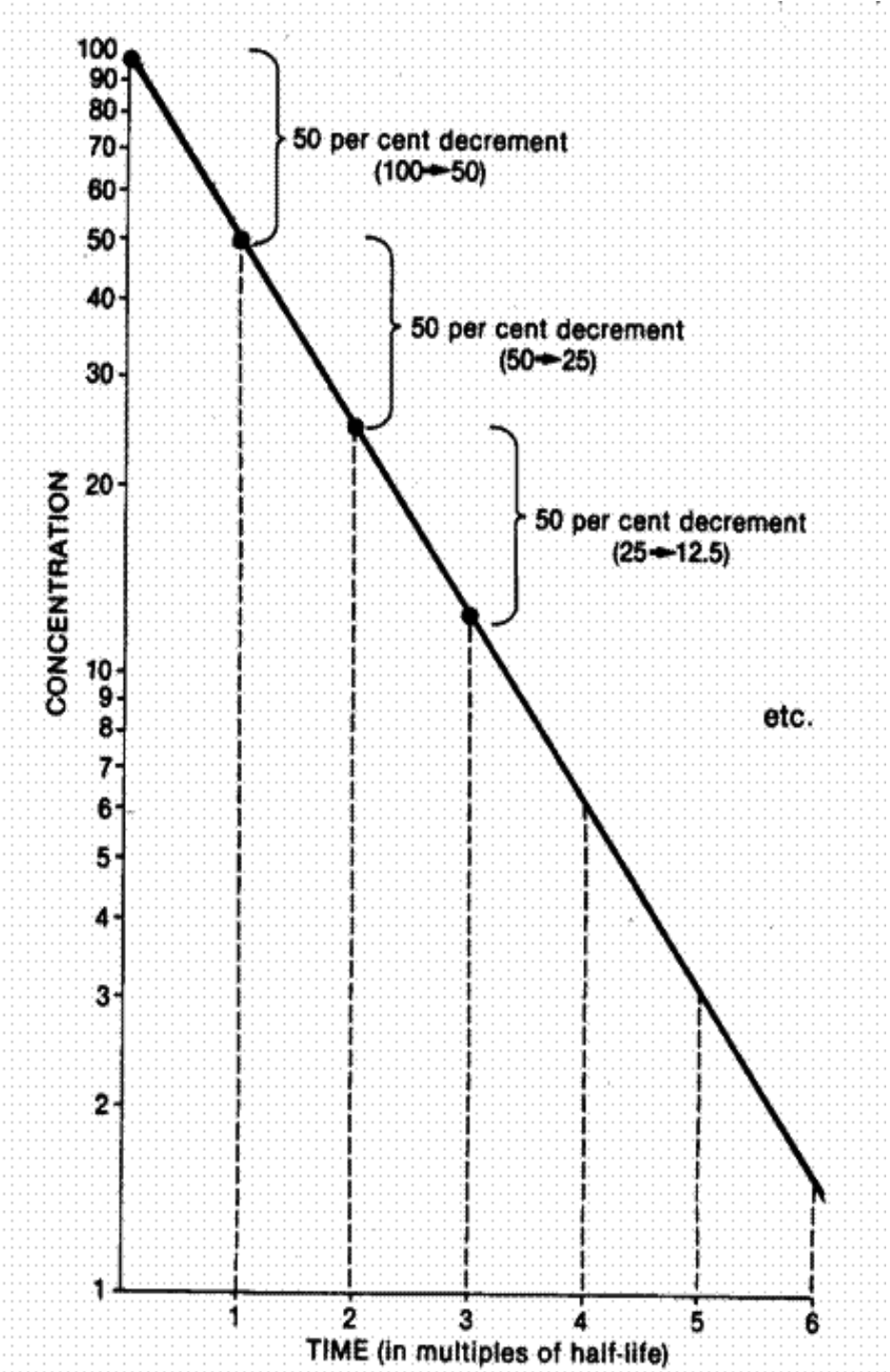
Concentration = 14.3 ng/ml

V_d = 140 Liters

= 2.0 Liters/kg (in a 70-kg person)


CONCENTRATION
TIME (in multiples of half-life)
50 per cent decrement (100→50)
50 per cent decrement (50→25)
50 per cent decrement (25→12.5)


CONCENTRATION
TIME (in multiples of half-life)
50 per cent decrement (100→50)
50 per cent decrement (50→25)
50 per cent decrement (25→12.5)


100
90
80
70
60
50
40
30
20
10
9
8
7
6
5
4
3
2
1
CONCENTRATION
50 per cent decrement
(100→50)
50 per cent decrement
(50→25)
50 per cent decrement
(25→12.5)
etc.
1
2
3
4
5
6
TIME (in multiples of half-life)

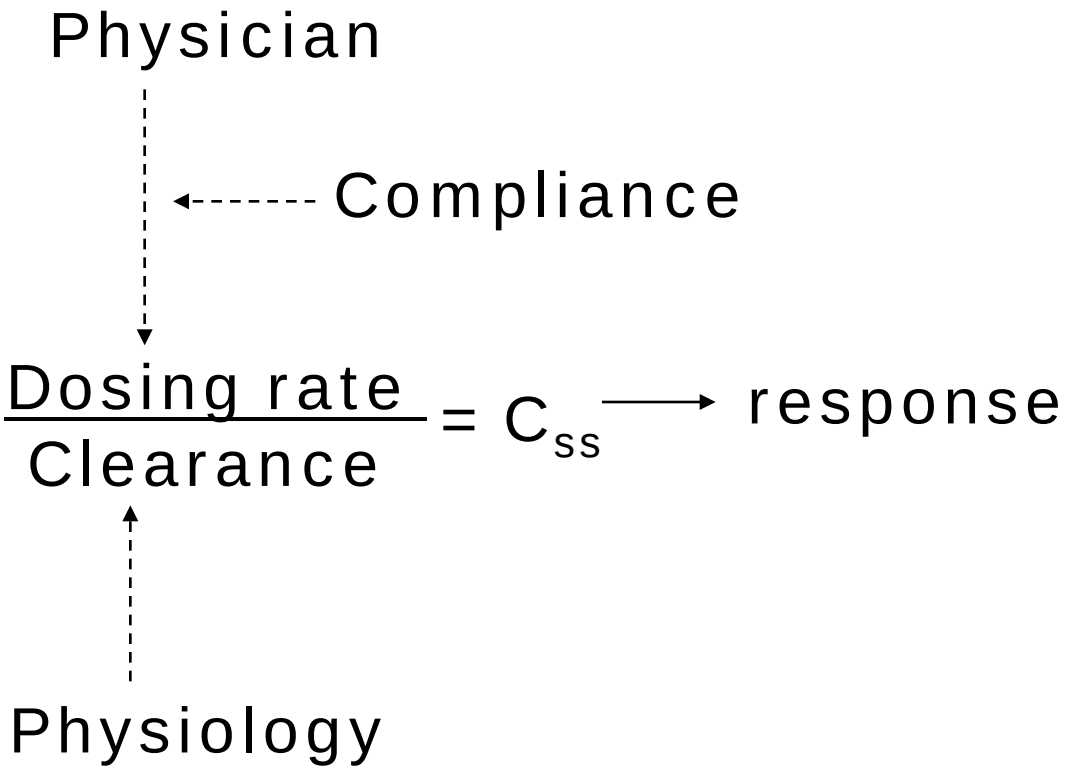
LINEAR vs. LOGARITHMIC CONCENTRATION SCALE

	Linear	Logarithmic
Visual image	Correct	Distorted
Graphically-based calculations	Dangerous	Possible

YOU CAN’T DRAW PICTURES OF CLEARANCE

CLEARANCE

- Independent variable best describing the capacity for drug removal
- Most have units of volume/time
- Usually accomplished by a clearing organ
- Upper limit: blood flow to clearing organ

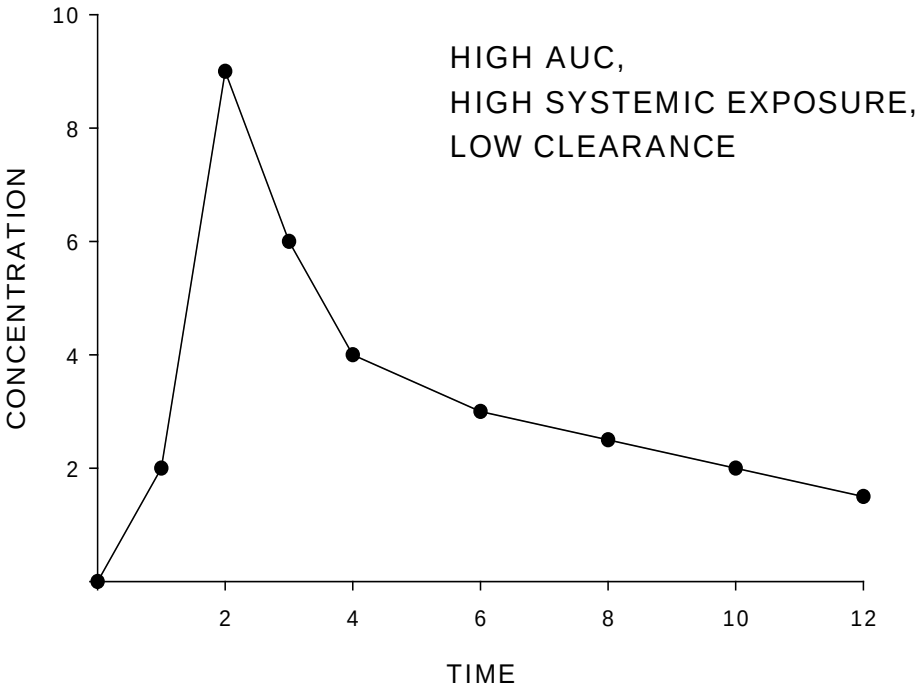

Physician
Compliance
Dosing rate
Clearance
= C_{ss}
response
Physiology

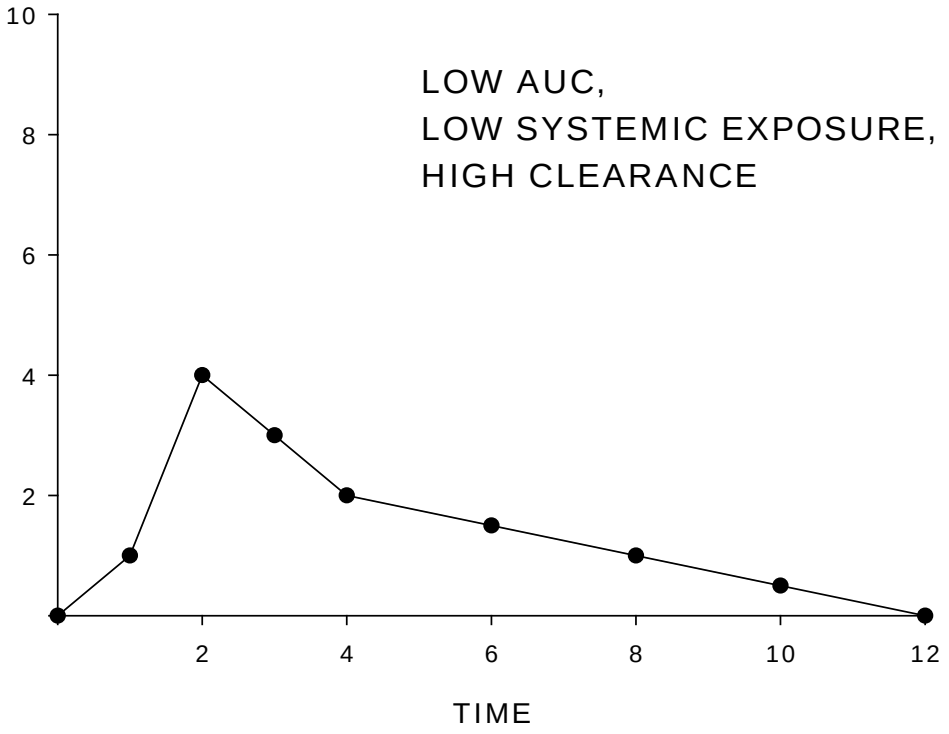
COMPLIANCE

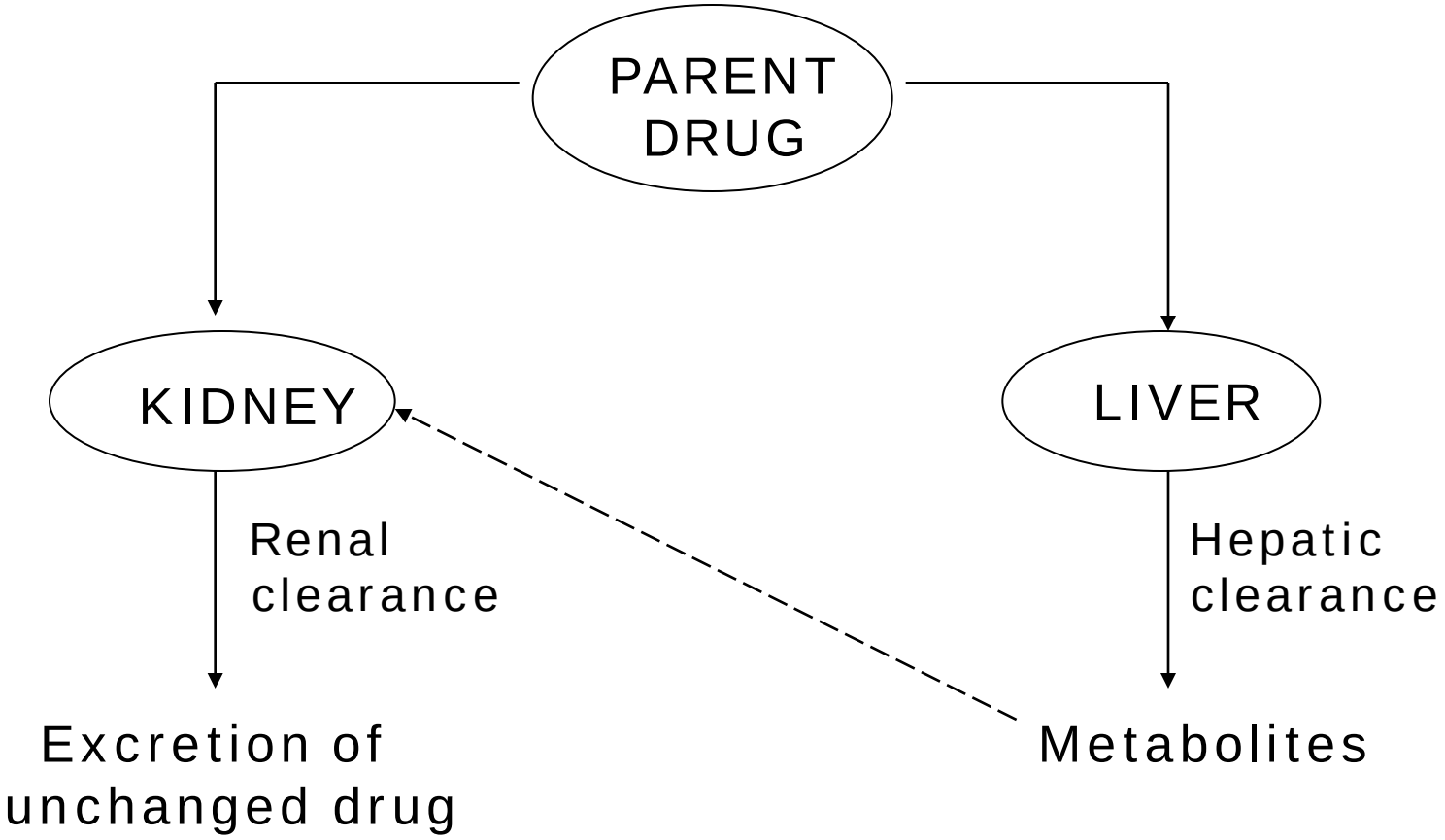
- Acting in accordance with another's command, demand, request, rule, or wish
- Acquiescence
- Disposition or tendency to yield to others

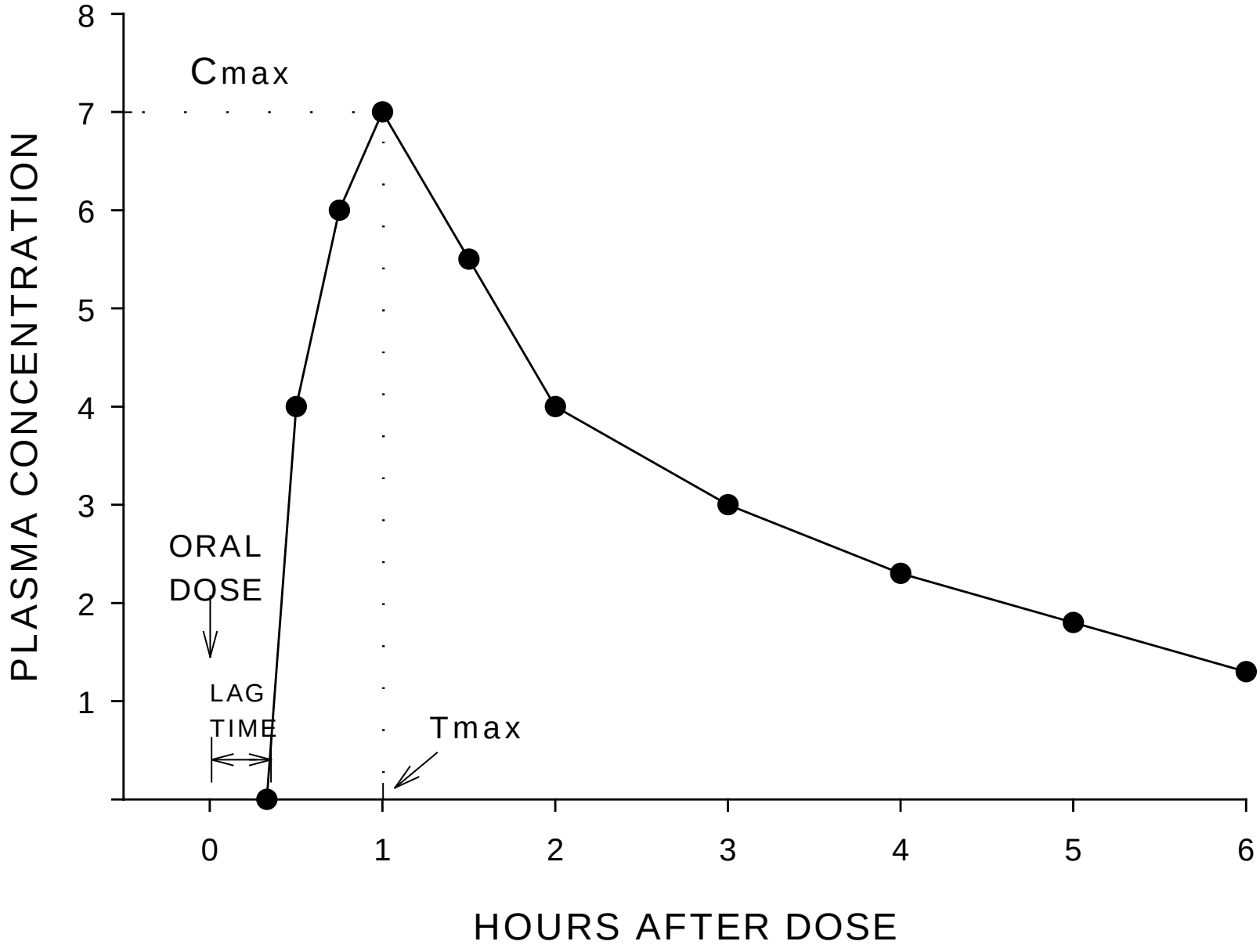
ADHERENCE

- Faithful attachment, devotion
- Close following
- Carrying out without deviation


HIGH AUC,
HIGH SYSTEMIC EXPOSURE,
LOW CLEARANCE
CONCENTRATION
TIME
10
8
6
4
2
2
4
6
8
10
12


LOW AUC,
LOW SYSTEMIC EXPOSURE,
HIGH CLEARANCE
TIME
10
8
6
4
2
2
4
6
8
10
12


PARENT DRUG
KIDNEY
LIVER
Renal clearance
Hepatic clearance
Excretion of unchanged drug
Metabolites


PLASMA CONCENTRATION
8
7
6
5
4
3
2
1
Cmax
ORAL
DOSE
LAG
TIME
Tmax
0
1
2
3
4
5
6
HOURS AFTER DOSE

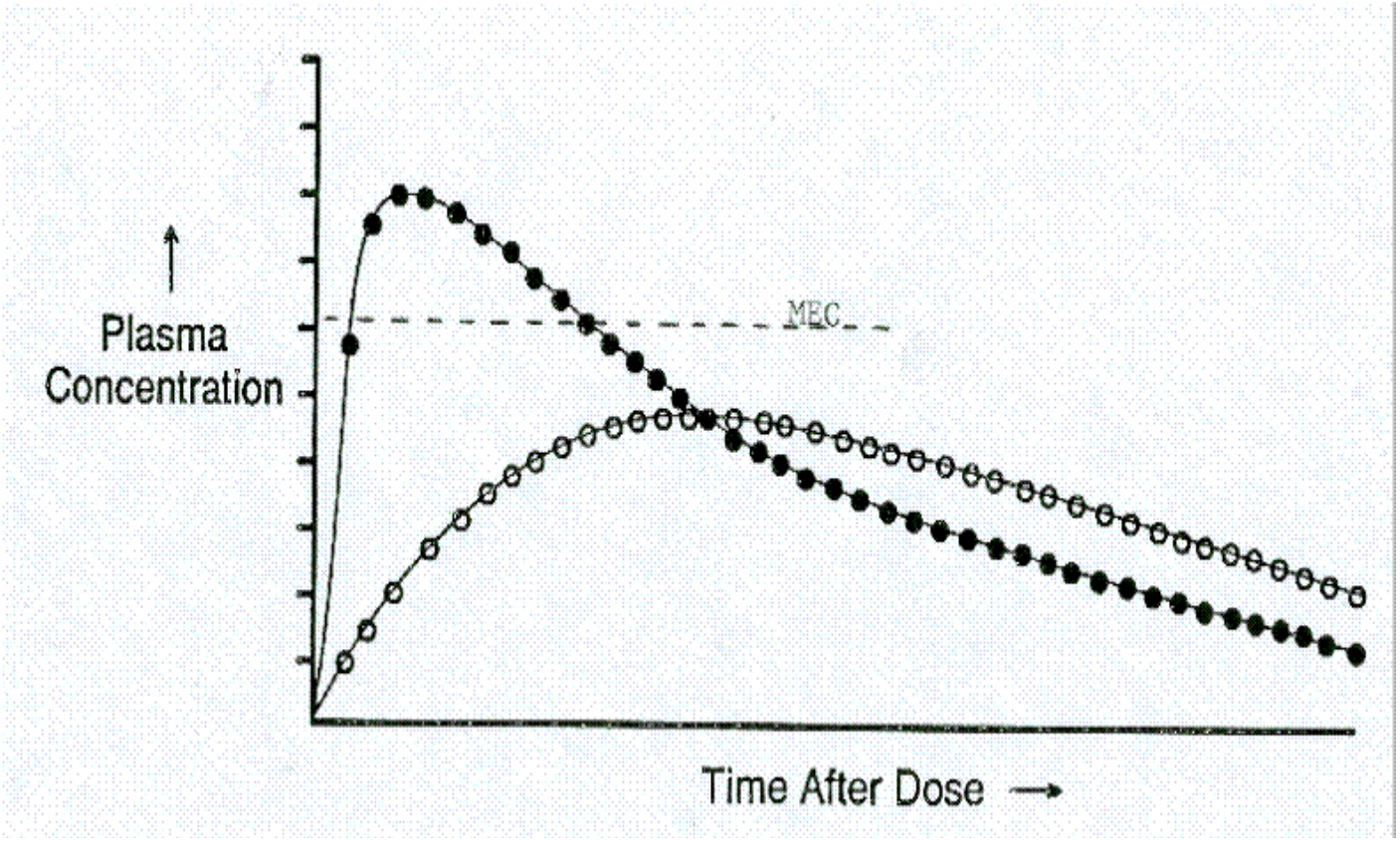
QUANTITATIVE MEASURES

C_{max} : Peak plasma concentration

T_{max} : Time of peak concentration

AUC : Area under the plasma concentration curve (systemic exposure)

Rate of absorption	C_{max}	T_{max}
Rapid	High	Short
Slow	Low	Long


Plasma
Concentration
MEC
Time After Dose

SYSTEMIC AVAILABILITY (ABSOLUTE BIOAVAILABILITY)

$$F = \frac{AUC_{PO}}{AUC_{IV}}$$

(AUC values must be total, not truncated)

Drug	F
Diazepam	>0.90
Alprazolam	>0.90
Acetaminophen	0.80
Zolpidem	0.70
Eletriptan	0.50
Triazolam	0.45
Midazolam	0.30
Ramelteon	0.02

RELATIVE ORAL BIOAVAILABILITY

$$\text{Relative F} = \frac{AUC_{\text{test product}}}{AUC_{\text{reference product}}}$$

BIOEQUIVALENCE OF GENERIC DRUGS

Fundamental premise:

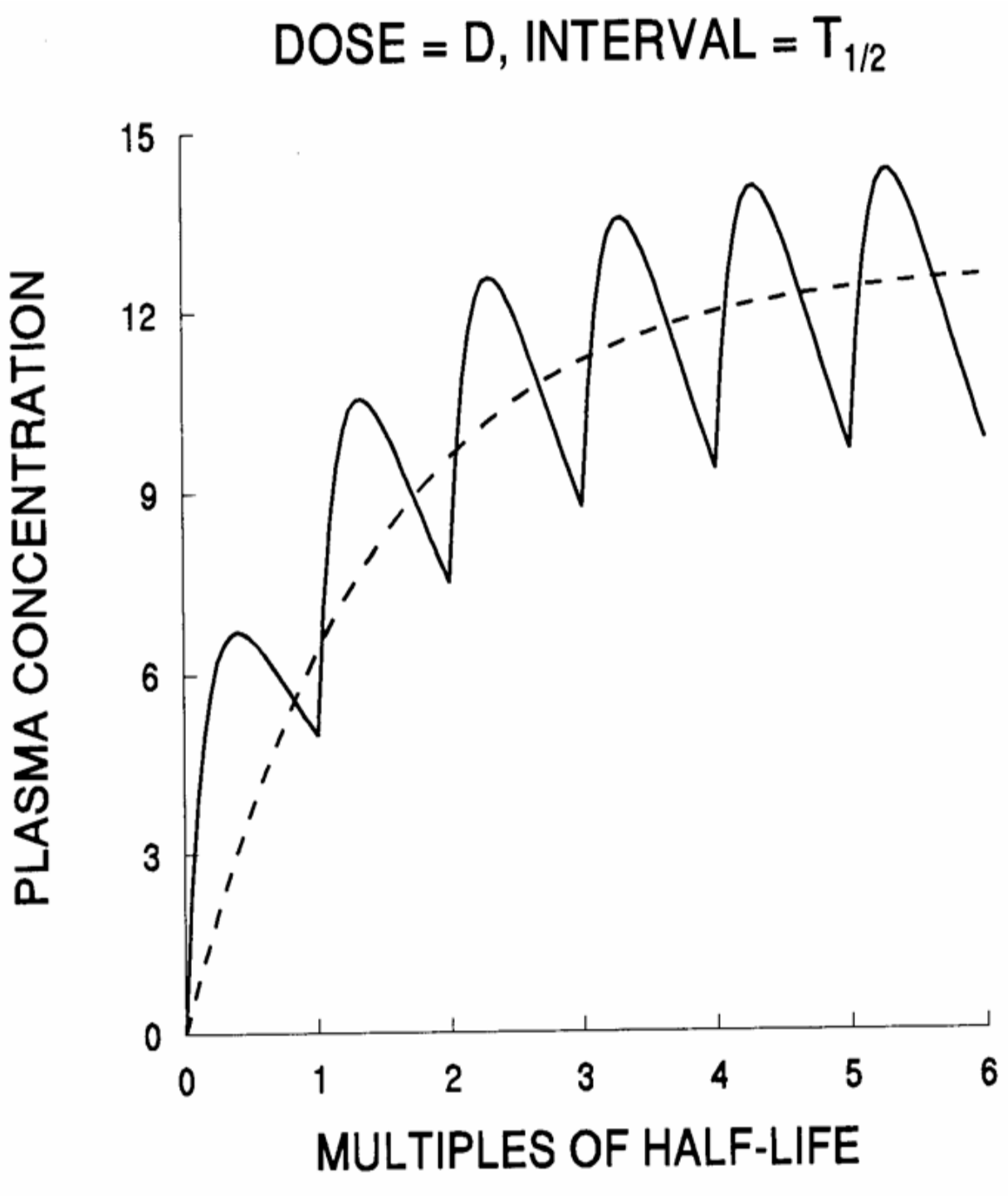
Bioequivalence

Implies

Therapeutic equivalence

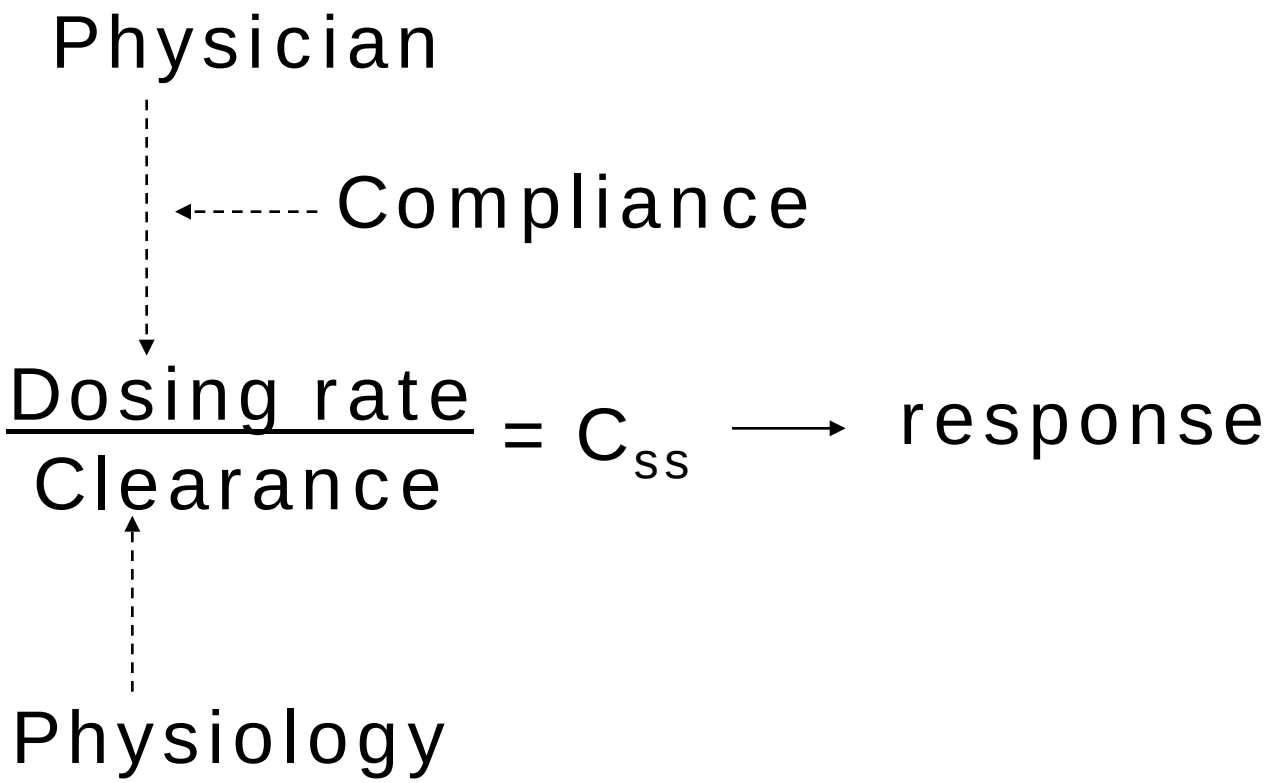
GENERIC SUBSTITUTION

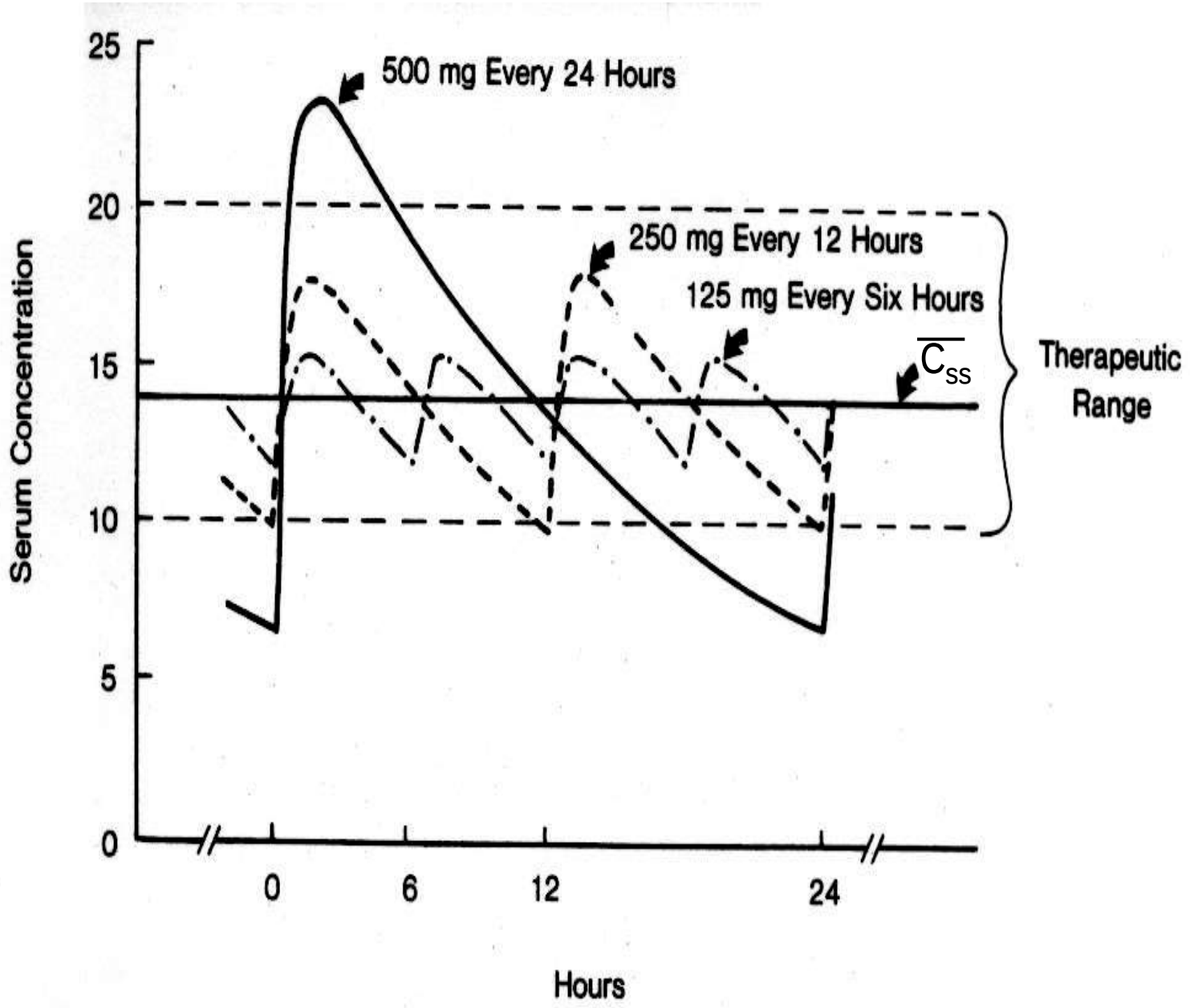
- Is part of the landscape
- Cannot be blamed for clinical changes without plasma level documentation


DOSE = D, INTERVAL = $T_{1/2}$
PLASMA CONCENTRATION
15
12
9
6
3
0
0
1
2
3
4
5
6
MULTIPLES OF HALF-LIFE

INTERDOSE FLUCTUATION

“Up and down” variation in plasma level, determined by how the total daily dose is divided into discrete doses.


Physician
Compliance
Dosing rate
Clearance
= C_{ss}
response
Physiology


25
20
15
10
5
0
Serum Concentration
500 mg Every 24 Hours
250 mg Every 12 Hours
125 mg Every Six Hours
$\overline{C_{ss}}$
Therapeutic Range
0
6
12
24
Hours

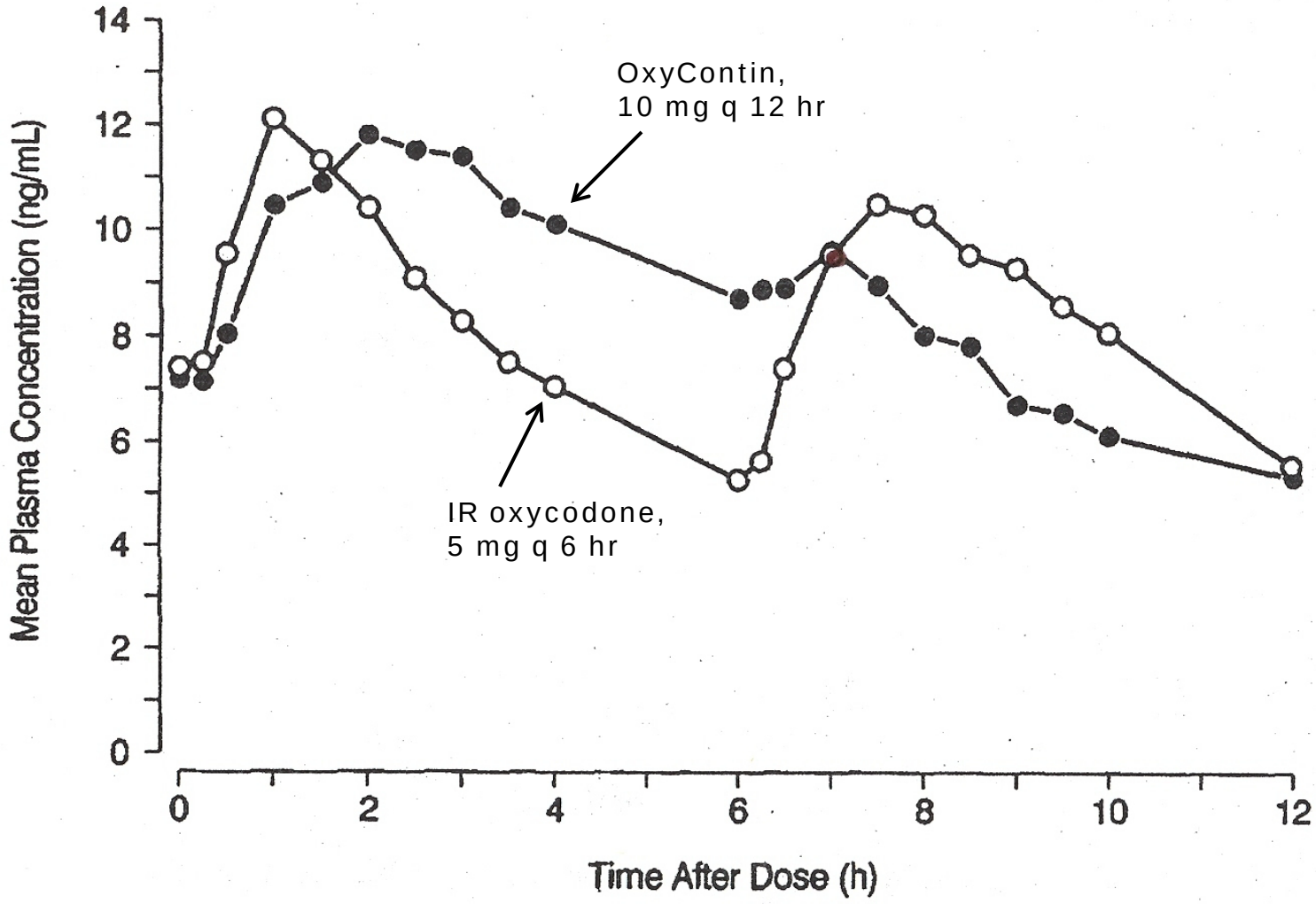
COMPLIANCE WITH ANTICONVULSANT THERAPY

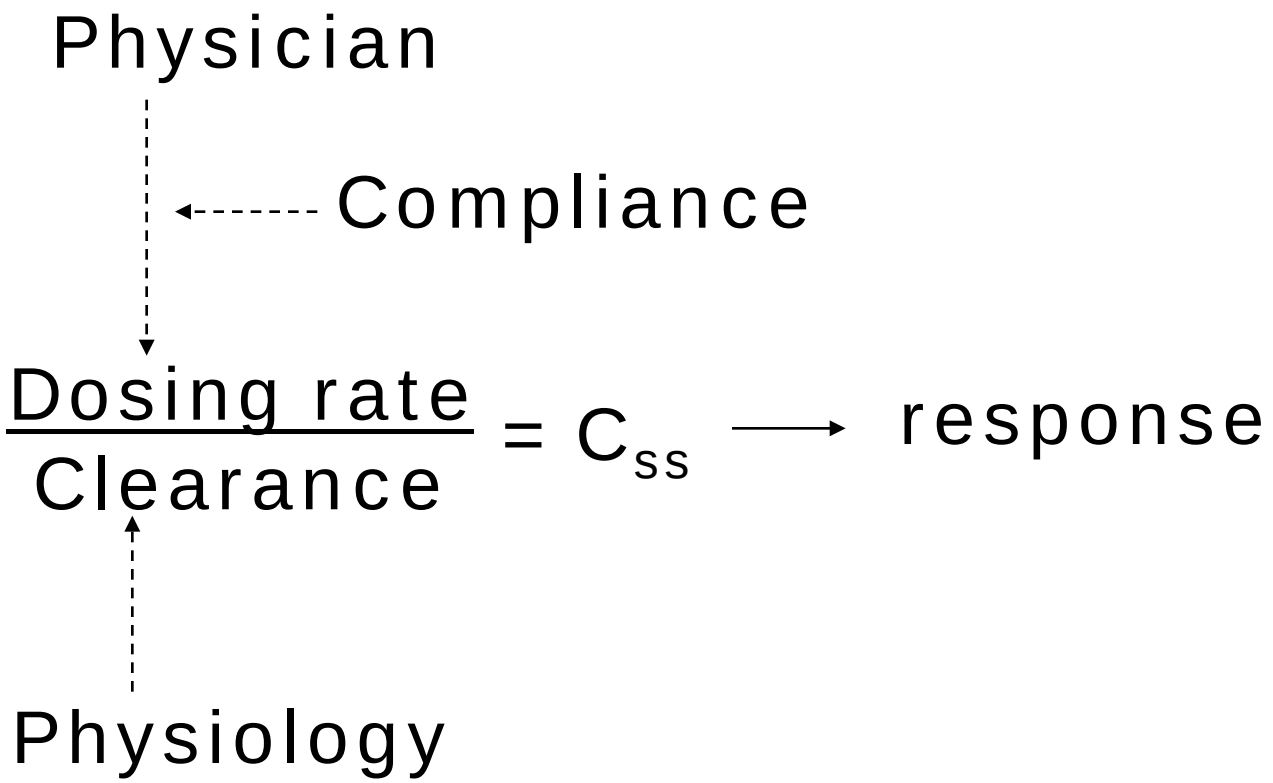
Doses Per day	% compliance
1	87%
2	81%
3	77%
4	39%

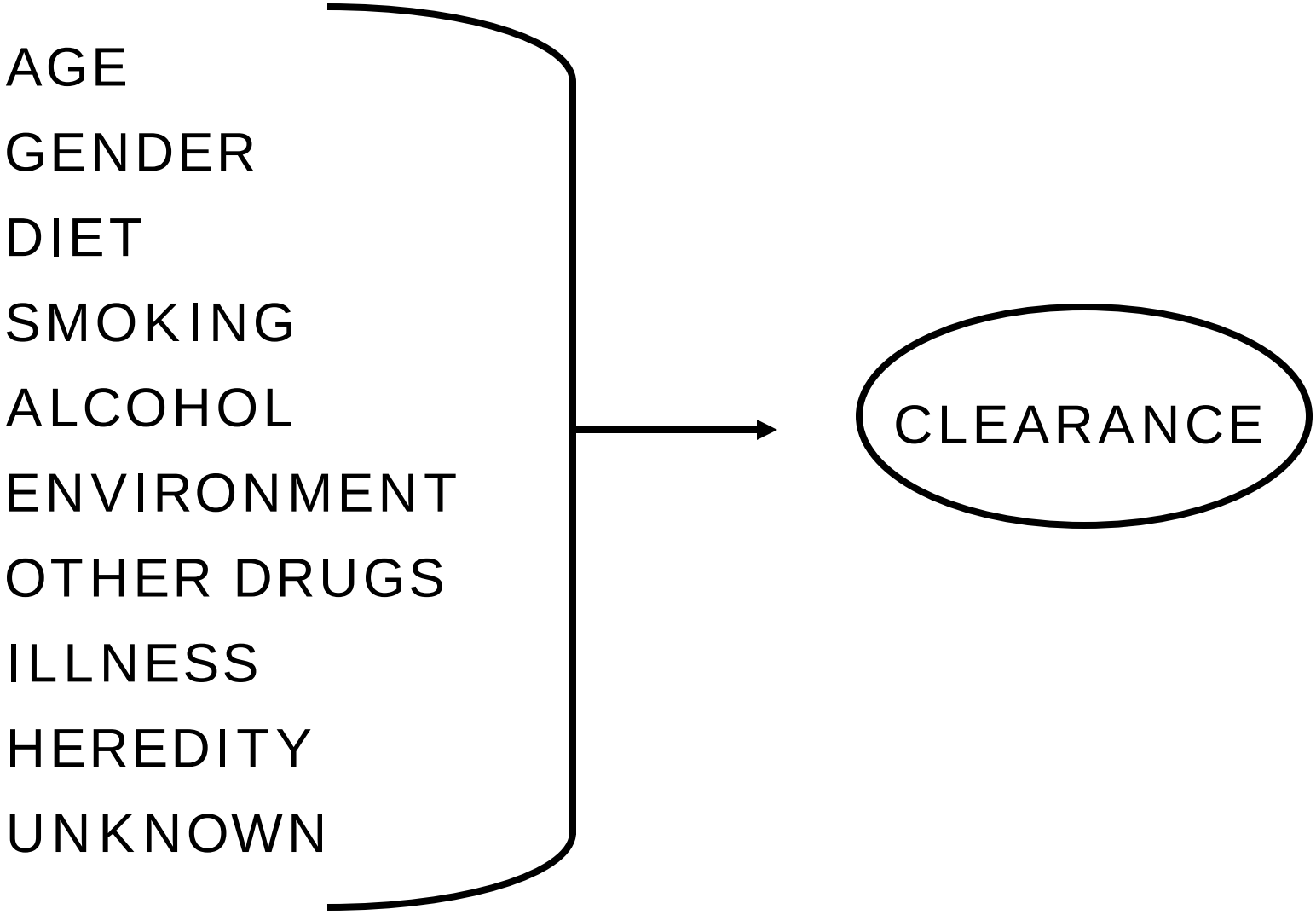
JAMA 1989; 261: 3273

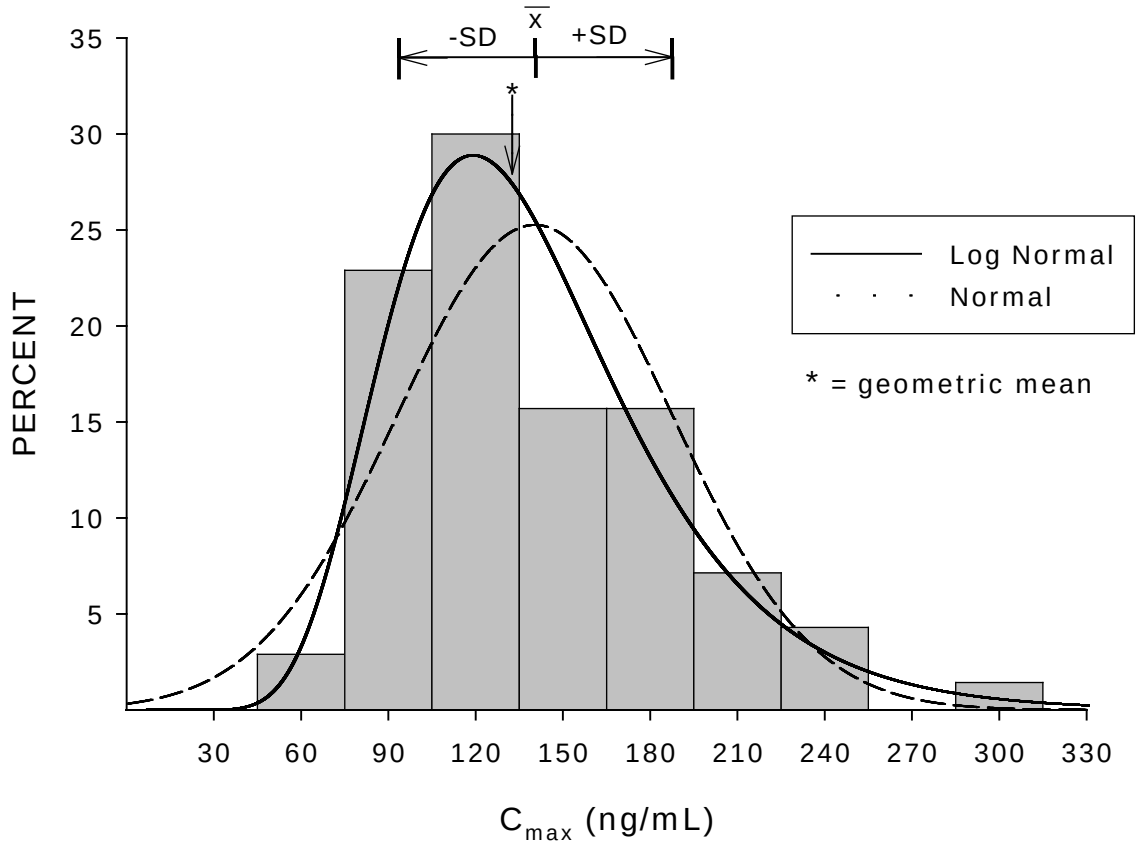
“Slow-release” preparations blunt the peaks, allowing less frequent dosage.

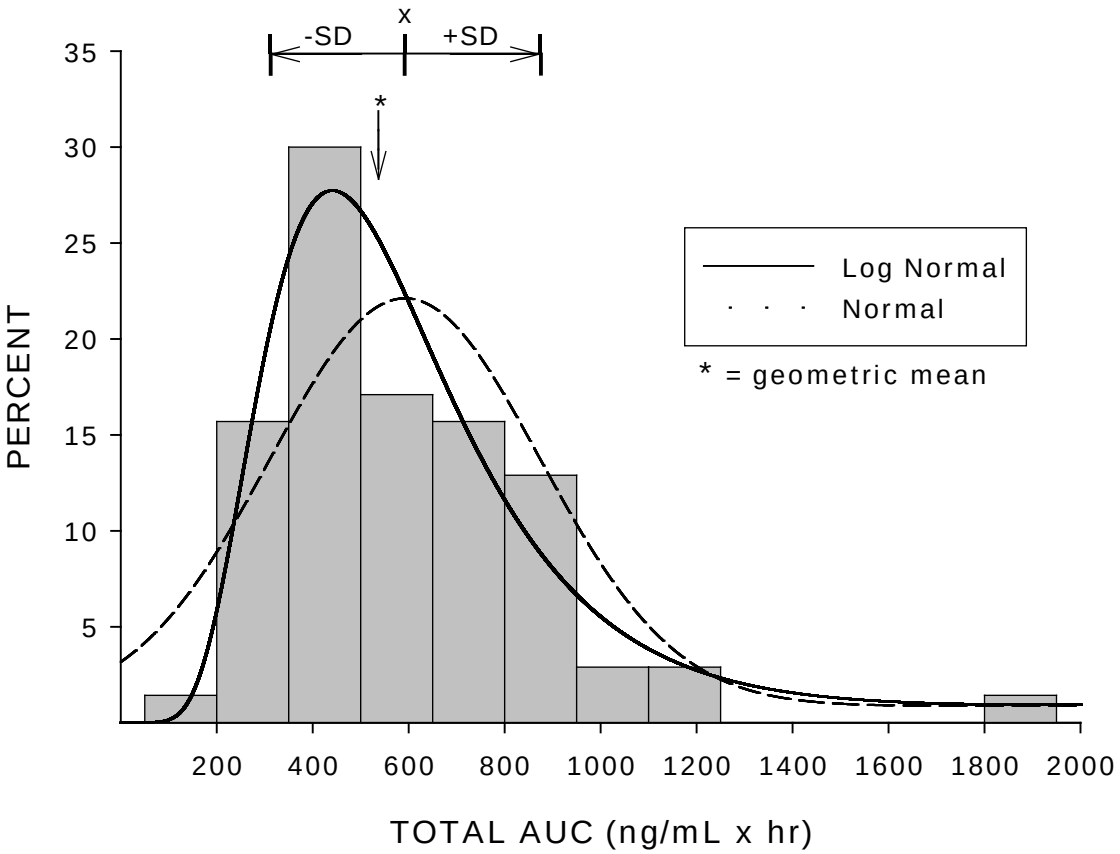
Clinical Therapeutics 1996; 18:95-105




Physician
Compliance
Dosing rate
Clearance
= C_{ss}
response
Physiology


AGE
GENDER
DIET
SMOKING
ALCOHOL
ENVIRONMENT
OTHER DRUGS
ILLNESS
HEREDITY
UNKNOWN
CLEARANCE


-SD
x̄
+SD
*
35
30
25
20
15
10
5
PERCENT
Log Normal
Normal
* = geometric mean
30
60
90
120
150
180
210
240
270
300
330
Cmax (ng/mL)


x
-SD
+SD
*
35
30
25
20
15
10
5
PERCENT
Log Normal
Normal
* = geometric mean
200
400
600
800
1000
1200
1400
1600
1800
2000
TOTAL AUC (ng/mL x hr)

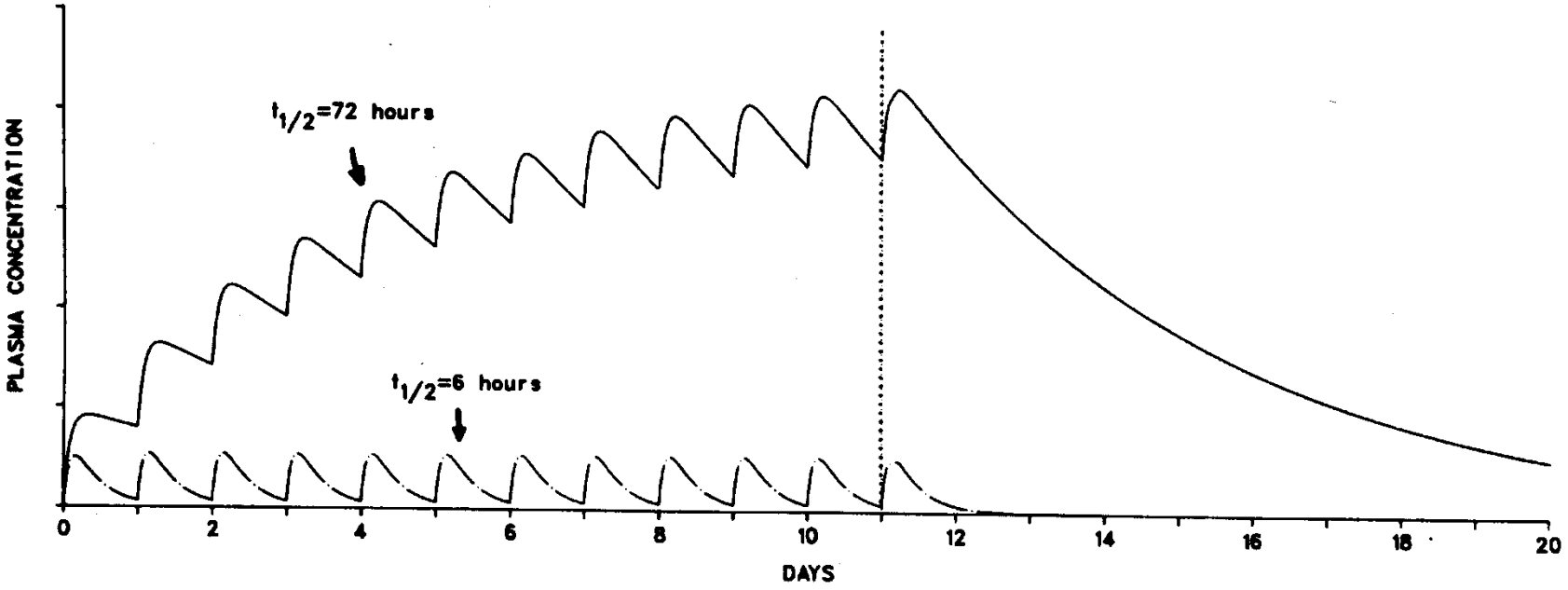
DRUG ACCUMULATION

- Not the same as C_{ss} or $\overline{C}_{ss}$
- A *relative* term: exposure at steady-state compared to first dose
- Depends on the relation between dose interval (T) and $t_{½}$

If $T >> t_{½}$, not much accumulation.

If $T << t_{½}$, a lot of accumulation.

Drug Metabolism Reviews 1983; 14: 251-292



GIVEN THE PREVALENCE OF POLYPHARMACY, CLINICALLY IMPORTANT DRUG INTERACTIONS ARE UNUSUAL

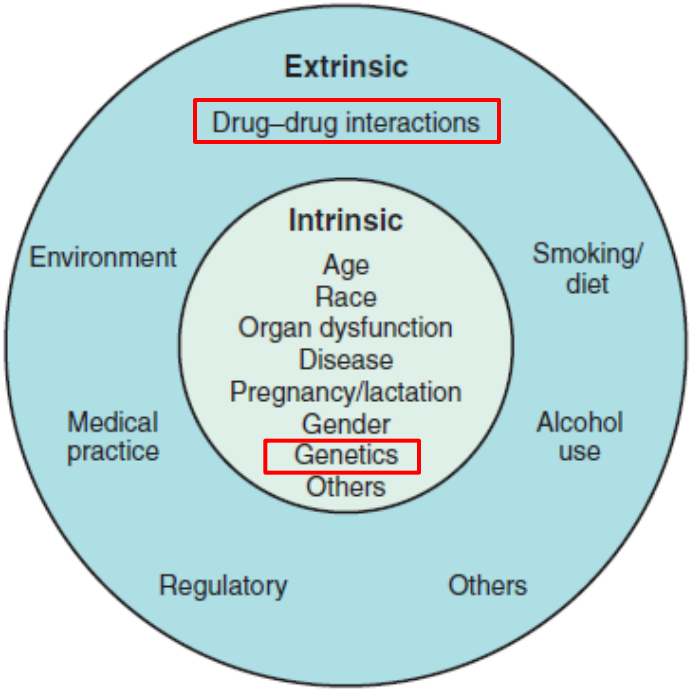
- Require increased vigilance or monitoring
- Require dose adjustment
- Require avoidance of a drug
- Are hazardous or life-threatening

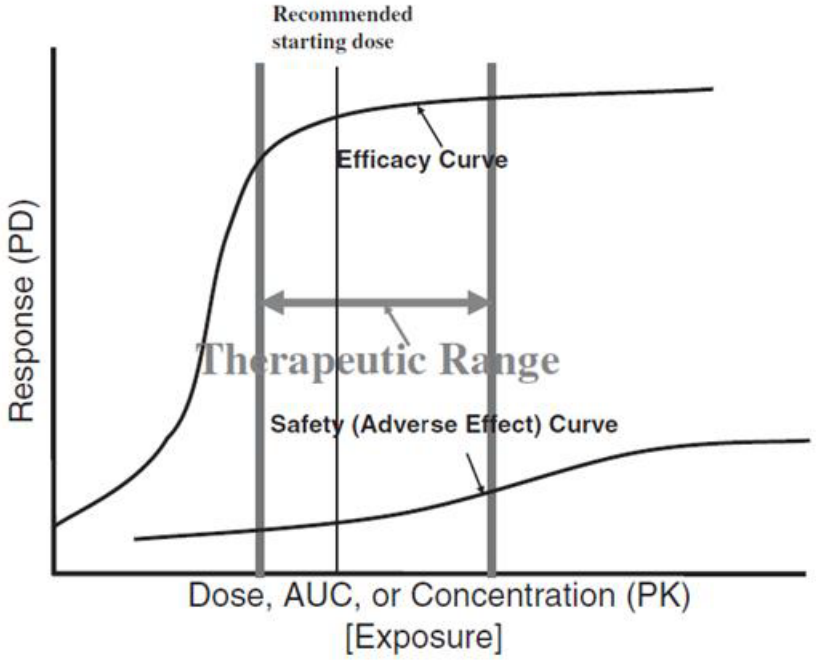
Drug-Drug Interactions and Pharmacogenomic Variation as Sources of Clinical Pharmacologic Variability: Principles and Evaluation in Drug Development

Karthik Venkatakrishnan, Ph.D

Evaluating Clinical Pharmacologic Variability in Drug **D**iscovery, **D**evelopment, **R**egulation and **U**tilization

1. Identify sources of variability
2. Quantify (estimate) effect
3. Assess clinical significance
4. Guide risk management and prescribing





Huang SM and Temple R. Clinical Pharmacology and Therapeutics. 84(3): 287-294, 2008
Huang SM and Lesko LJ. Journal of Clinical Pharmacology. 44: 559-569, 2004

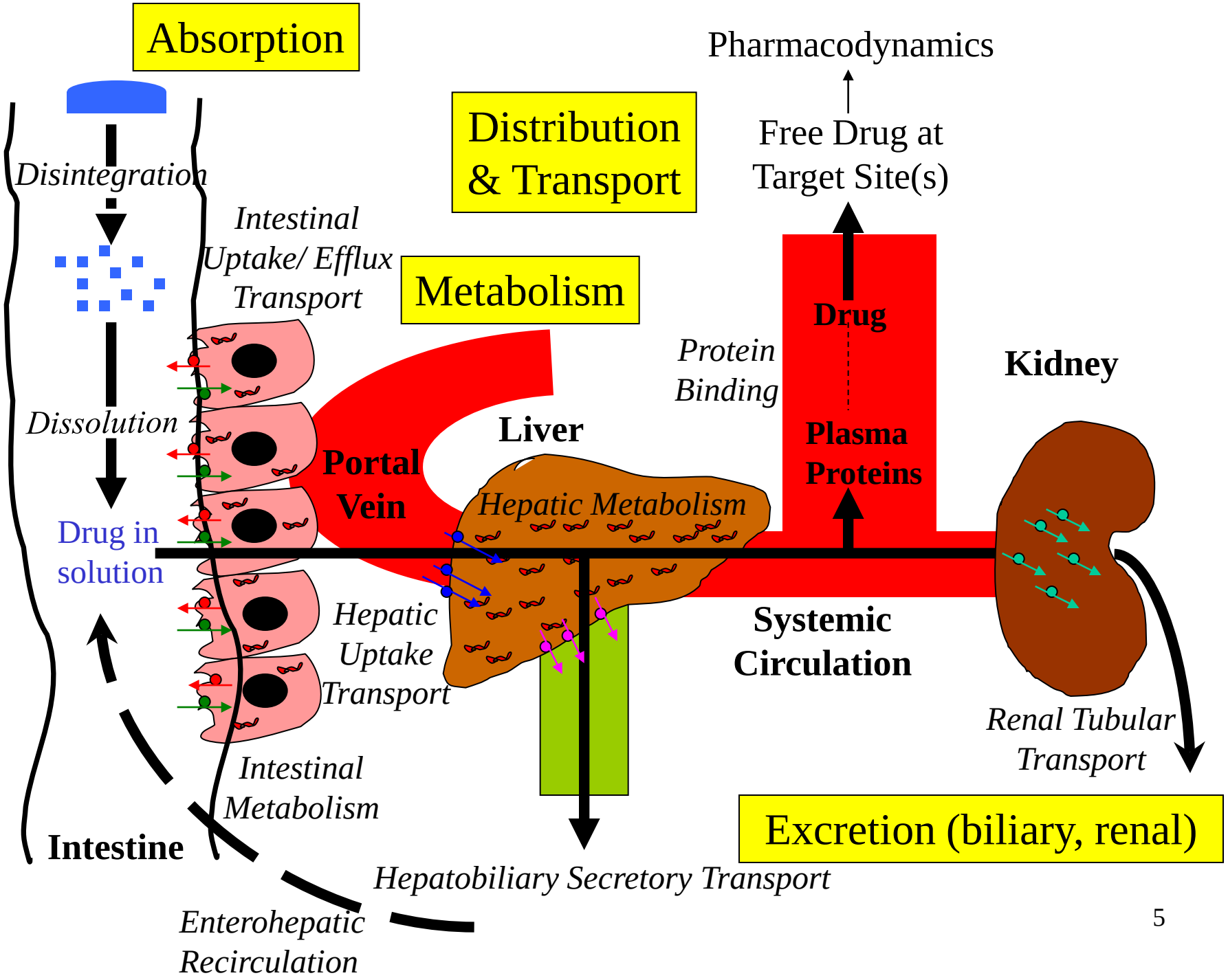
Drug-Drug Interactions

- A clinically significant drug-drug interaction (DDI) occurs when the therapeutic or toxic effects of a medication are altered by administration with another drug.

- Mechanistic Classification
  - Pharmacokinetic Interactions
    - Drug X alters the absorption (A), distribution (D), metabolism (M) or elimination (E) of Drug Y resulting in altered blood/ target organ levels leading to potential effects on efficacy and/or safety
  - Pharmacodynamic Interactions
    - Drug X alters the pharmacologic effect (efficacy and/or safety) of Drug Y without affecting its pharmacokinetics

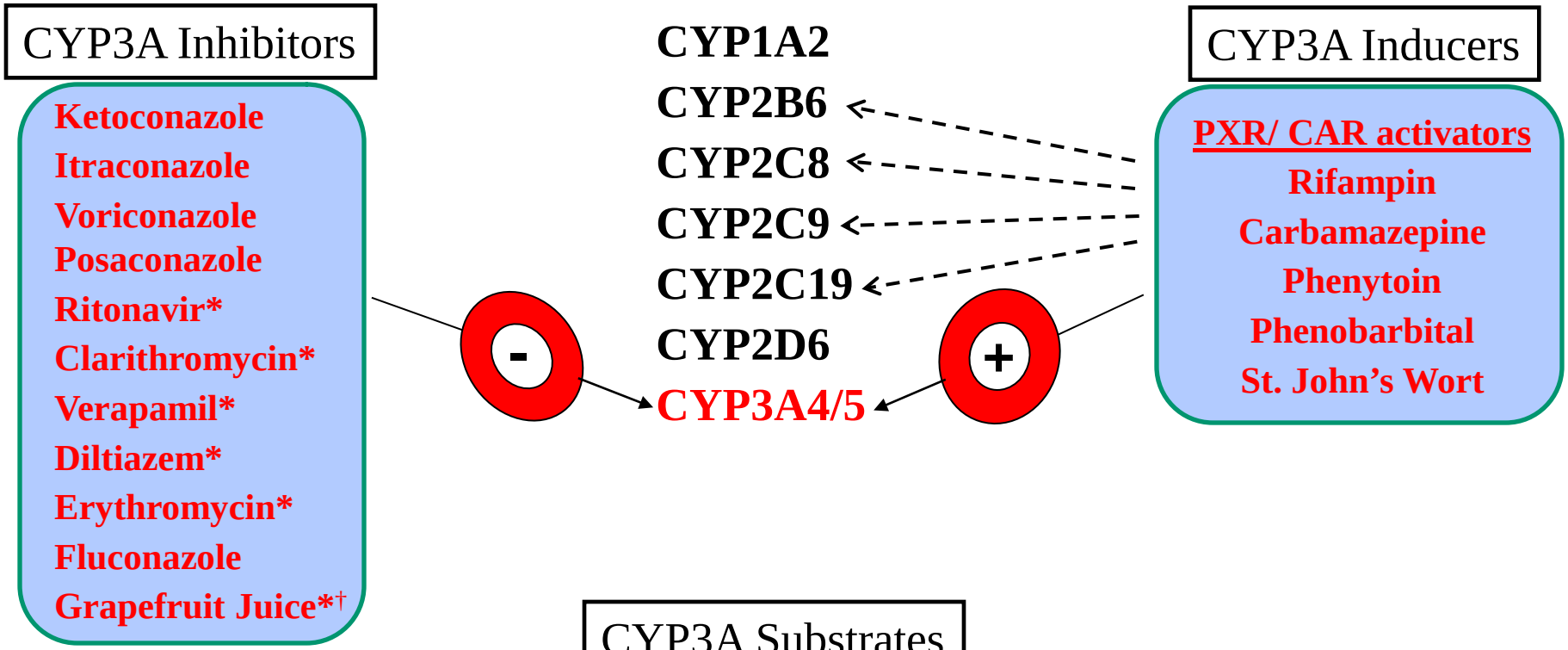
Pharmacogenomic Variation

- Genetic polymorphisms can alter the activity and/ or expression of molecular determinants of pharmacology (PK or PD), thereby influencing the therapeutic and/ or toxic effects of a medication
- Examples of Molecular Mechanisms
  - Single Nucleotide Polymorphisms
    - Coding Regions (Synonymous vs. Non-synonymous)
    - Noncoding regions (e.g., Promoter/ Enhancer; Intronic)
  - Insertions and Deletions
  - Copy Number Variation (CNV)
- Categories of Pharmacogenomic Variation
  - ADME Pharmacogenomics
    - Germline genomic variation -- drug metabolizing enzymes/ transporters
  - Target Pharmacogenomics
    - Germline variation -- drug targets/ pathways relevant to efficacy or safety
    - Somatic variation in cancer genome (Oncology)
    - Genetic variation in microbial genome (Infectious diseases)


Absorption
Pharmacodynamics
Distribution & Transport
Free Drug at Target Site(s)
Disintegration
Intestinal Uptake/ Efflux Transport
Metabolism
Drug
Protein Binding
Kidney
Dissolution
Liver
Portal Vein
Plasma Proteins
Hepatic Metabolism
Drug in solution
Hepatic Uptake Transport
Systemic Circulation
Renal Tubular Transport
Intestinal Metabolism
Intestine
Excretion (biliary, renal)
Hepatobiliary Secretory Transport
Enterohepatic Recirculation

Clinically Important Drug Metabolizing Cytochromes P450

Selected examples of Clinically Significant
Substrates, Inhibitors and Inducers of **CYP3A**



CYP3A Substrates

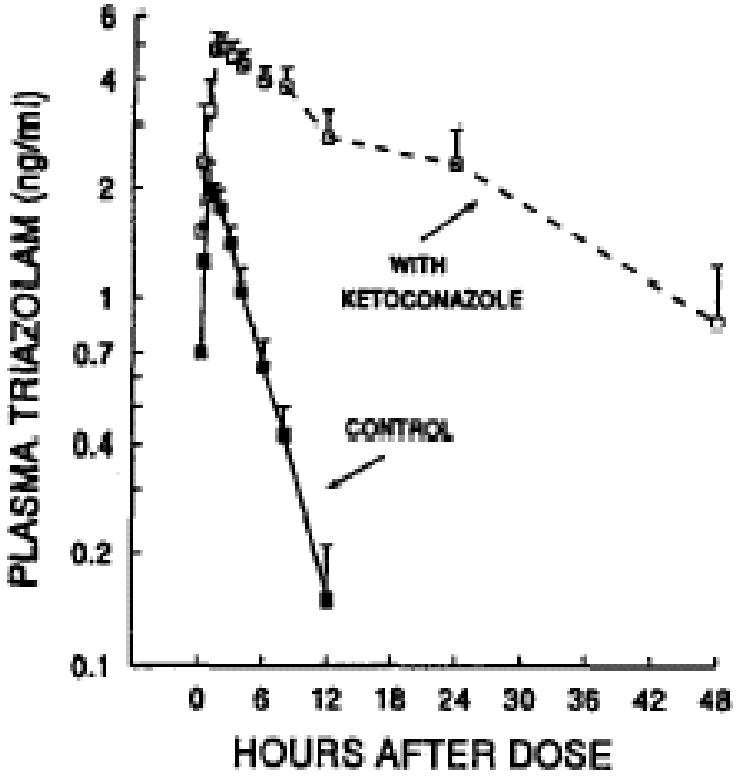
Midazolam, Alprazolam, Pimozide, Quetiapine, Nifedipine, Simvastatin, Atorvastatin, Cyclosporine A, Tacrolimus, Sirolimus, Sildenafil, Everolimus, Vincristine, Docetaxel (~50% of clinically used small molecule drugs are metabolized by CYP3A)

*Mechanism-based inactivator (time-dependent inhibitor)
†Intestine-selective CYP3A inhibitor

Examples of CYP3A Inhibition DDI

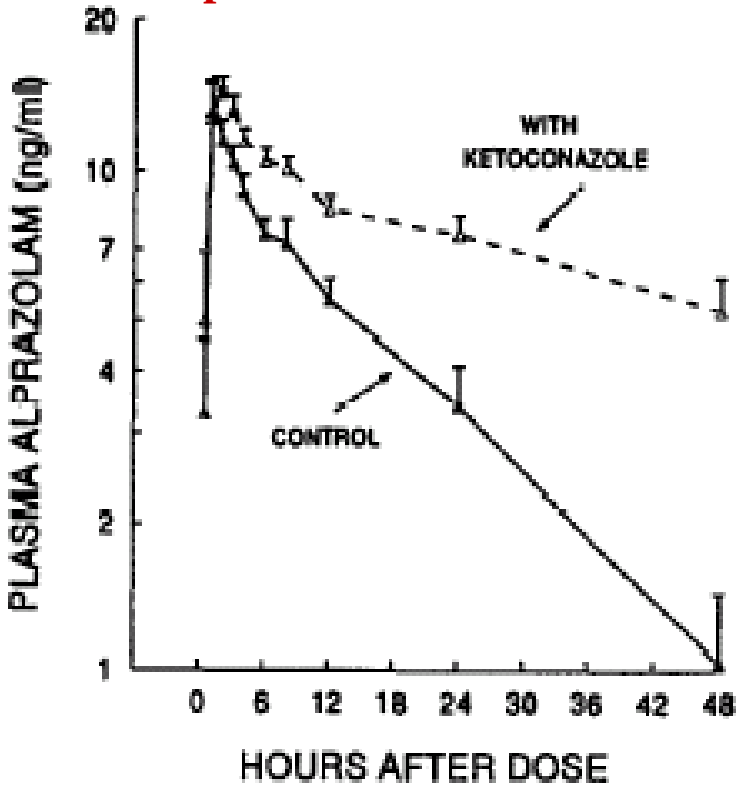
Effect of Ketoconazole on Triazolam vs. Alprazolam PK

Triazolam



C_{max}: 2.1-fold ↑
AUC: **14-fold ↑**
$t_{1/2}$: 6-fold ↑

Alprazolam

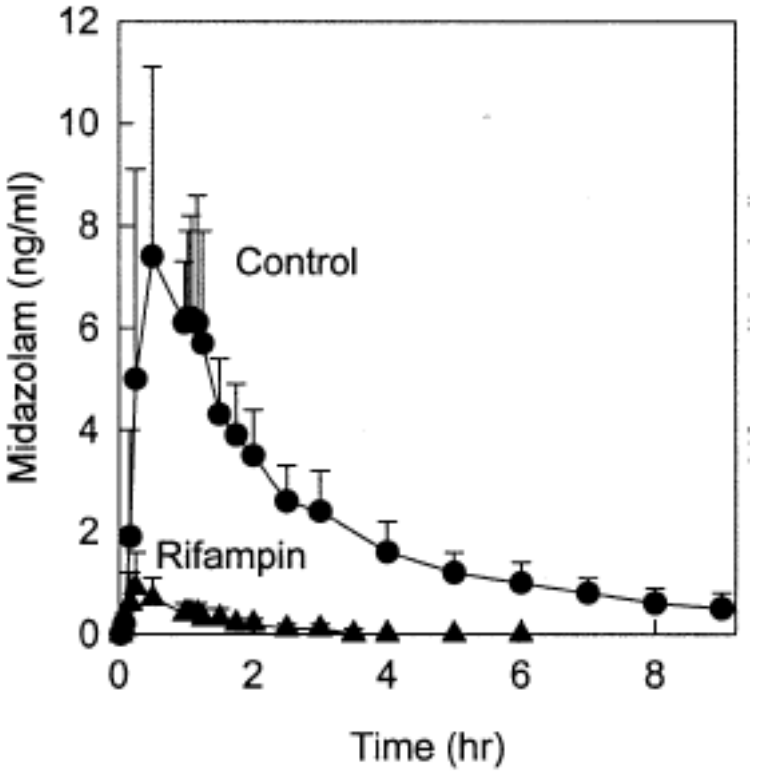


C_{max}: 1.1-fold ↑
AUC: **4-fold ↑**
$t_{1/2}$: 4-fold ↑

Greenblatt DJ et al., Clin Pharmacol Ther. 64: 237-47, 1998

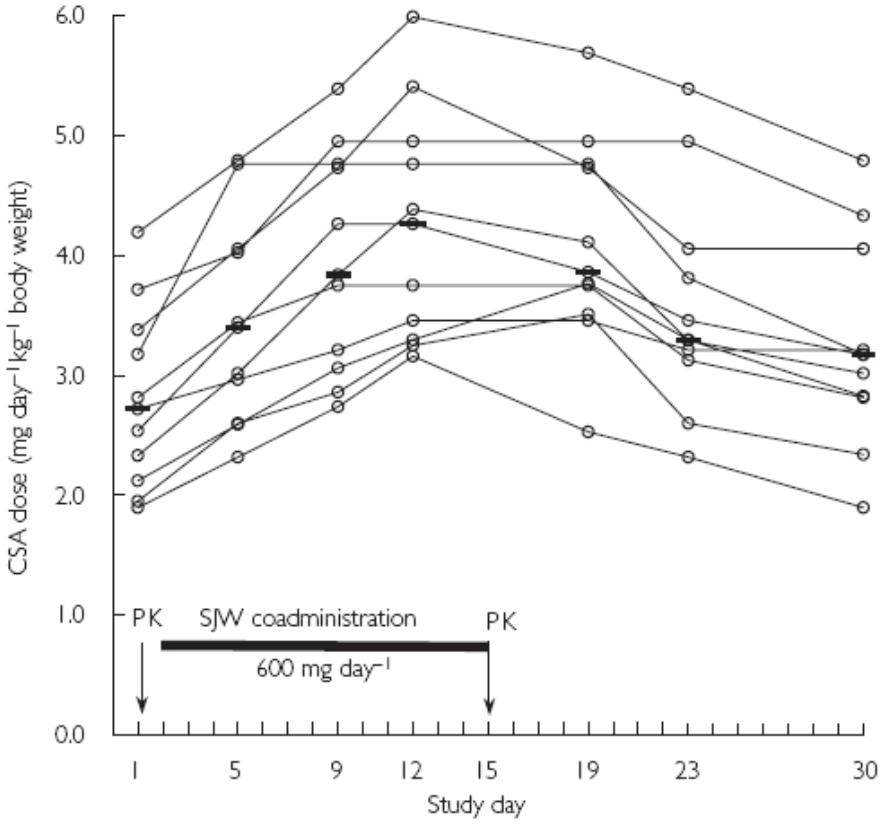
Examples of CYP3A Induction DDI

Midazolam – Rifampin Interaction



Cyclosporine A – St. John's Wort Interaction

Effect on Dose requirement



Kharasch ED et al., Clin Pharmacol Ther 76:452-66, 2004

Bauer S et al., Br J Clin Pharmacol 55: 203–211, 2003

CYP2D6 Genetic Polymorphisms

- CYP2D6 is one of the best characterized drug-metabolizing enzymes with clinically important genetic polymorphisms
- Multiple alleles result in a spectrum of activity depending on the specific diplotype in an individual
  - Extensive metabolizers (EM) – “normal” activity (AS 1-2)
  - Intermediate metabolizers (PM) – reduced activity (AS 0.5)
  - Poor metabolizers (PM) – virtually absent activity (AS 0)
  - Ultrarapid metabolizers (URM) – increased activity (AS > 2)
- *CYP2D6* allele frequencies differ between racial/ ethnic groups resulting in corresponding differences in PM/ URM frequencies.
  - PM: 6-10% of Caucasians, 2% of Asians, ~10% of African Americans
  - URM: 1-10% in Caucasians, substantially higher (16-28%) in North African/ Middle Eastern populations.

Examples of Clinical Implications of CYP2D6 Pharmacogenetics

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Codeine Therapy in the Context of *Cytochrome P450 2D6* (*CYP2D6*) Genotype

KR Crews[1], A Gaedigk[2], HM Dunnenberger[3], TE Klein[4], DD Shen[5,6], JT Callaghan[7,8], ED Kharasch[9] and TC Skaar[7]

CYP2D6 Genotype Information to Guide Pimozide Treatment in Adult and Pediatric Patients: Basis for the US Food and Drug Administration's New Dosing Recommendations

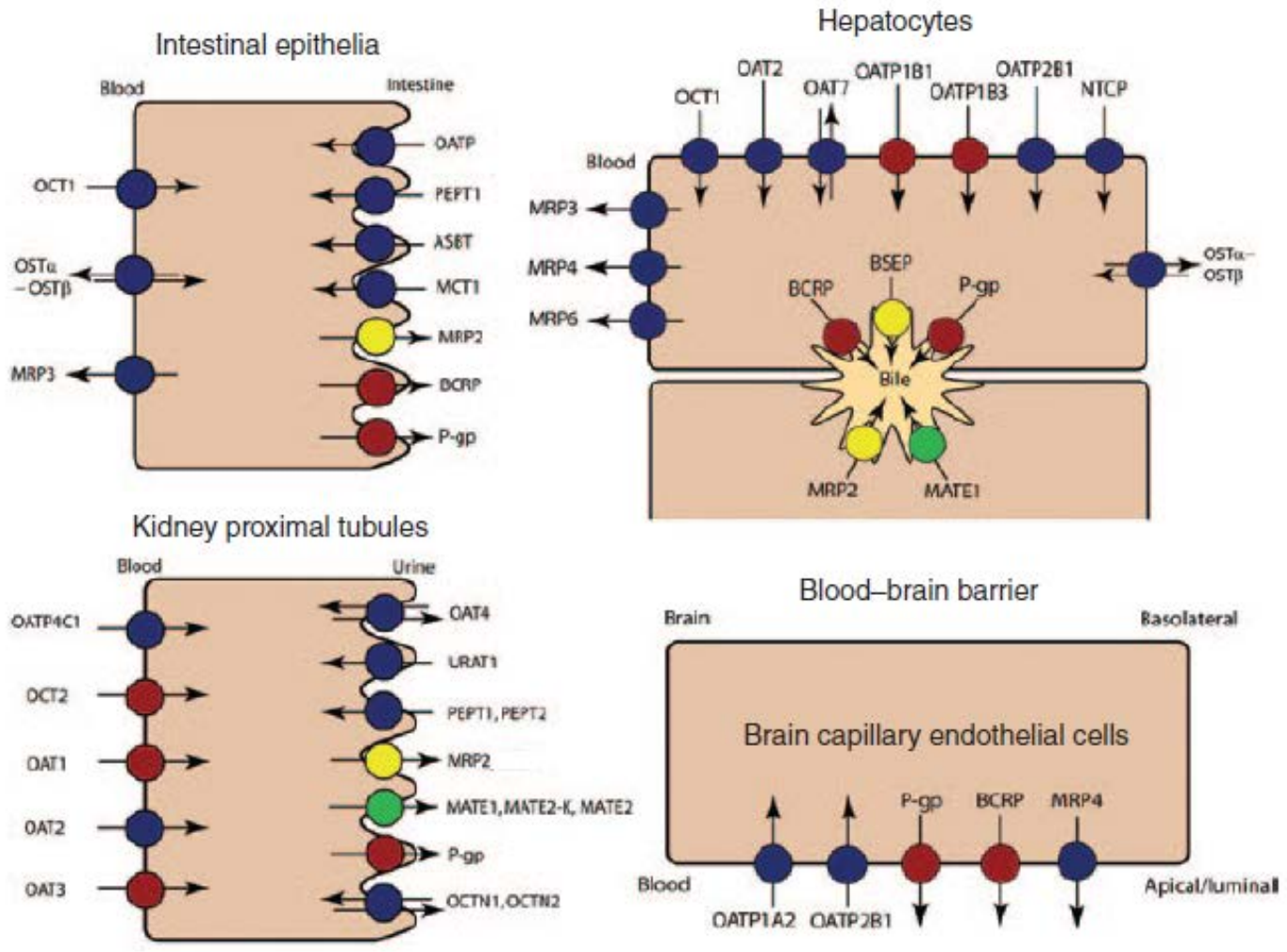
Hobart L. Rogers, PharmD, PhD; Atul Bhattaram, PhD; Issam Zineh, PharmD, MPH; Jogarao Gobburu, MBA, PhD; Mitchell Mathis, MD; Thomas P. Laughren, MD; and Michael Pacanowski, PharmD, MPH

- **Codeine**
  - Bioactivated to morphine via CYP2D6 mediated metabolism
  - URMs at increased risk for morphine toxicity; PMs at risk for inadequate analgesia.
  - CPIC guidelines recommend avoiding codeine use in URMs and PMs
- **Pimozide**
  - CYP2D6-mediated metabolism is a major contributor to overall clearance
    - Population PK model-based oral clearance: 55 L/hr in EM and 15 L/hr in PM
  - Pimozide produces concentration-dependent QT prolongation.
  - USPI revised to require CYP2D6 genotyping at doses > 4 mg/d
  - Maximum dose of 4 mg is specified for PMs (vs. 10 mg for IM/EM patients)

Crews KR et al., Clinical Pharmacology and Therapeutics . 91: 321-6, 2012.
Rogers HL et al., Journal of Clinical Psychiatry. 73: 1187-90, 2012.

Drug Transporters

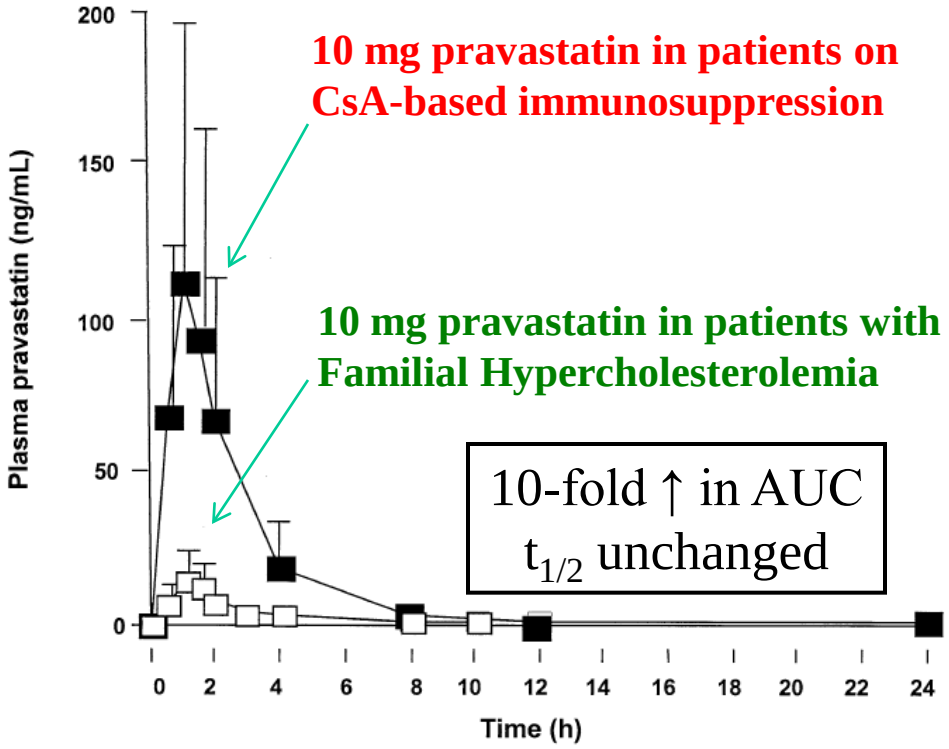
Emerging Molecular Determinants of Drug-Drug Interactions



Zamek-Gliszczynski et al., Clin Pharmacol Ther. 92: 553-556, 2012
Giacomini et al., Nature Rev. Drug Discov. 9: 215-236, 2010

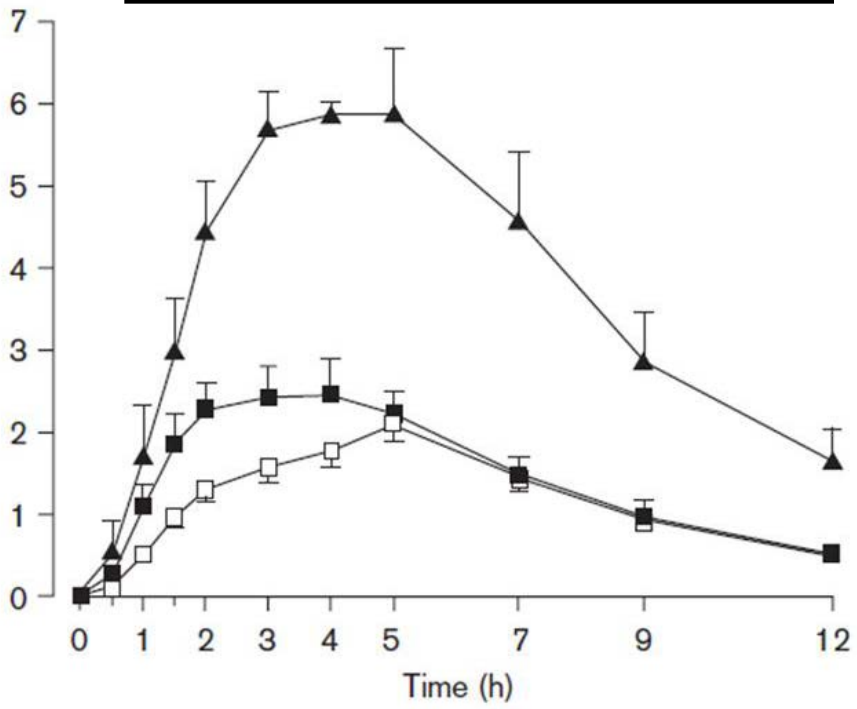
Transporter DDI and Pharmacogenomics: OATP1B1 as an Illustrative Example

Pravastatin-Cyclosporine DDI



Effect of c.521T>C SNP on simvastatin Acid PK

CC vs. TT: 3.2-fold ↑ in AUC

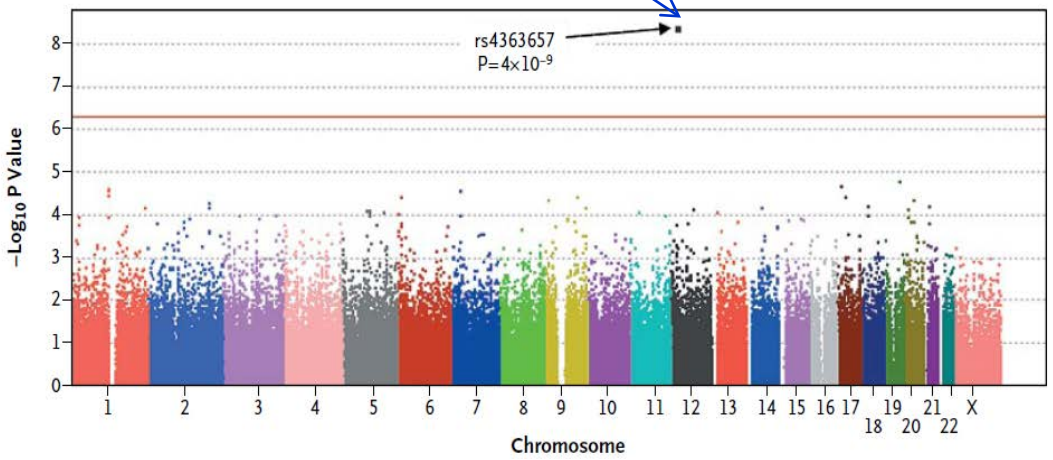


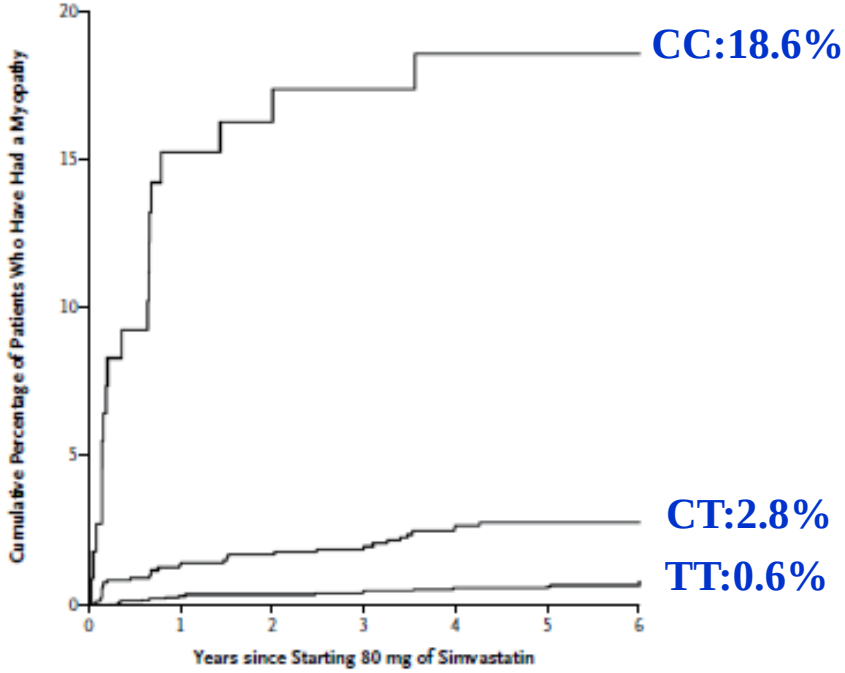
Hedman M et al., Clinical Pharmacology and Therapeutics. 75: 101-109, 2004.
Pasanen MK et al., Pharmacogenetics and Genomics. 16: 873-9, 2006.
Niemi M et al., Pharmacological Reviews. 63: 157-181, 2011.

OATP1B1 c.521T>C SNP and Statin Myopathy

Illustration of Genomewide Association Approach

In strong linkage disequilibrium
With rs4149056 (c.521T>C)





- 80 mg/d simvastatin
- 85 cases with myopathy
- 90 controls

SEARCH Collaborative Group, Link E et. al., New England Journal of Medicine. 359: 789-799, 2008.

Assessment of Drug-Drug Interactions in Drug Development

Drugs Withdrawn from the U.S. Market due to DDIs (1998-2003)

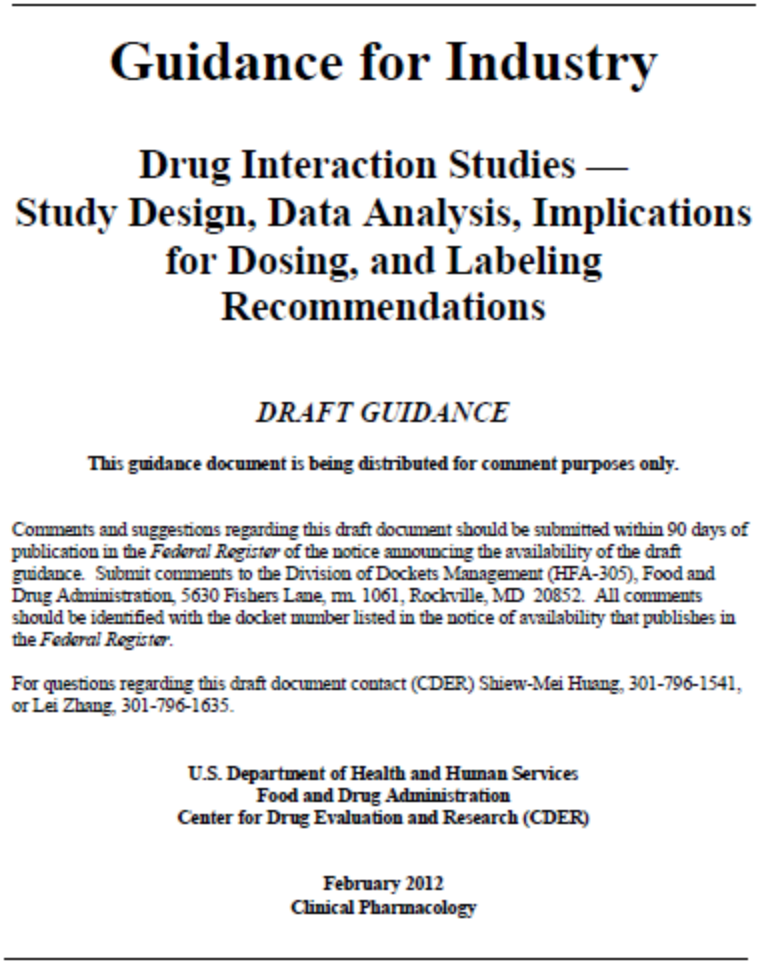
Impact on Contemporary Drug Development

- Mibefradil
  - Mechanism-based CYP3A inhibitor and P-gp inhibitor
  - 26 drugs spanning several therapeutic areas contraindicated
  - Withdrawn within a year of approval
- Terfenadine, Astemizole, Cisapride
  - Sensitive CYP3A Substrates and HERG inhibitors
- Cerivastatin
  - Rhabdomyolysis and fatal drug interactions with gemfibrozil

→ Increased focus on DDI risk assessment in drug discovery and development
→ Experimental *in vitro* models of DDIs to guide clinical risk assessment
→ Mathematical models of *in vitro* to clinical predictions of DDI magnitude
→ Comprehensive regulatory guidances (US and EU) and scientifically guided translation of DDI information into prescribing guidance
→ Strong commitment (academia, industry, regulators) to continually update current opinion based on emerging science

Huang and Lesko, J Clin Pharmacol. 44: 559-69, 2004

Draft US FDA Guidance (2012) and EMA Guideline (2012) Documents



Guidance for Industry

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

DRAFT GUIDANCE

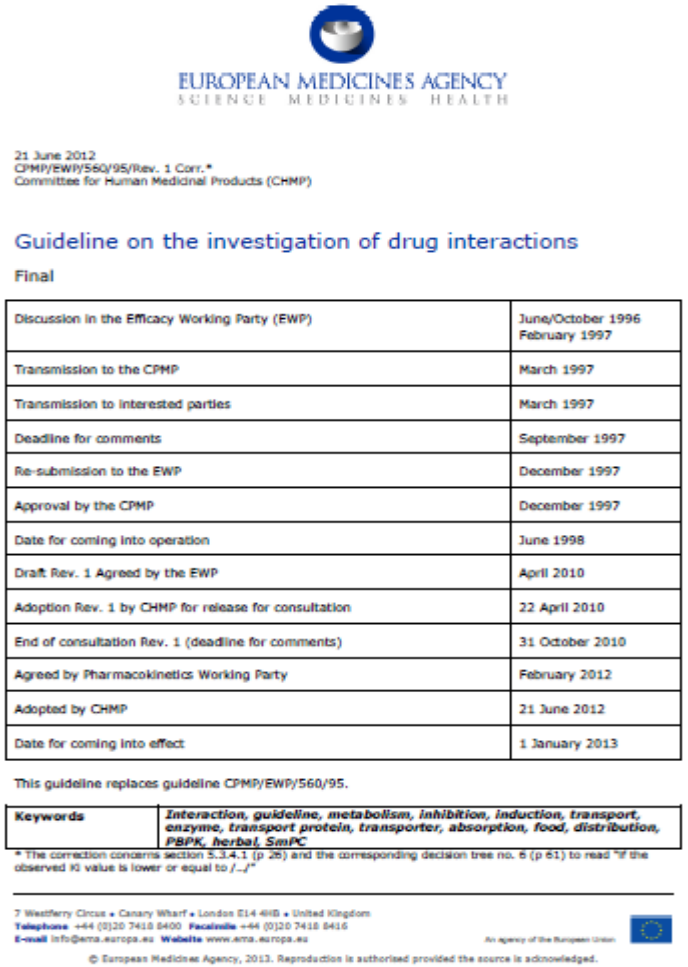
This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Shiew-Mei Huang, 301-796-1541, or Lei Zhang, 301-796-1635.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2012
Clinical Pharmacology



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 June 2012
CPMP/EWP/560/95/Rev. 1 Corr.*
Committee for Human Medicinal Products (CHMP)

Guideline on the investigation of drug interactions

Final

Discussion in the Efficacy Working Party (EWP)	June/October 1996 February 1997
Transmission to the CPMP	March 1997
Transmission to interested parties	March 1997
Deadline for comments	September 1997
Re-submission to the EWP	December 1997
Approval by the CPMP	December 1997
Date for coming into operation	June 1998
Draft Rev. 1 Agreed by the EWP	April 2010
Adoption Rev. 1 by CHMP for release for consultation	22 April 2010
End of consultation Rev. 1 (deadline for comments)	31 October 2010
Agreed by Pharmacokinetics Working Party	February 2012
Adopted by CHMP	21 June 2012
Date for coming into effect	1 January 2013

This guideline replaces guideline CPMP/EWP/560/95.

Keywords	***Interaction, guideline, metabolism, inhibition, induction, transport, enzyme, transport protein, transporter, absorption, food, distribution, PBPK, herbal, SmPC***

* The correction concerns section 5.3.4.1 (p 26) and the corresponding decision tree no. 6 (p 61) to read "if the observed KI value is lower or equal to /../"

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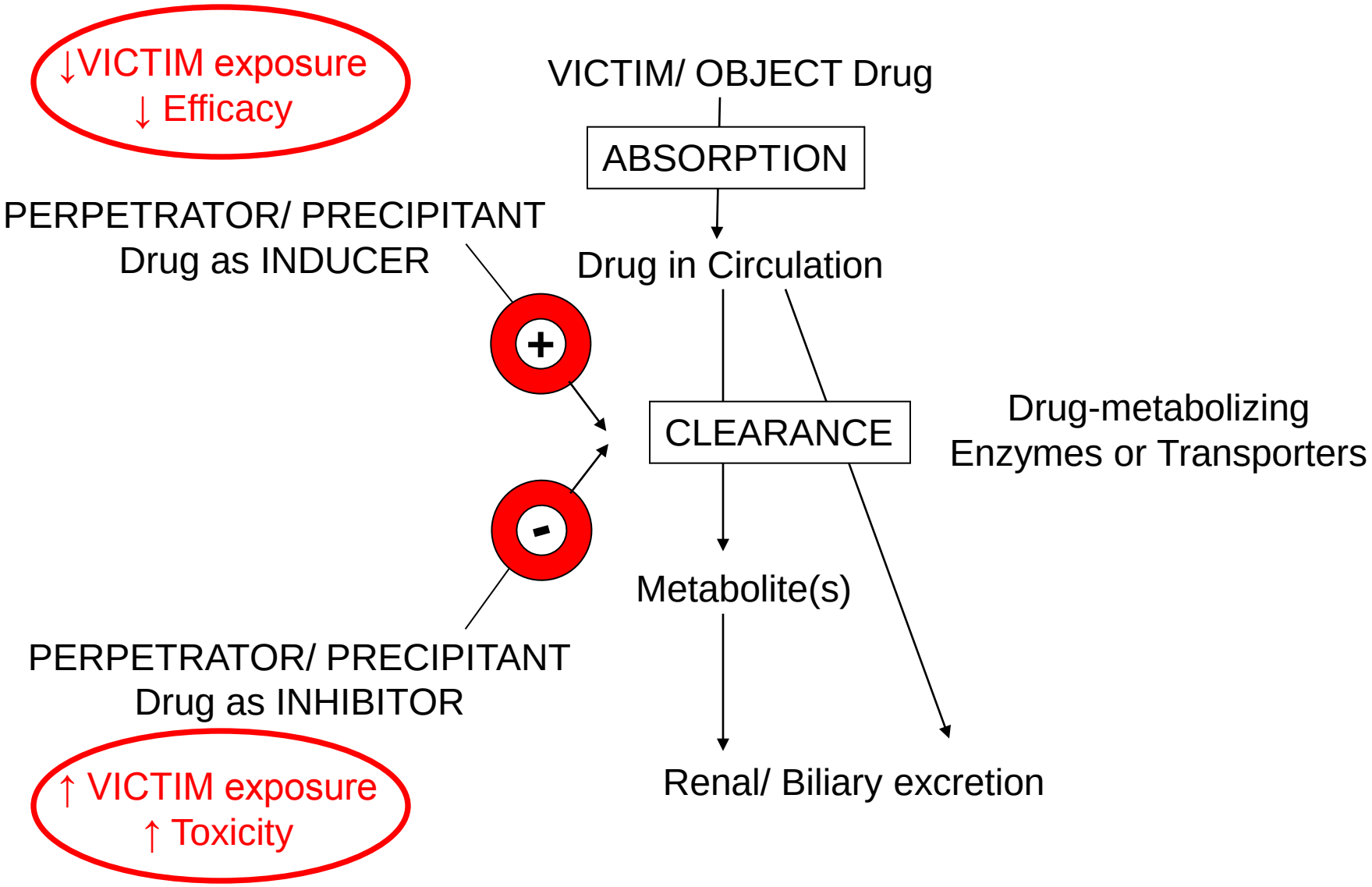
E-mail info@ema.europa.eu Website www.ema.europa.eu
An agency of the European Union

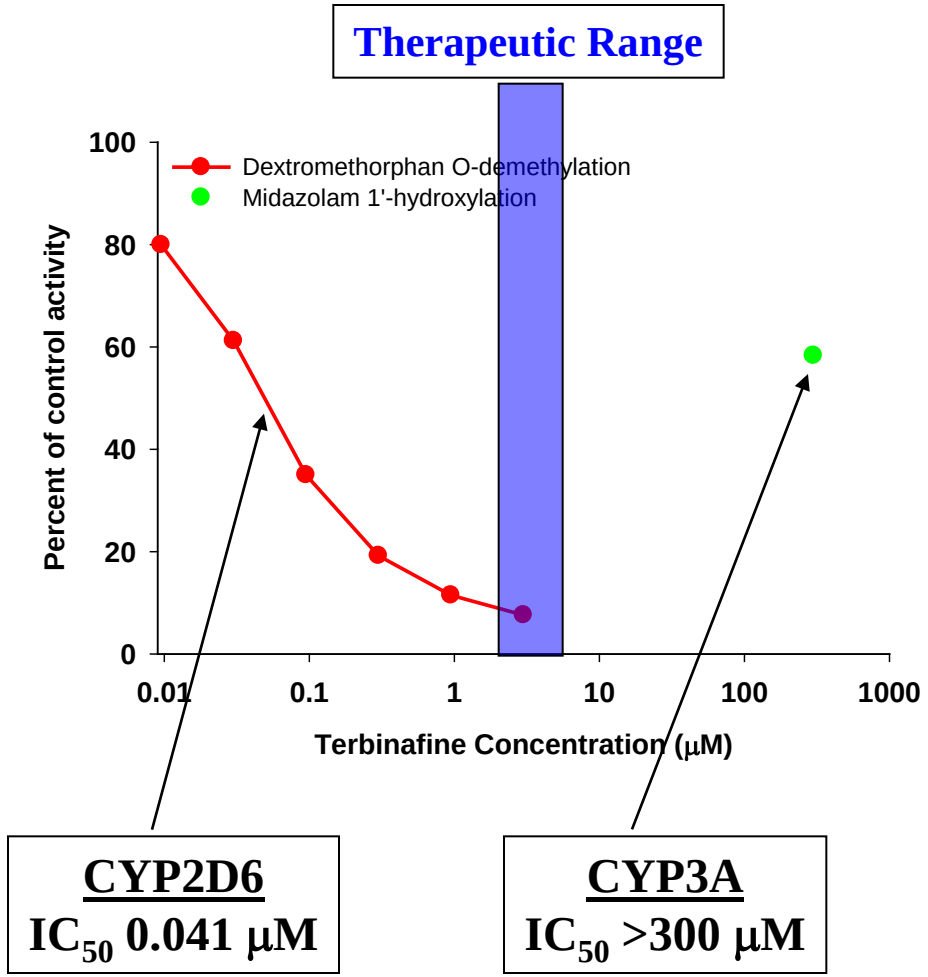
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm292362.pdf

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf


↓VICTIM exposure
↓ Efficacy
VICTIM/ OBJECT Drug
ABSORPTION
PERPETRATOR/ PRECIPITANT
Drug as INDUCER
Drug in Circulation
+
CLEARANCE
Drug-metabolizing
Enzymes or Transporters
-
Metabolite(s)
PERPETRATOR/ PRECIPITANT
Drug as INHIBITOR
↑ VICTIM exposure
↑ Toxicity
Renal/ Biliary excretion

CYP Inhibition DDI Risk Assessment: Case Study

Effects of terbinafine on CYP2D6 and CYP3A4/5 activities in human liver microsomes



- Terbinafine vs. CYP2D6: [I]/K**i** >> 1
  - **Interaction Likely**
  - In a clinical DDI study, terbinafine increased AUC of the CYP2D6 substrate desipramine by ~ 5-fold
- Terbinafine vs. CYP3A: [I]/K**i** < 0.1:
  - **Remote possibility of interaction**
  - In a clinical DDI study, terbinafine did not affect the AUC of the CYP3A substrate midazolam

In vitro data from J Pharmacol Exp Ther. 316:336–348, 2006

Translation to Therapeutics – Scenario 1

Patient on a stable dose of Metoprolol for hypertension, requiring systemic antifungal therapy for onychomycosis.

Metoprolol clearance is primarily via metabolism by CYP2D6

Terbinafine is a CYP2D6 inhibitor ✗

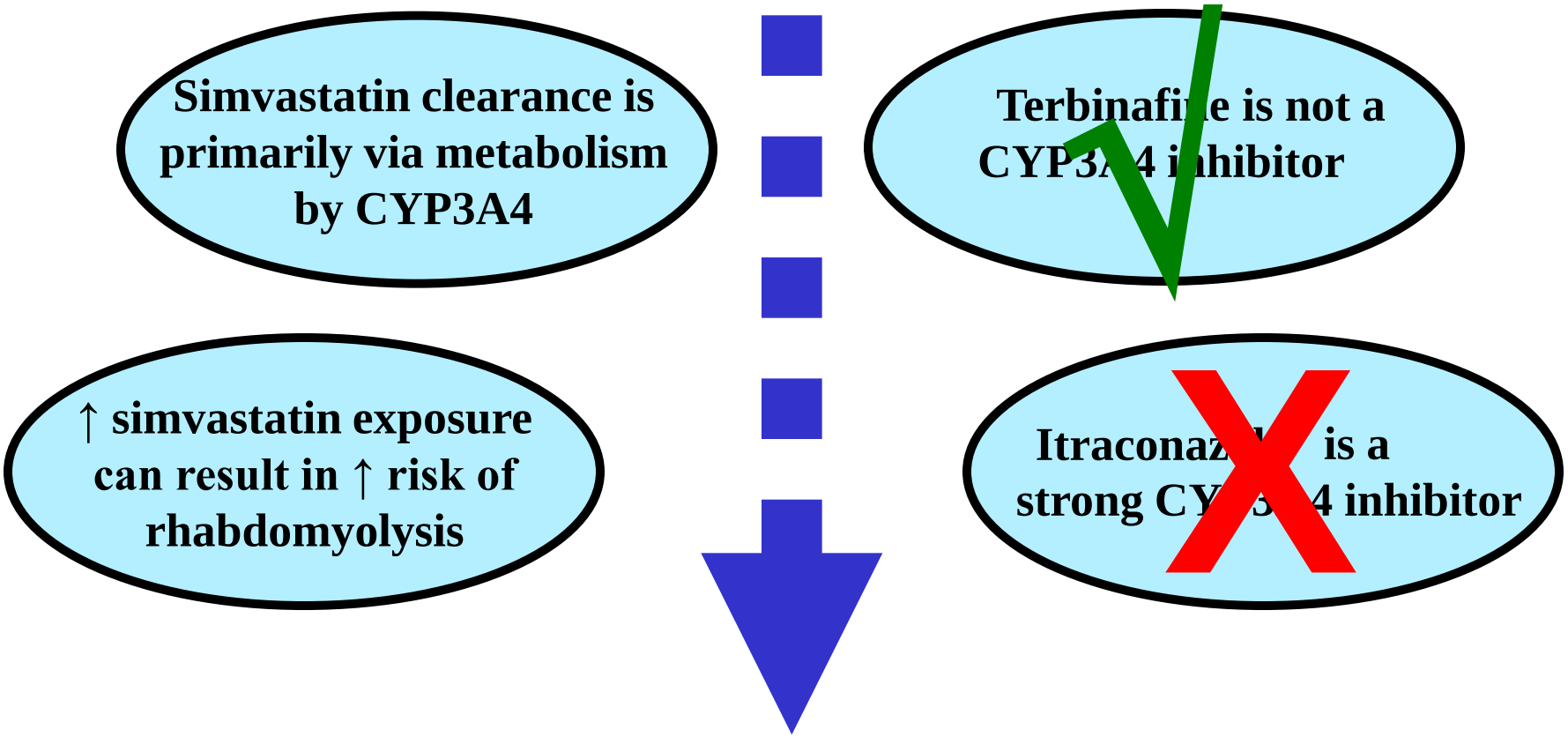
↑ metoprolol exposure can result in bradycardia and decreased cardioselectivity of β-blockade

Itraconazole is not a CYP2D6 inhibitor ✓

Consider Itraconazole instead of Terbinafine

Translation to Therapeutics – Scenario 2

Patient on a stable dose of Simvastatin for dyslipidemia, requiring systemic antifungal therapy for onychomycosis.



Consider Terbinafine instead of Itraconazole

Recent Scientific Advances in the Quantitative Predictions of Clinical DDIs from *In Vitro* Data

2008-2009

DRUG METABOLISM AND DISPOSITION
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DMD 37:1658–1666, 2009

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Printed in U.S.A.

Comparison of Different Algorithms for Predicting Clinical Drug-Drug Interactions, Based on the Use of CYP3A4 in Vitro Data: Predictions of Compounds as Precipitants of Interaction[S]

Odette A. Fahmi, Susan Hurst, David Plowchalk, Jack Cook, Feng Guo, Kuresh Youdim, Maurice Dickins, Alex Phipps, Amanda Darekar, Ruth Hyland, and R. Scott Obach

2010-2011

Applications of Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation During Regulatory Review

P Zhao[1], L Zhang[1], JA Grillo[1], Q Liu[1], JM Bullock[1], YJ Moon[1], P Song[1], SS Brar[1], R Madabushi[1], TC Wu[1], BP Booth[1], NA Rahman[1], KS Reynolds[1], E Gil Berglund[2], LJ Lesko[1] and S-M Huang[1]

CLINICAL PHARMACOLOGY & THERAPEUTICS www.nature.com/cpt

- Example of application to Cabazitaxel
  - Produced CYP3A inhibition *in vitro*
  - $C_{max}/K_i > 0.1$ -- DDI risk with CYP3A substrates could not be dismissed as unlikely
  - PB-PK model-based simulations predicted <1.1-fold increase in midazolam exposure
  - Model-based predictions concluded lack of clinically relevant CYP3A inhibition to support labeling without need for a clinical DDI study

Fahmi et al., Drug Metab Dispos., 37(8):1658-66, 2009
Zhao et al., Clin Pharmacol Ther 89:259-6, 2011

Study Design and Data Analysis Considerations

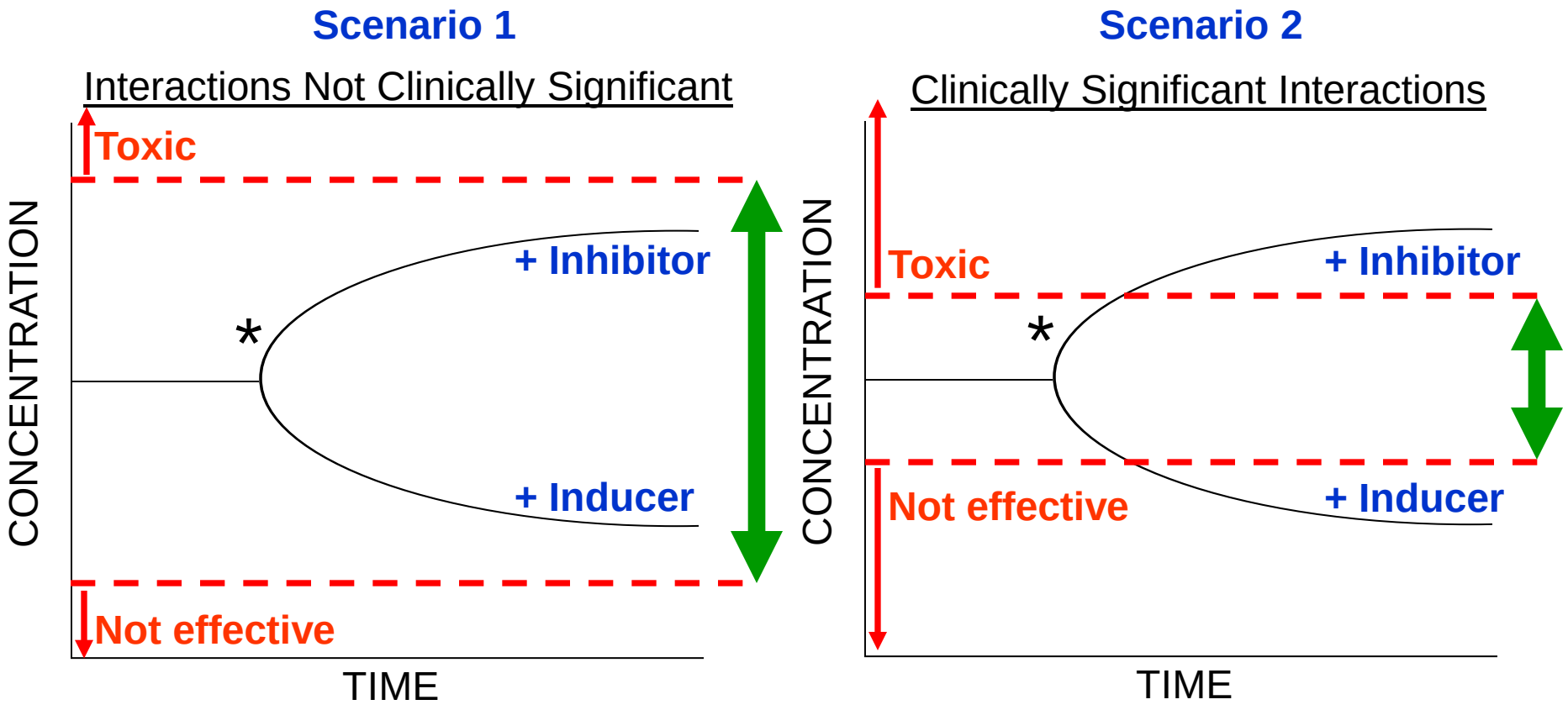
- Ensure adequate number of subjects to estimate DDI magnitude or genotype effect (e.g., AUC ratio) with adequate precision.
- Inference based on interpretation of 90% confidence intervals of DDI magnitude rather than p-values.

Study	**AUC_I/AUC_C Geometric Mean Ratio (90% CI)**	**p-value**	**Interpretation**
A	0.91 (0.85, 0.98)	<0.05	Not clinically significant
B	1.15 (0.60, 2.2)	>0.1, NS	Inconclusive

- Considerations in design of PG-PK association studies
  - Frequency of genotypes of interest (e.g., EM vs. PM sub-populations)
  - Expected effect size (e.g., from *in vitro* drug metabolism data)
  - Prospective genotyped cohorts vs. Retrospective Analysis
  - Integration of genotype as a covariate in population PK analyses
  - Informative PK sampling schemes

Determinants of Clinical Significance of a Drug-Drug Interaction

1. Interaction Magnitude
2. Therapeutic Index of Object/ Victim Drug



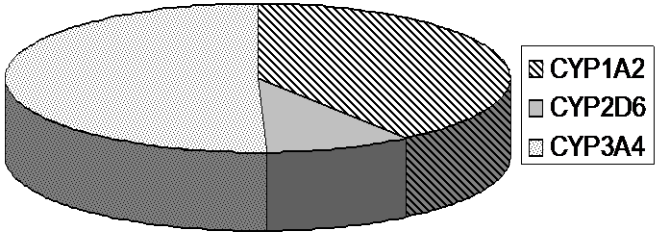
Adapted from Greenblatt DJ and Shader RI, Pharmacokinetics in Clinical Practice, 1985

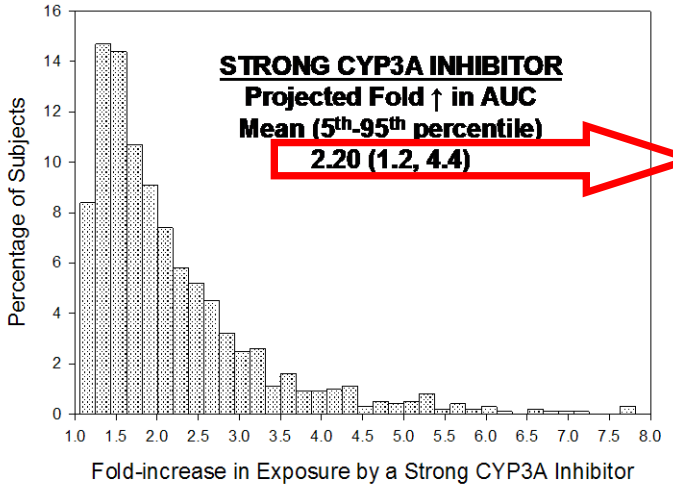
Scenarios/ Examples Illustrating Applications of Concepts in Drug Development Settings

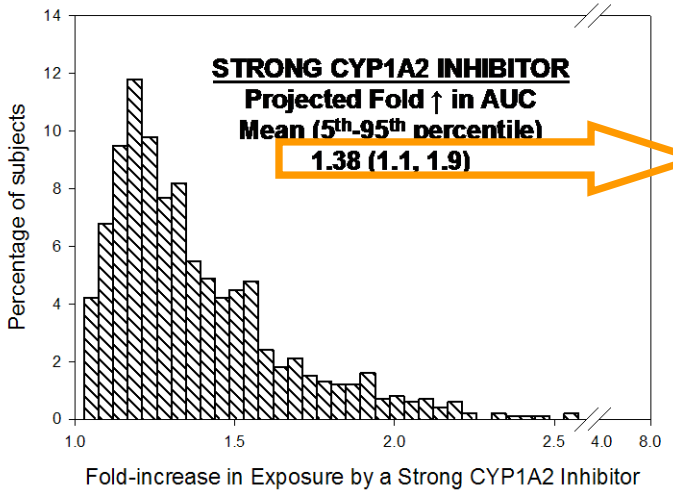
Scenario 1: PB-PK Model-Based Risk Assessment

Investigational Agent Entering First-In-Human Clinical Development in a Patient Population Likely to be on Multiple Concomitant Medications

***In Vitro* Metabolic Phenotype**







Venkatakrishnan K et al., Clinical Pharmacokinetics 49(11): 703-727, 2010

Scenario 1: DDI Risk Management in Clinical Development

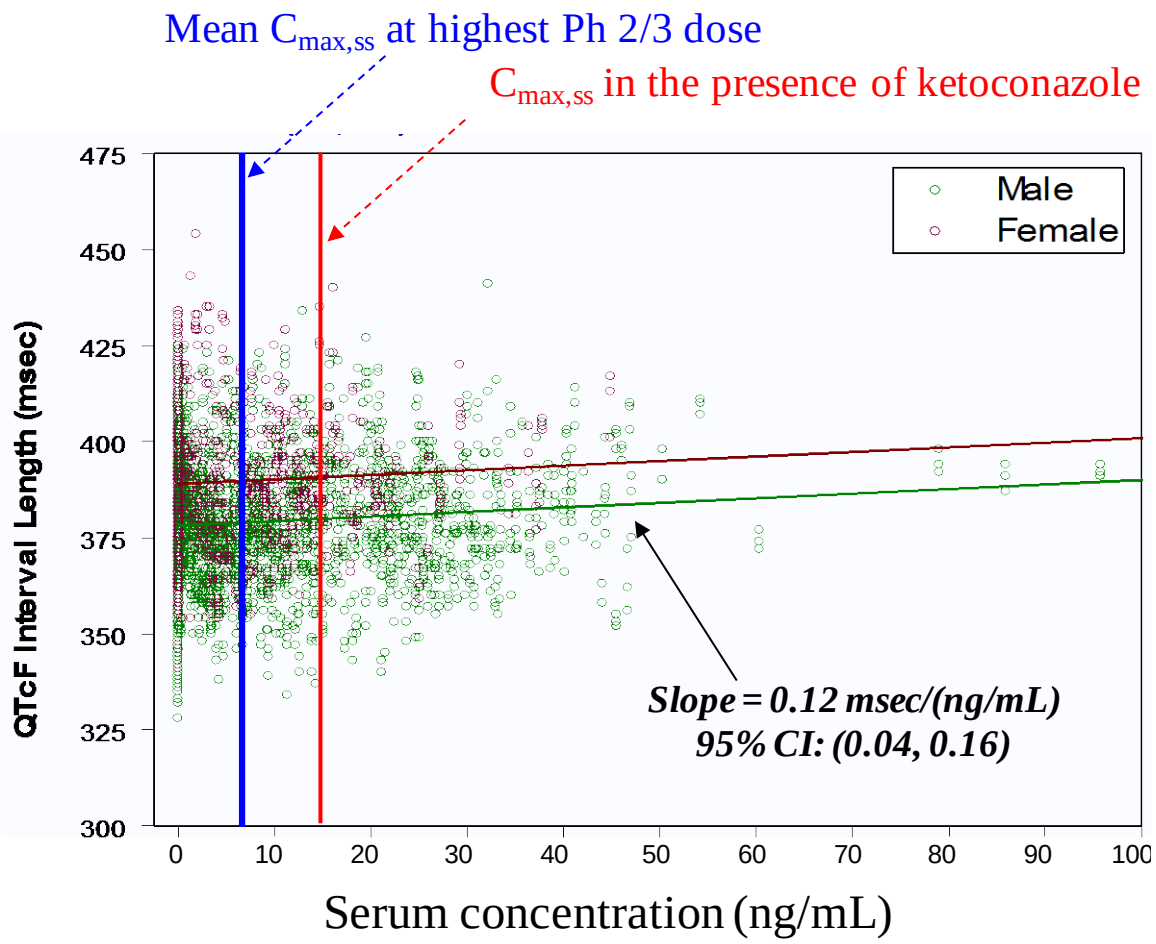
Investigational Agent Entering First-In-Human Clinical Development in a Patient Population Likely to be on Multiple Concomitant Medications

- Excluded concomitant medications in FIH trial
  - Strong and moderate inhibitors and inducers of CYP3A
  - Strong inhibitors and inducers (e.g., heavy smoking) of CYP1A2
- Simulations support lack of need for excluding CYP2D6 PMs
- DDI simulations and risk assessment to be updated using observed clinical PK in FIH study
  - Will guide ketoconazole DDI study design (e.g., NME dose selection) based on
    - Projected magnitude of DDI and associated inter-subject variability
    - Clinical safety profile and Therapeutic Index in Phase 1

Venkatakrishnan K et al., Clinical Pharmacokinetics 49(11): 703-727, 2010

Scenario 2: Integrating DDI Results with PK/Safety Relationships

CYP3A Substrate NME with potential for dose-related QTc prolongation



- PK/QTc model-predicted ΔQTcF at T_{max} at the highest Phase 2/ 3 dose
  - 0.8 ms (95% CI: 0.4 - 1.2)
- Ketoconazole DDI study showed ~2-fold increase in NME exposure
- PK/QTc model-predicted ΔQTcF at T_{max} at the highest Phase 2/ 3 dose under strong CYP3A inhibition
  - < 2 msec
  - << 5 ms ICH E14 threshold
- Enabled conclusion that clinically significant QT prolongation is unlikely over the proposed Ph 2/3 dose range even in the context of a DDI with a strong CYP3A inhibitor

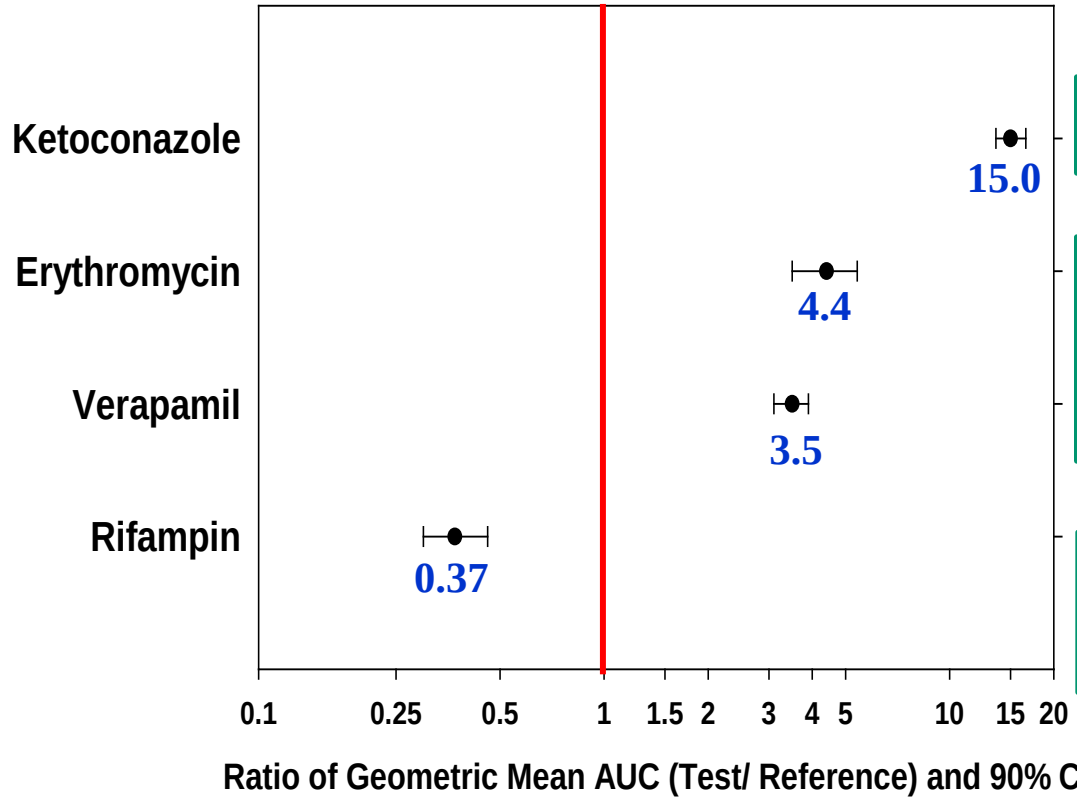
Translating Clinical DDI Results to Prescribing Guidance

Illustration with Everolimus (Afinitor®)

Sensitive CYP3A4 substrate

Recommended Dosage in multiple oncology indications* = 10 mg QD

* Advanced HR+ BC, advanced PNET, advanced RCC, or renal angiomyolipoma with TSC



- Avoid strong CYP3A4 inhibitors.

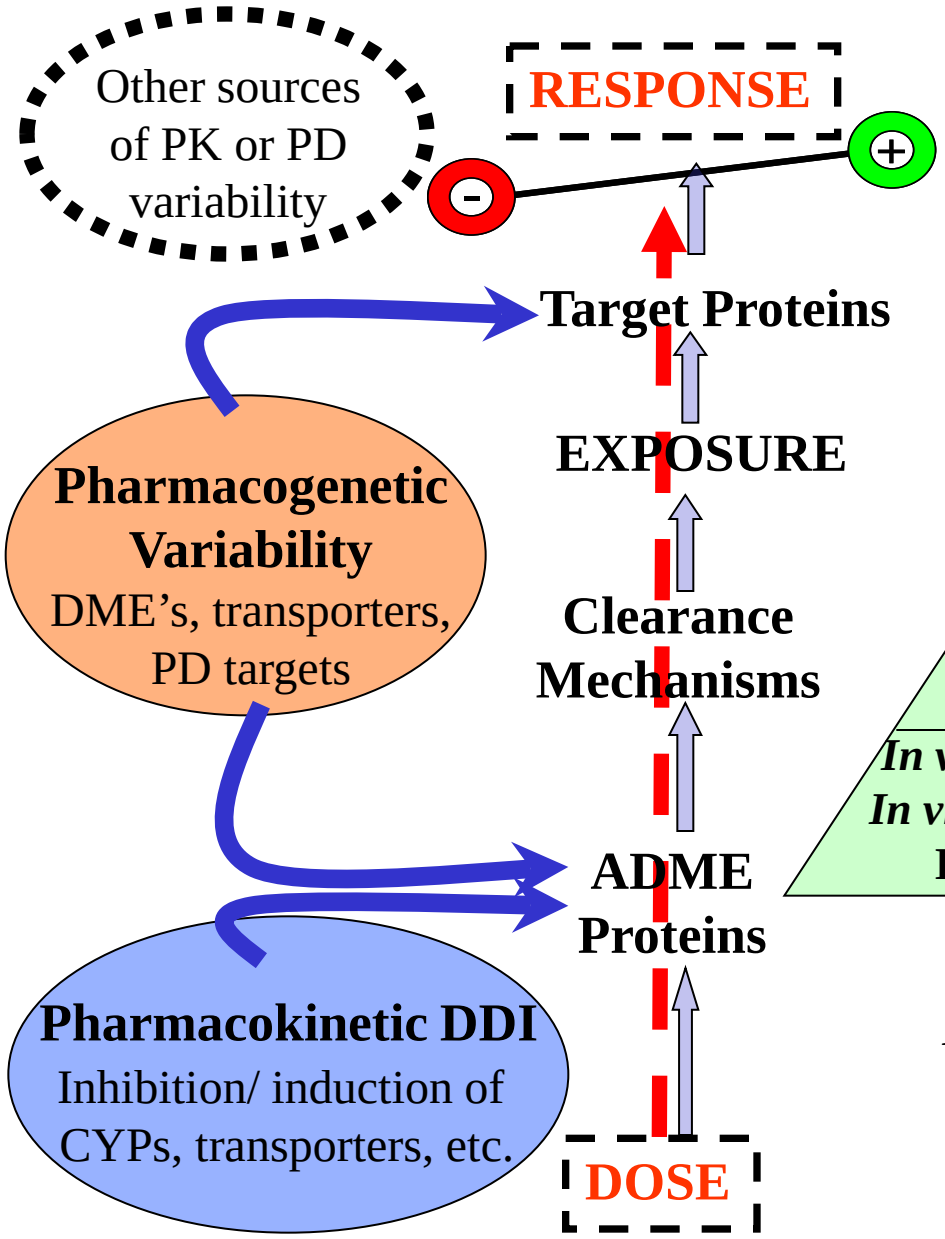
- Use caution with moderate CYP3A4 inhibitors, reduce dose to 2.5 mg.
- A dose increase to 5 mg may be considered, depending on tolerance.

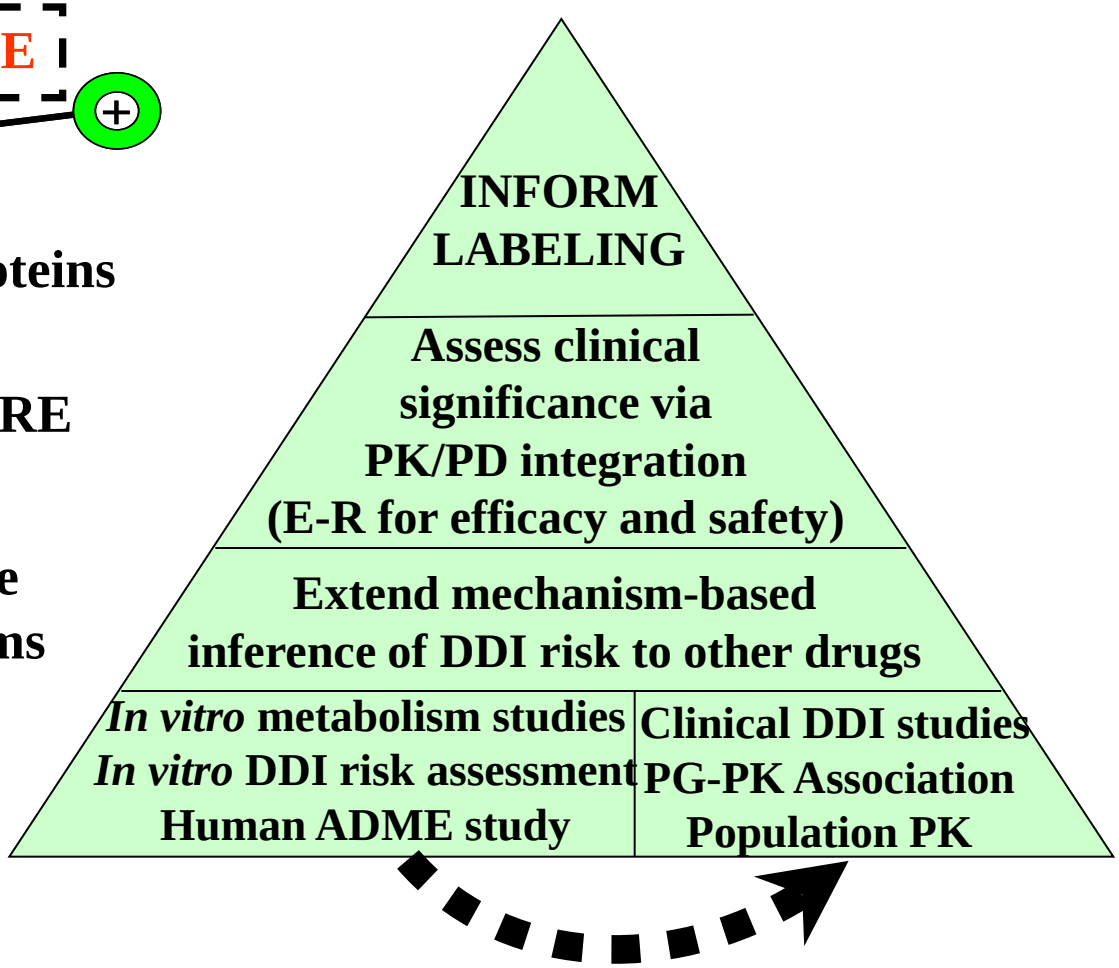
- Avoid strong CYP3A4 inducers.
- If required, consider dose increase in 5 mg increments to a maximum of 20 mg

Kovarik JM et al., Biopharmaceutics and Drug Disposition 27: 421-6, 2006

Afinitor® United States Prescribing Information (Revised 08/2012)

Integrated Approach to DDI and PGx in Drug Development





IDENTIFY MOLECULAR DETERMINANTS
RATIONALIZE CLINICAL STRATEGY
ELIMINATE UNNECESSARY STUDIES
INFORM STUDY DESIGN

Venkatakrishnan K. In Encyclopedia of Drug Metabolism and Drug Interactions, 2012.