Pharmacodynamics & Pharmacokinetics: PI and PIL considerations

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School of Pharmacy / Unit for Drug Research & Development

SAAPRA 16 November 2012

Innovation through diversity ™

WCP 2014 17TH WORLD CONGRESS OF BASIC & CLINICAL PHARMACOLOGY

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Presentation

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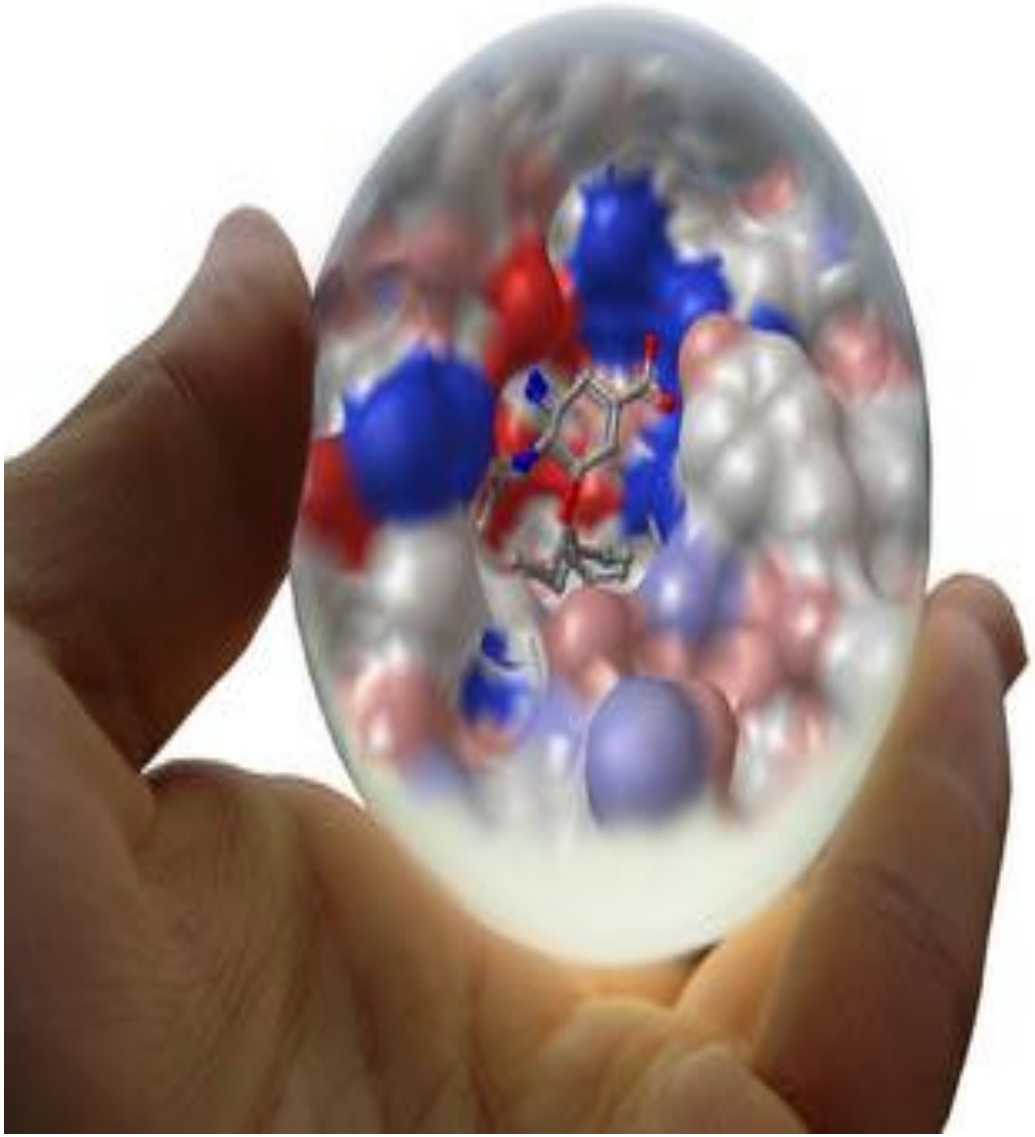
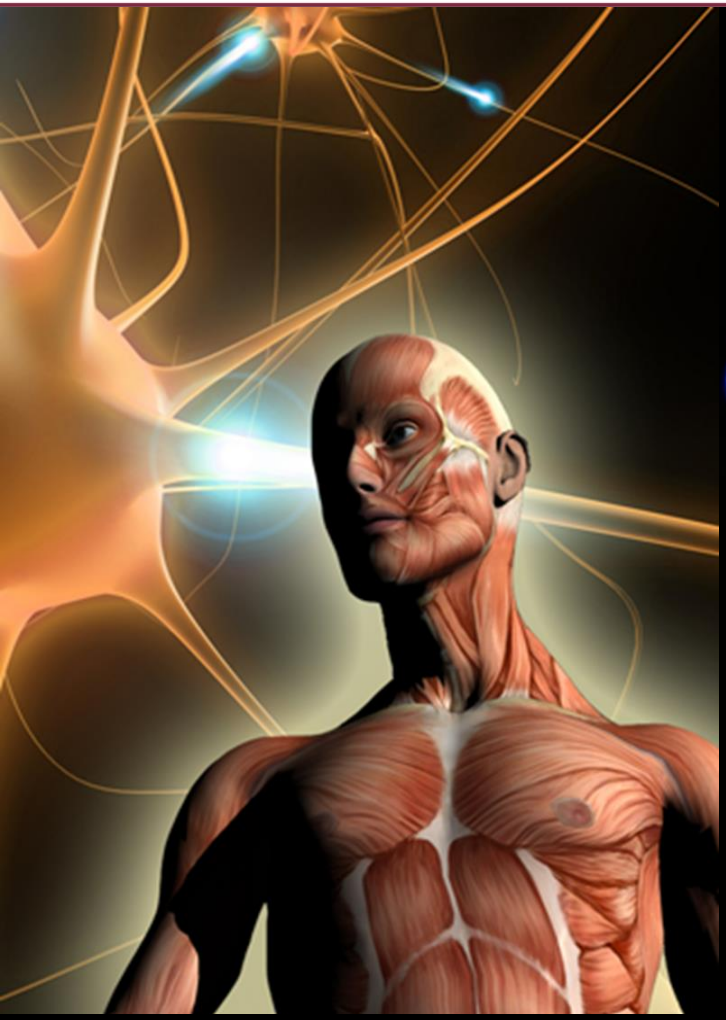
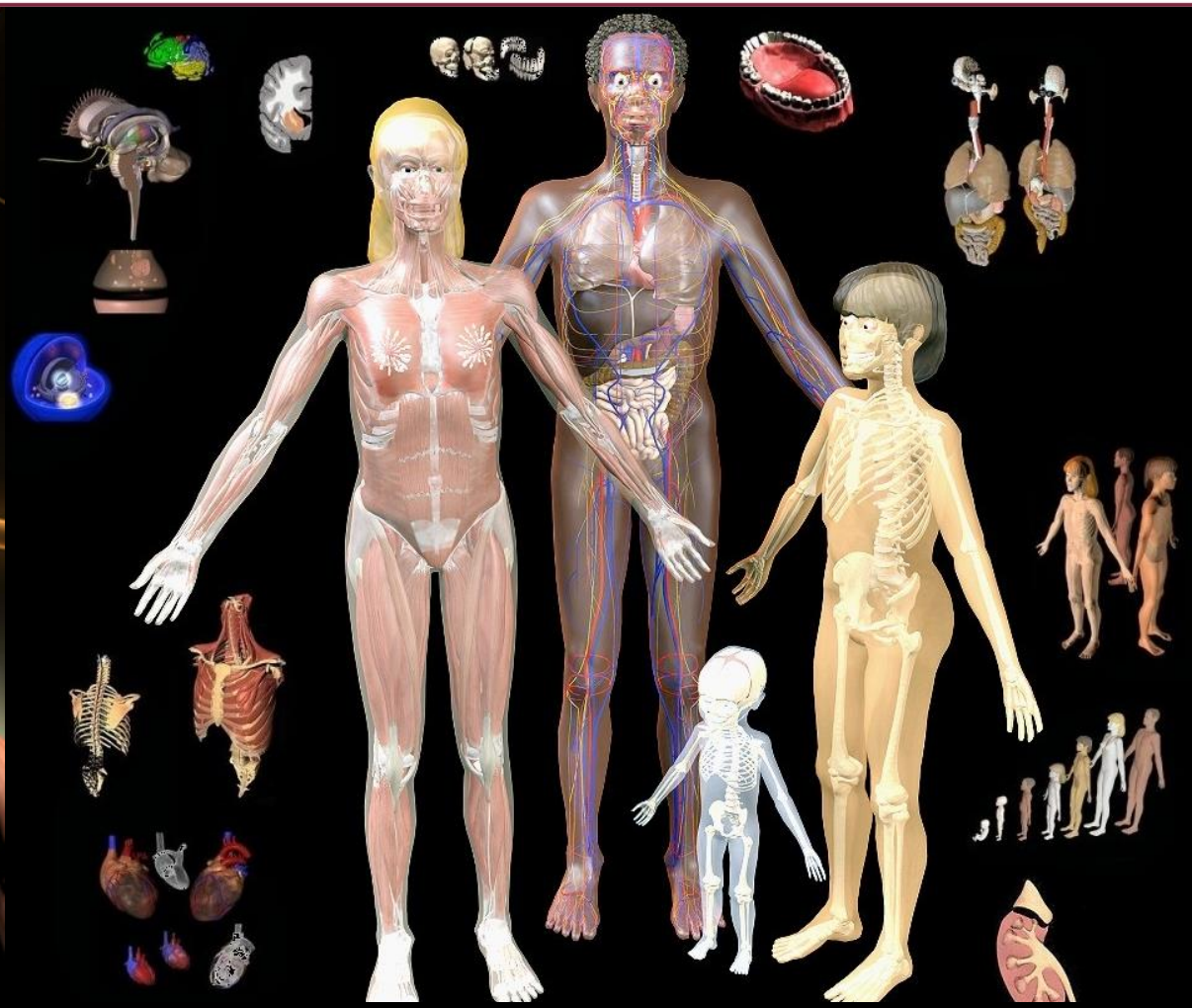
- **Introduction:**
  - **Drug Discovery Research**
- **Background: PK/PD**
- **Pharmacodynamics**
  - **(CTD Modules 4&5)**
- **Pharmacokinetics**
  - **(CTD Modules 4&5)**
- **Specific Considerations**
- **MCC**
  - **Regulatory Framework**
- **Additional Information**
- **Conclusion**



INTRODUCTION
AND
BACKGROUND

The human





The Human Body

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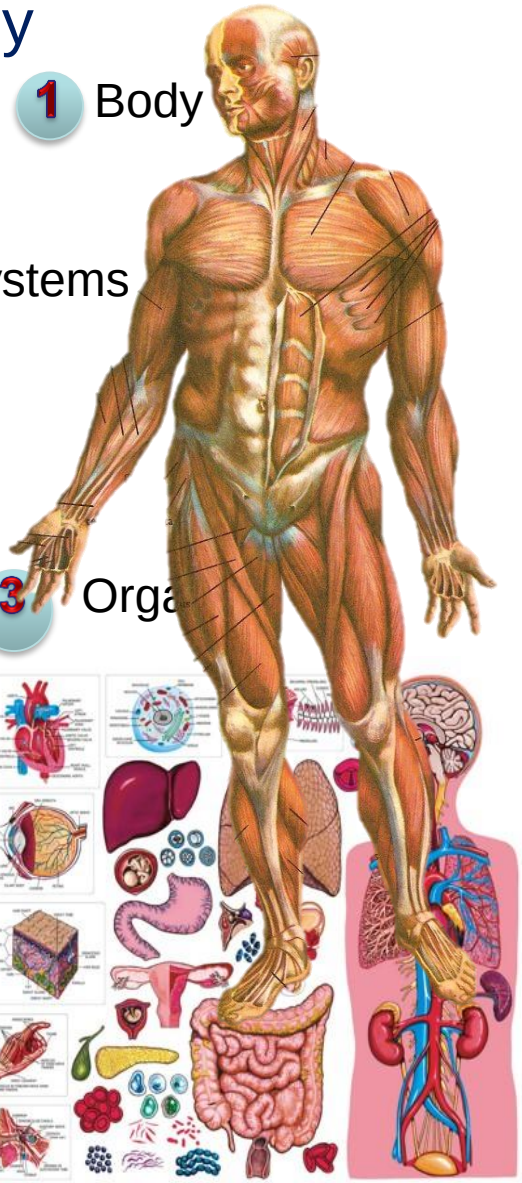
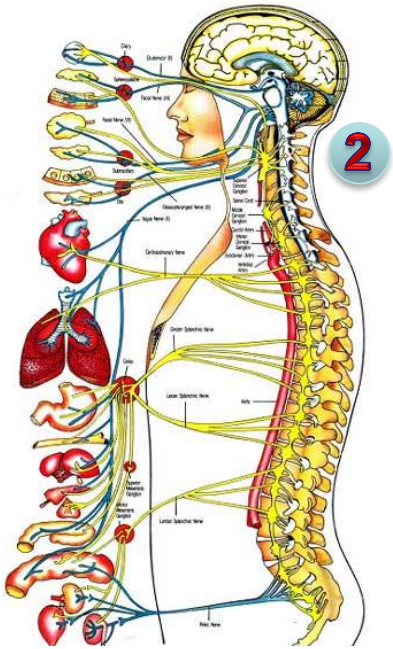
Integrative and Organ Systems Pharmacology

1 Body

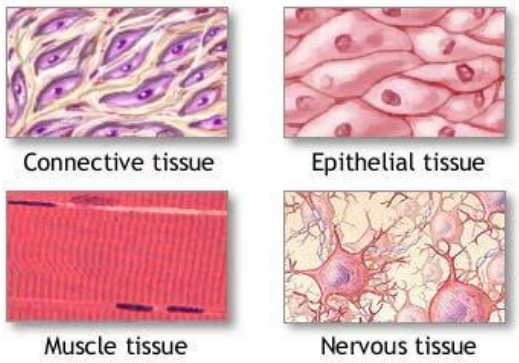


2 Systems

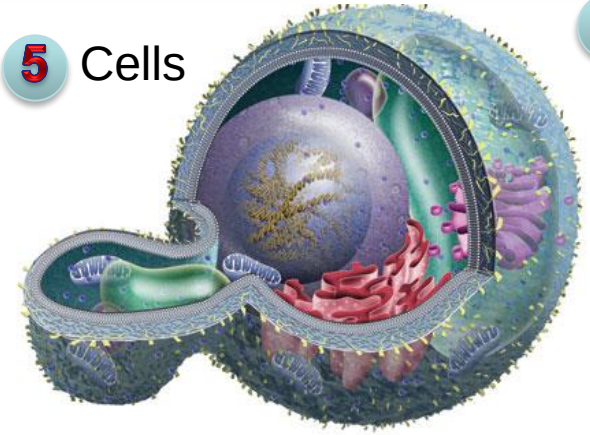


3 Orga

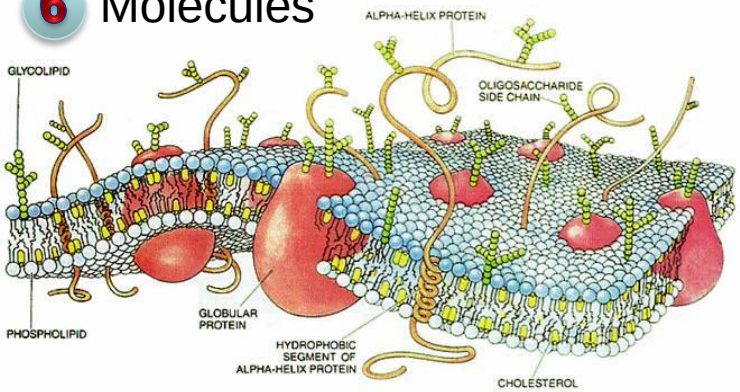
4 Tissue



5 Cells



6 Molecules



7 Protons, neutrons, electrons,
"Higgs boson particle"

The Disease

The Medicine

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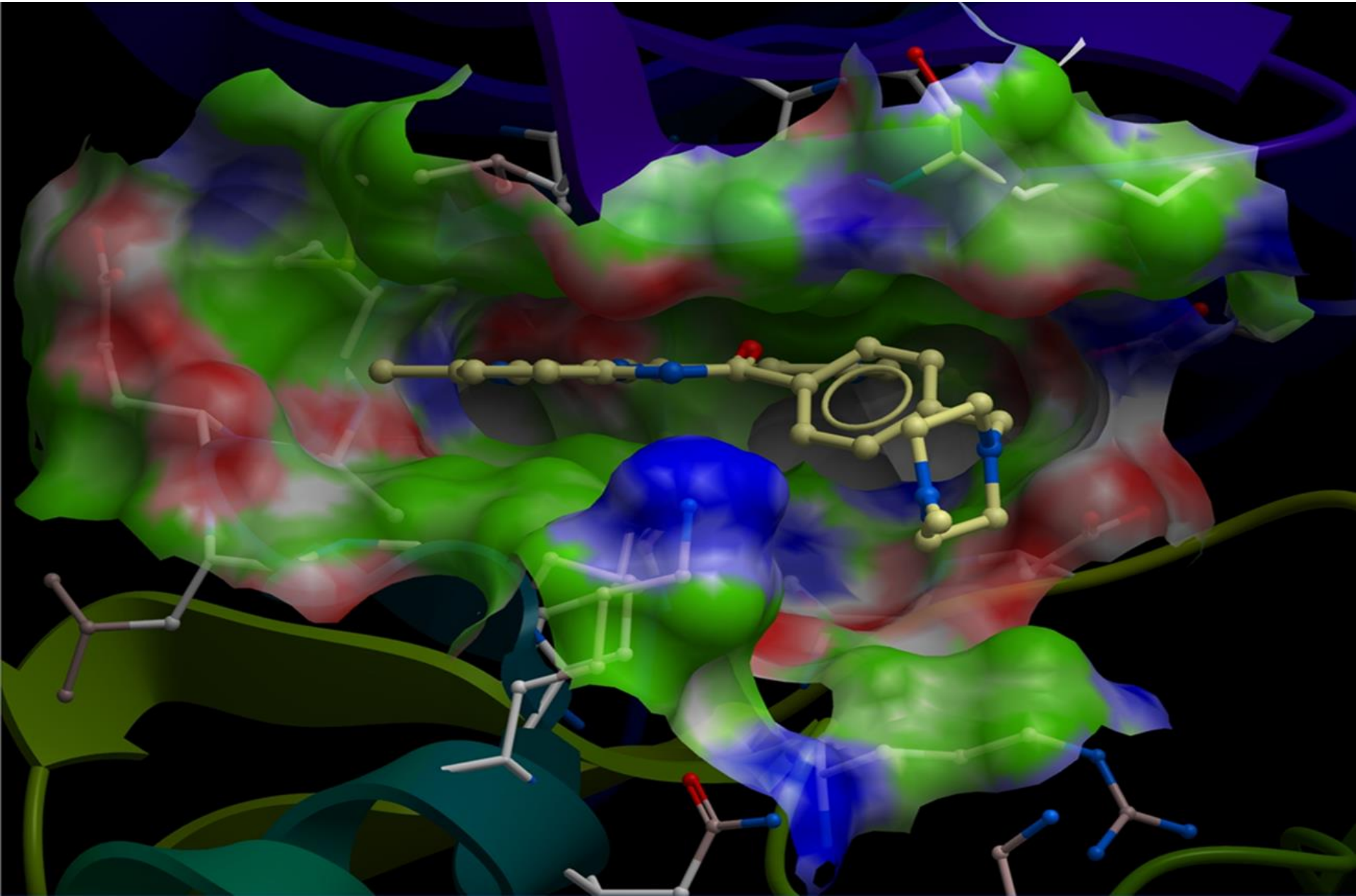
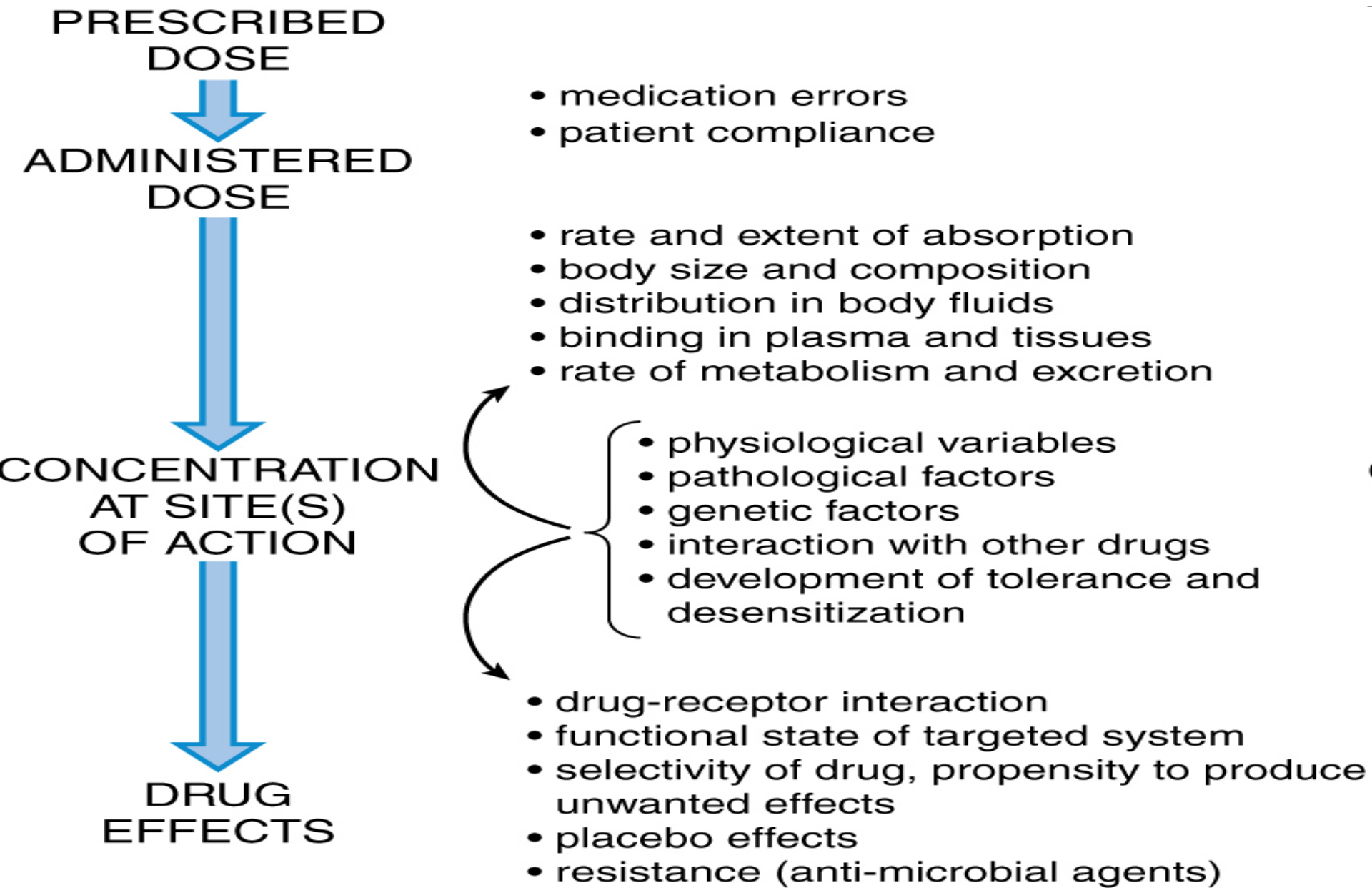


Specific considerations of drug therapy



Drug Discovery, Research & Development

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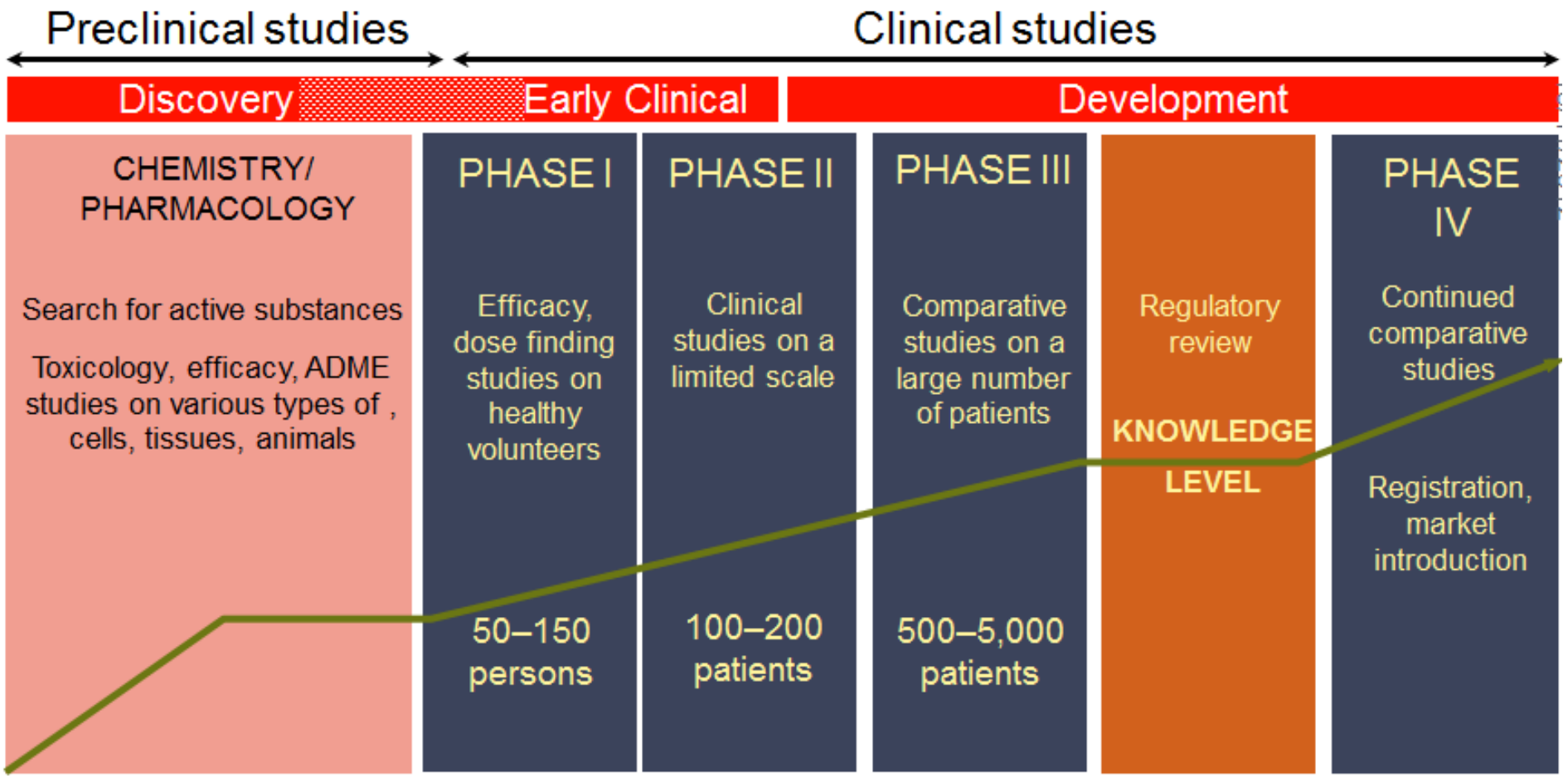

Pharmacology

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Pharmacodynamics (PD)

"What the drug does to the body"

Quantitative analysis of relation of the drug effect (E) to drug concentration at an effect site (Ce)

Pharmacokinetic (PK)

"What the body does to the drug"

Quantitative analysis of the kinetics (time course) and steady state (SS) relationships of drug

IUPHAR
international union of basic and clinical pharmacology

CTD Module 4: Non-Clinical Studies
SPC Relevant Scientific information

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- 1.Pharmacology
  - 1.Primary Pharmacodynamics
  - 2.Secondary Pharmacodynamics
  - 3.Safety Pharmacology
  - 4.Pharmacodynamic Drug Interactions
- 2.Pharmacokinetics
  - 1.Analytical Methods and Validation
  - 2.Absorption
  - 3.Distribution
  - 4.Metabolism
  - 5.Excretion
  - 6.Pharmacokinetic Drug Interactions
  - 7.Other Pharmacokinetic Studies

Toxicology:

- Acute toxicity
- Subchronic toxicity
- Tissue specific toxicity
- Tolerability

***In vivo* testing** *Animal model*

- Drug action:
- Behaviour and reaction
- Physiology
- Histopathology

PHARMACODYNAMICS (M 4)

Pharmacodynamics (PD) Pre-clinical

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– **"What the drug does to the body"**

- Drug Mode of Action, Potency, Efficacy
- Molecular level and Animal Studies (Module 4):
  - What type of drug is it?
  - Describe its action at?
  - Selective or non-selective?
  - Binding reversible or irreversible?
  - The doses and the effects?
- Human (Module 5):
  - Dose/dose relationships, onset of action and duration of action
  - Discontinuation of treatment
  - Beneficial effects on mortality and morbidity
- Therapeutic Index/Therapeutic Window – safety aspect

Mode of action – outcome

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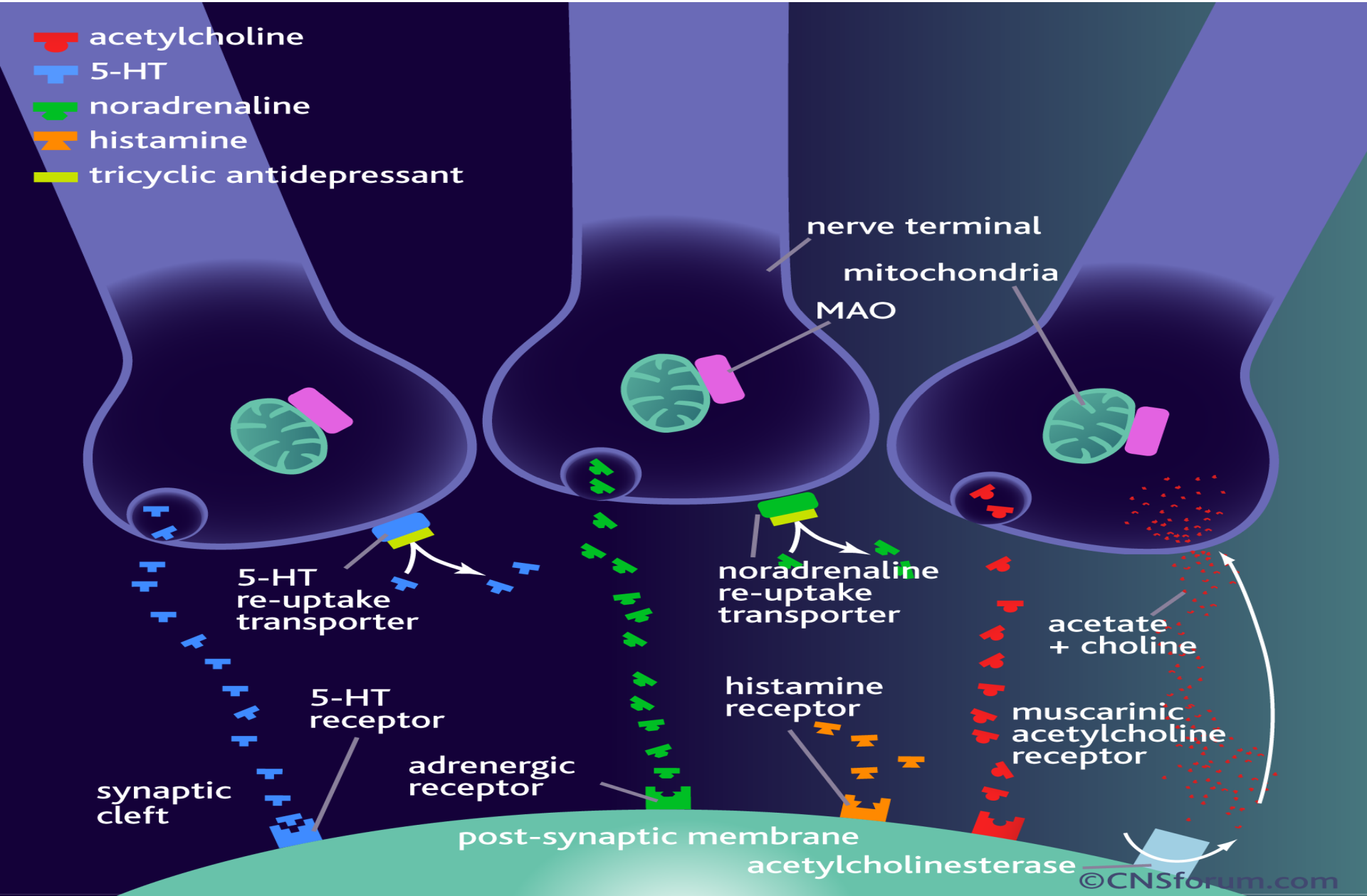
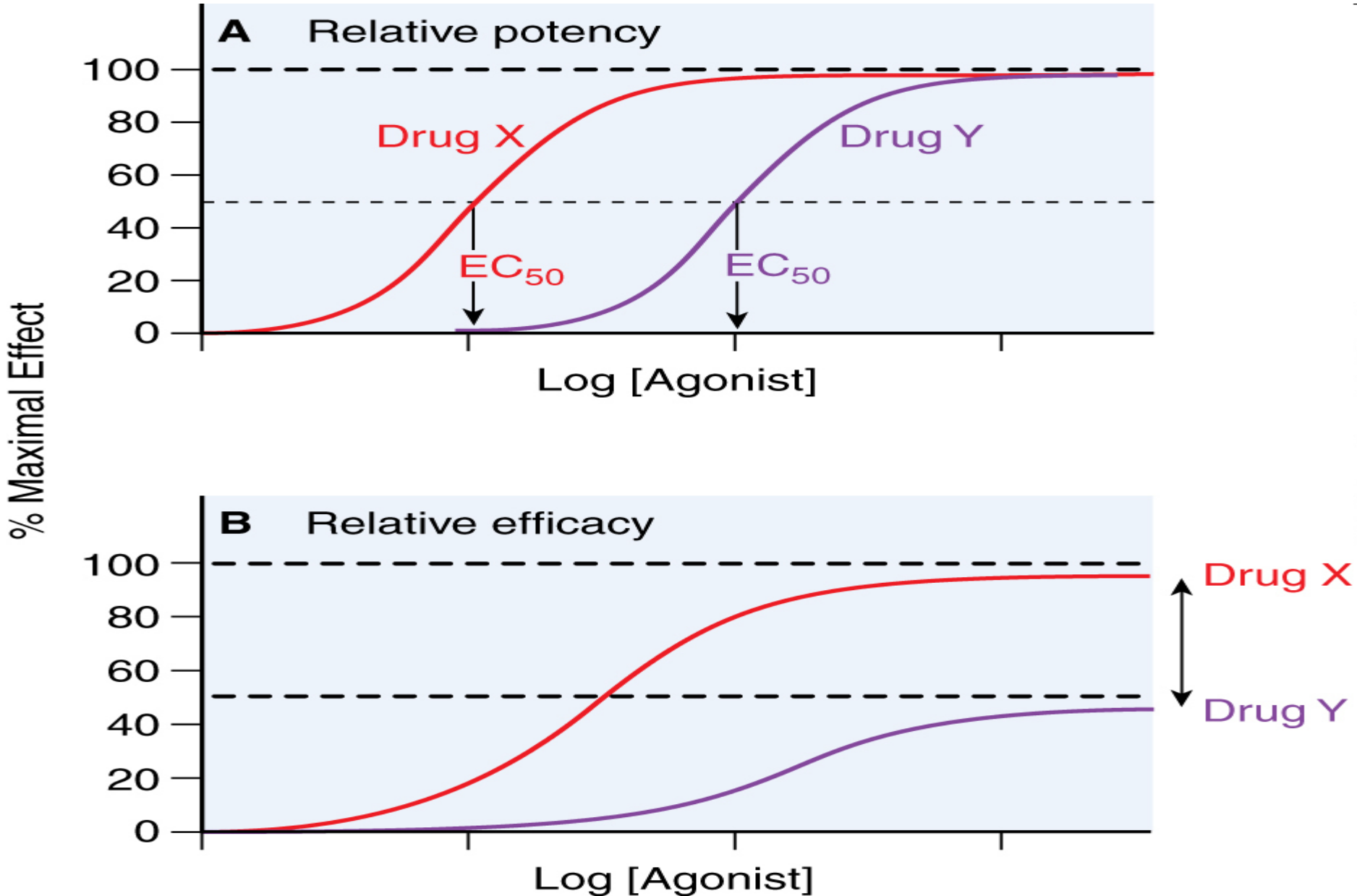
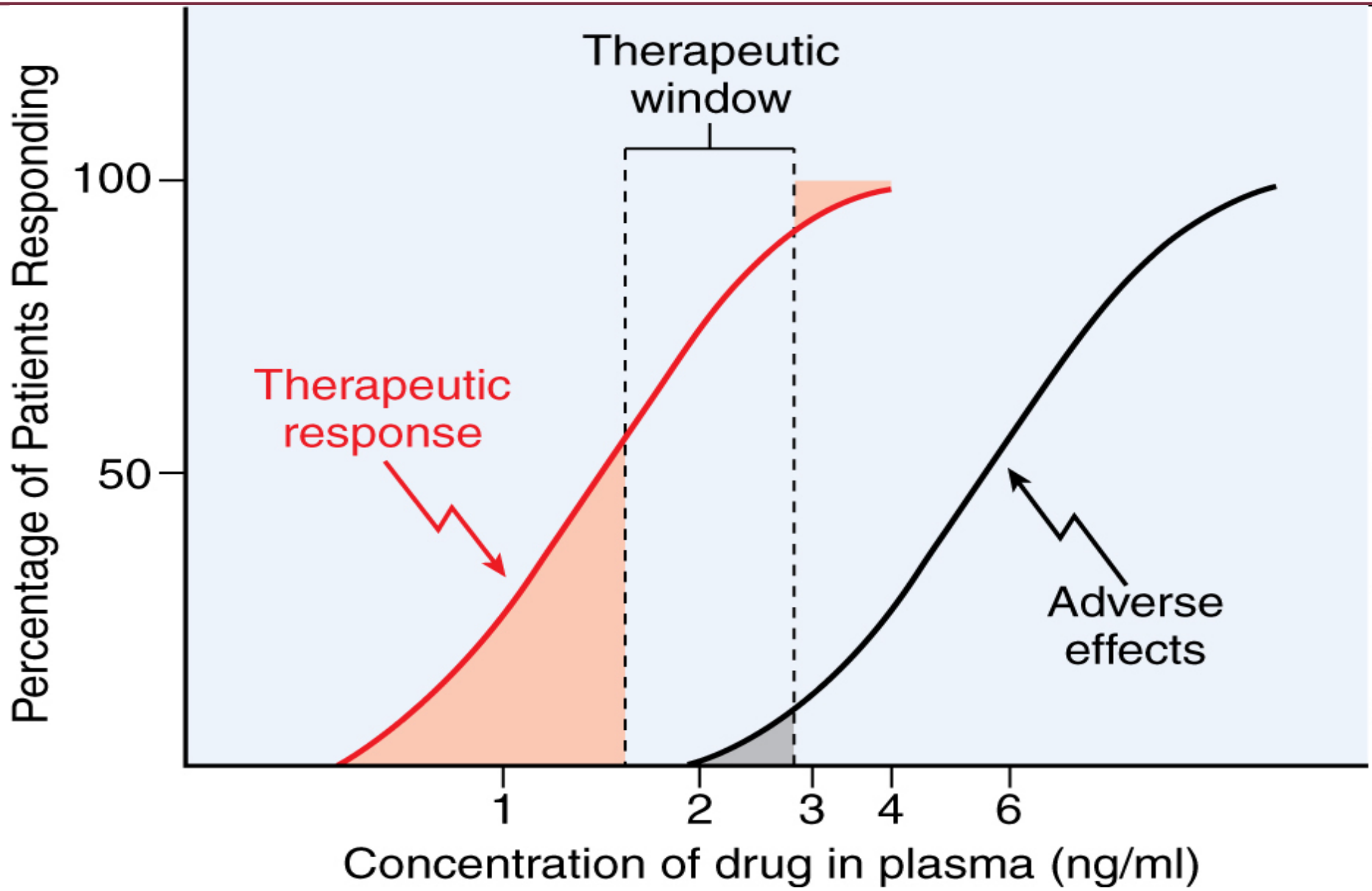


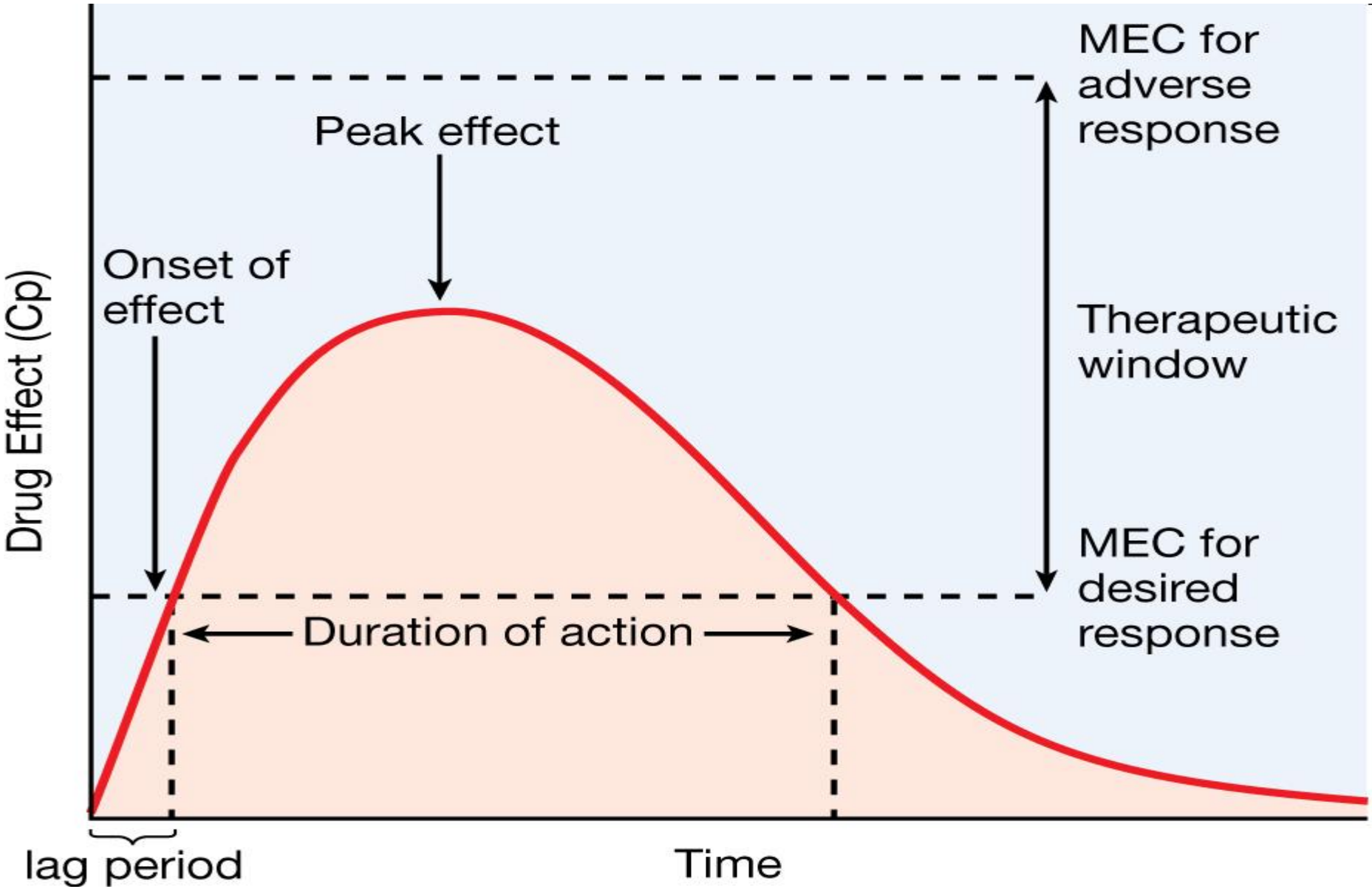
Potency and Efficacy



Therapeutic Response – Window and Adverse Effects



Drug Effect and Therapeutic Window



PHARMACODYNAMICS (M 5)

CTD Module 5: Clinical
SPC Relevant Scientific information

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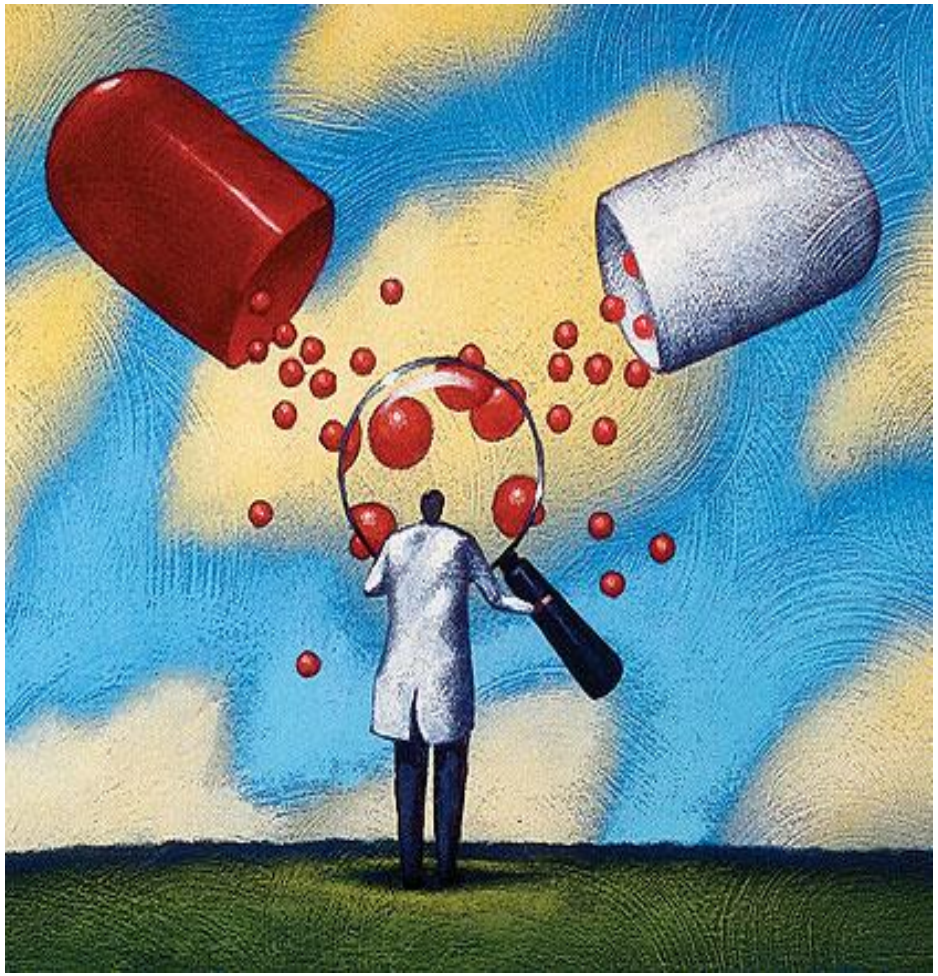
- 5.1 Pharmacodynamic properties

- - Mechanism of action
- - Pharmacodynamic effects
- - Clinical efficacy

  - - Dose/effect relationships?
  - - onset of action and duration of action?
  - - Discontinuation of treatment?
  - - Beneficial effects on mortality and morbidity?
  - - Other effects?
  - - Safety?



PHARMACOKINETICS (M 4 & 5)

CTD Module 4: Non-Clinical Studies
SPC Relevant Scientific information

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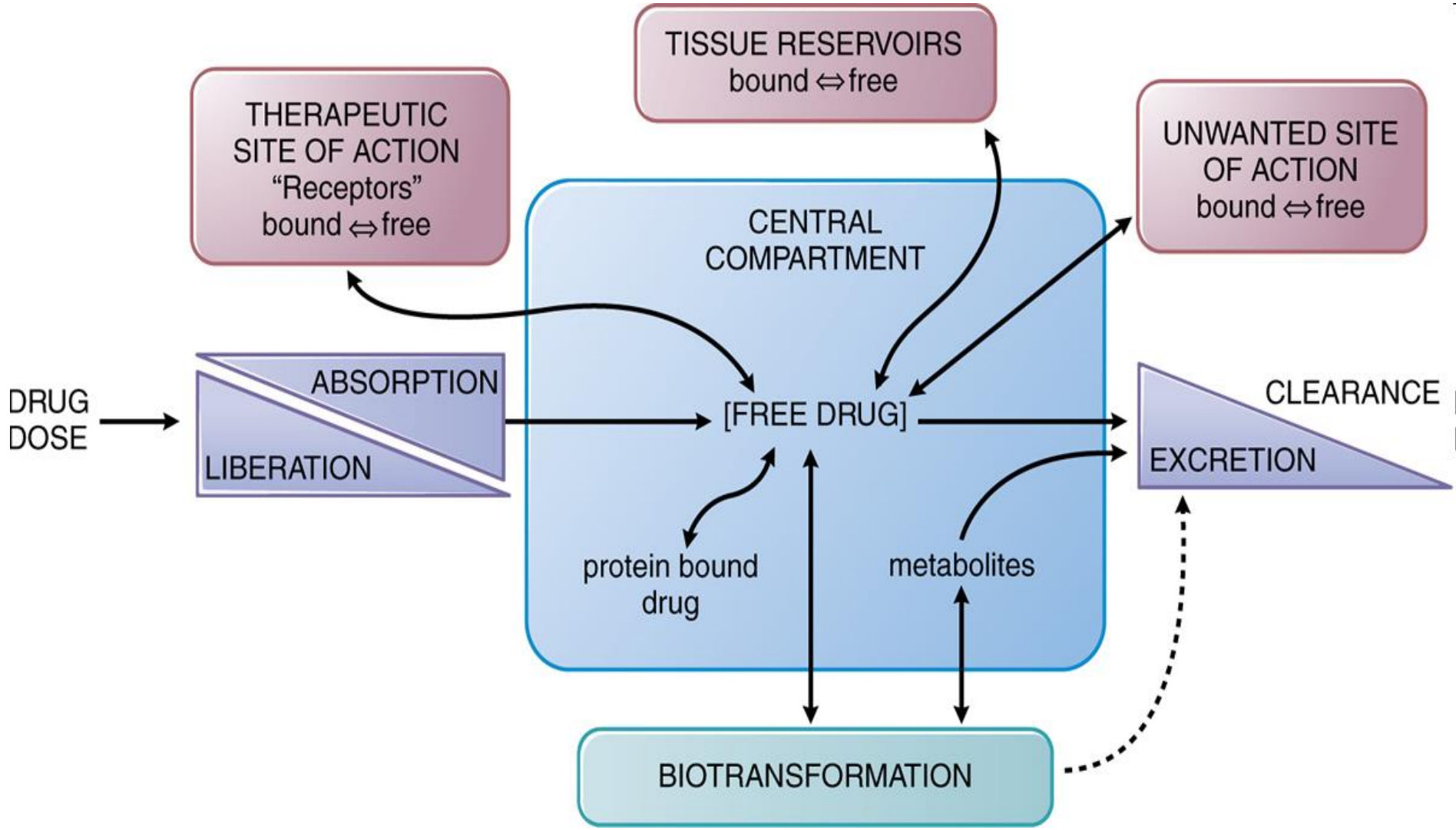
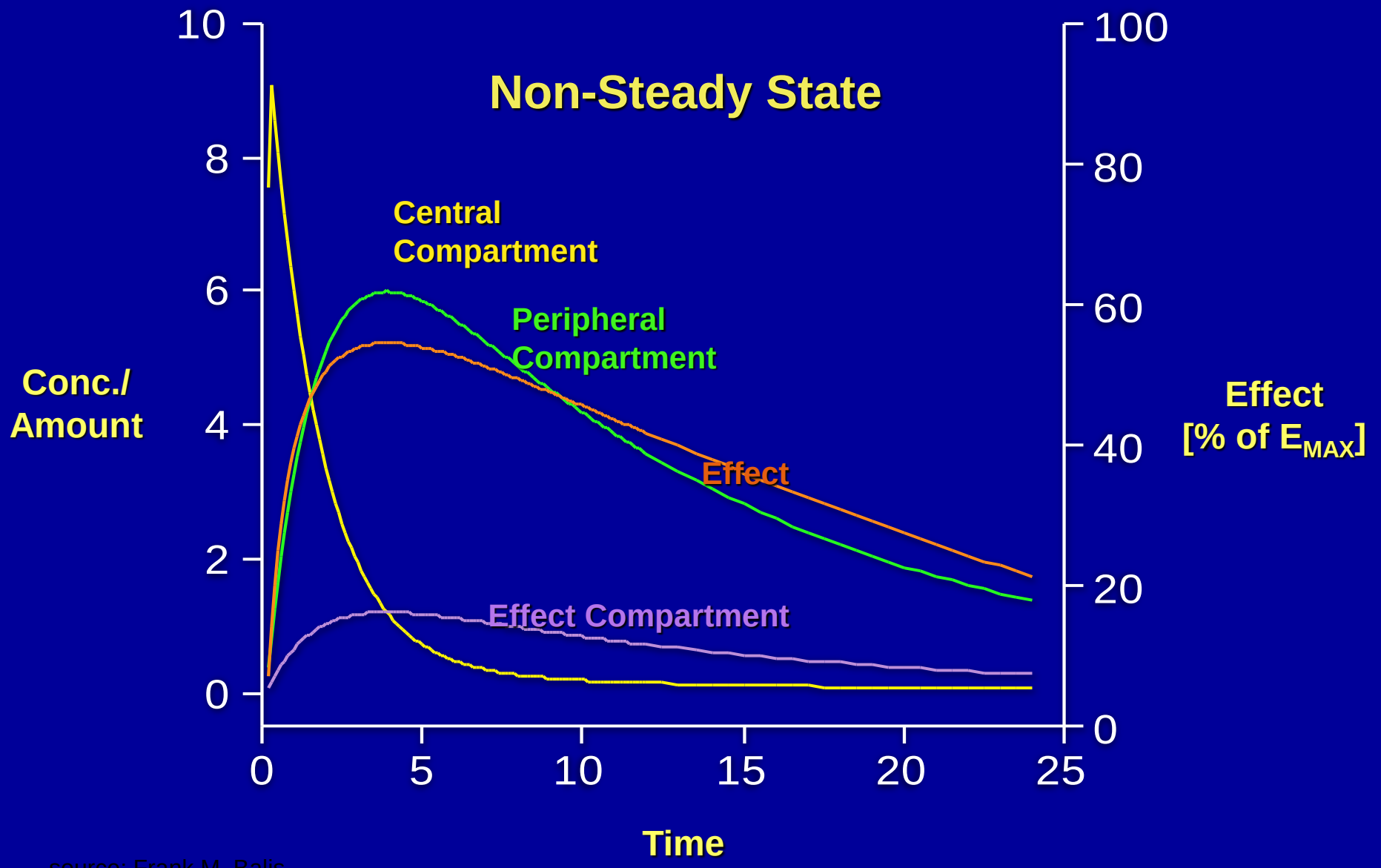
  - 2.Absorption
  - 3.Distribution
  - 4.Metabolism
  - 5.Excretion
  - 6.Pharmacokinetic Drug Interactions
  - 7.Other Pharmacokinetic Studies

Interrelationship of absorption, distribution, binding, metabolism, and excretion and its sites of action.



Concentration and Effect vs. Time



source: Frank M. Balis

Pharmacokinetics (PK)

- Quantitative analysis of the kinetics (time course) and steady state (SS) relationships of drug

"What the body does to the drug"

ADME

- Absorption
- Distribution
- Metabolism
- Excretion

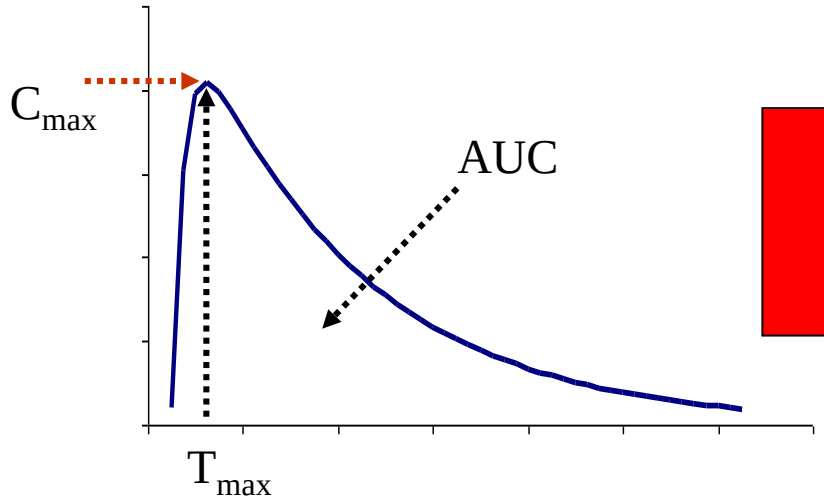
} Elimination

Pharmacokinetic concepts

Important PK parameters

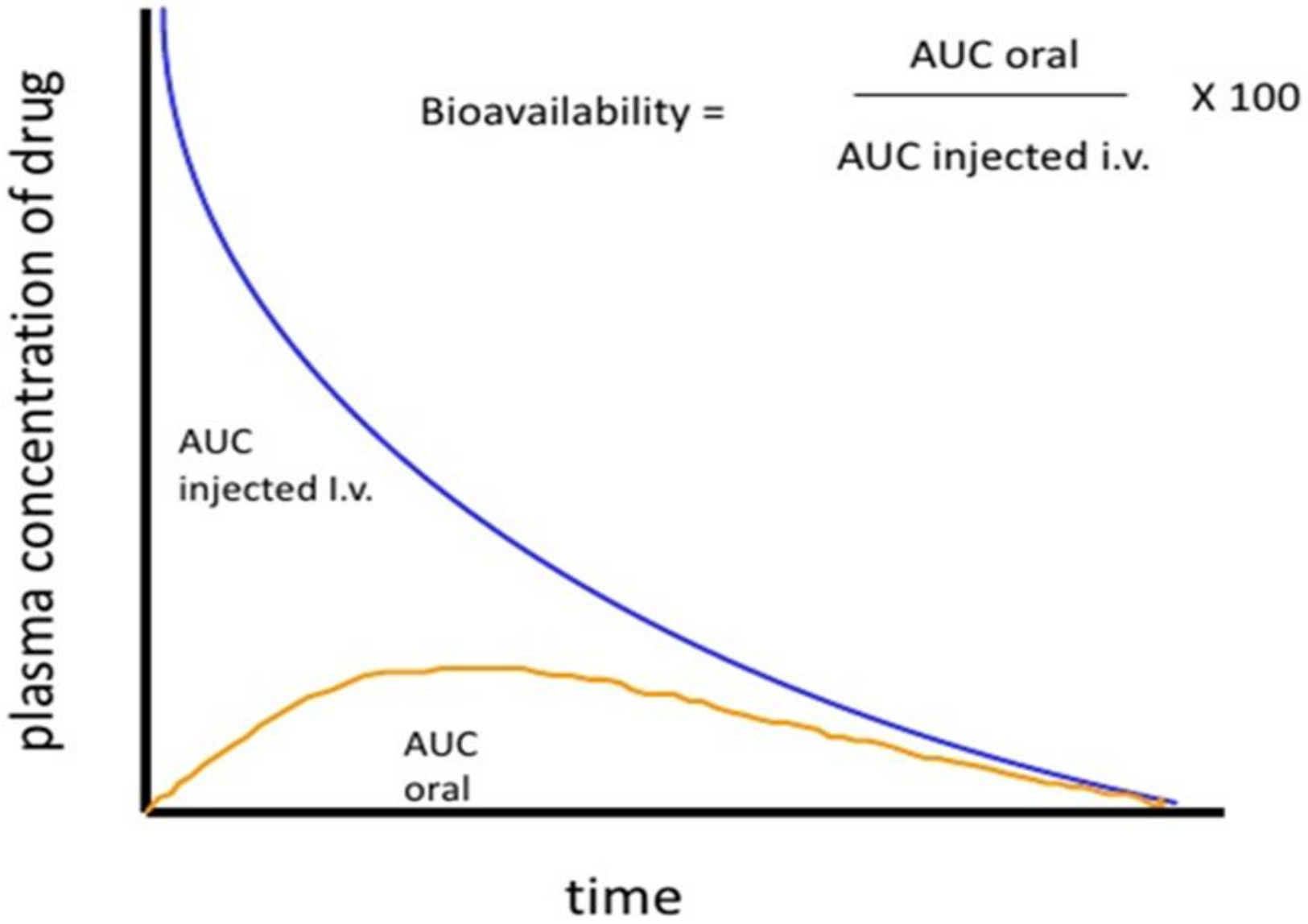
AUC:
area under the concentration-time curve
⇒ measure of the extent of absorption

Cmax:
the observed maximum concentration of a drug
⇒ measure of the rate of absorption



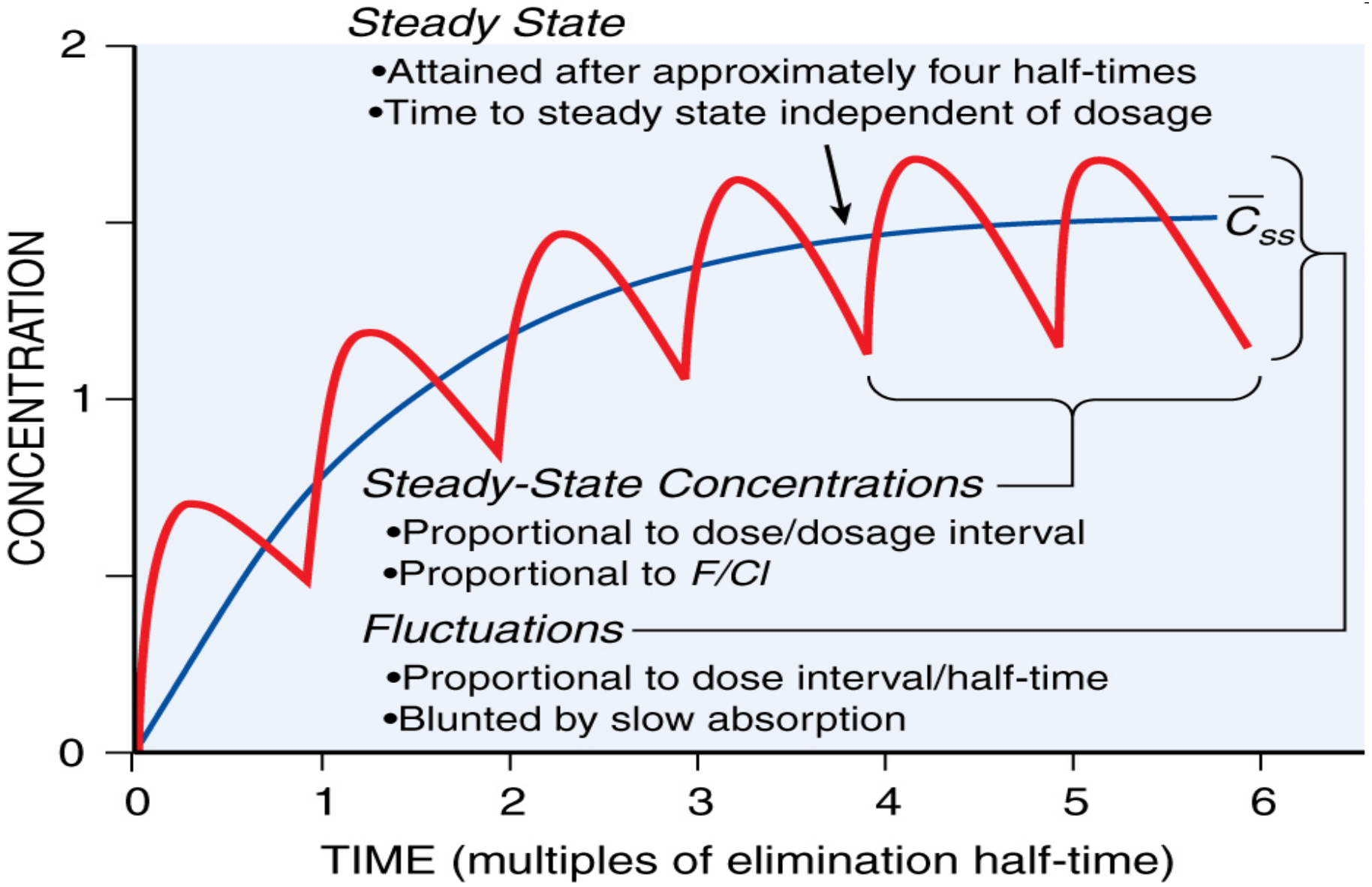
tmax:
time at which Cmax is observed
⇒ measure of the rate of absorption

Bioavailability



$$\text{Bioavailability} = \frac{\text{AUC oral}}{\text{AUC injected i.v.}} \times 100$$

Steady State



Steady State vs. Kinetic Studies

- Many PK/PD concepts are for SS
  - Clearance; Volume of distribution
  - SS PD effect for given SS concentration

  (time to PD SS may be longer than time to plasma SS)

- But some studies are kinetic
  - e.g., single oral dose or I.V. bolus
  - Tracer kinetic studies; PET
  - Aim may be infer SS under repeated dosing

Linear vs Non-linear System

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"Linear Pharmacokinetics"

- double the dose $\Rightarrow$ concentration doubles

  AUC proportional to dose

- *Superposition principle (example)*:

If {I.V. bolus} $\Rightarrow C_{iv}(t)$ and {oral dose} $\Rightarrow C_{oral}(t)$,
then {both dosing together} $\Rightarrow$

$$C(t) \equiv C_{iv}(t) + C_{oral}(t)$$

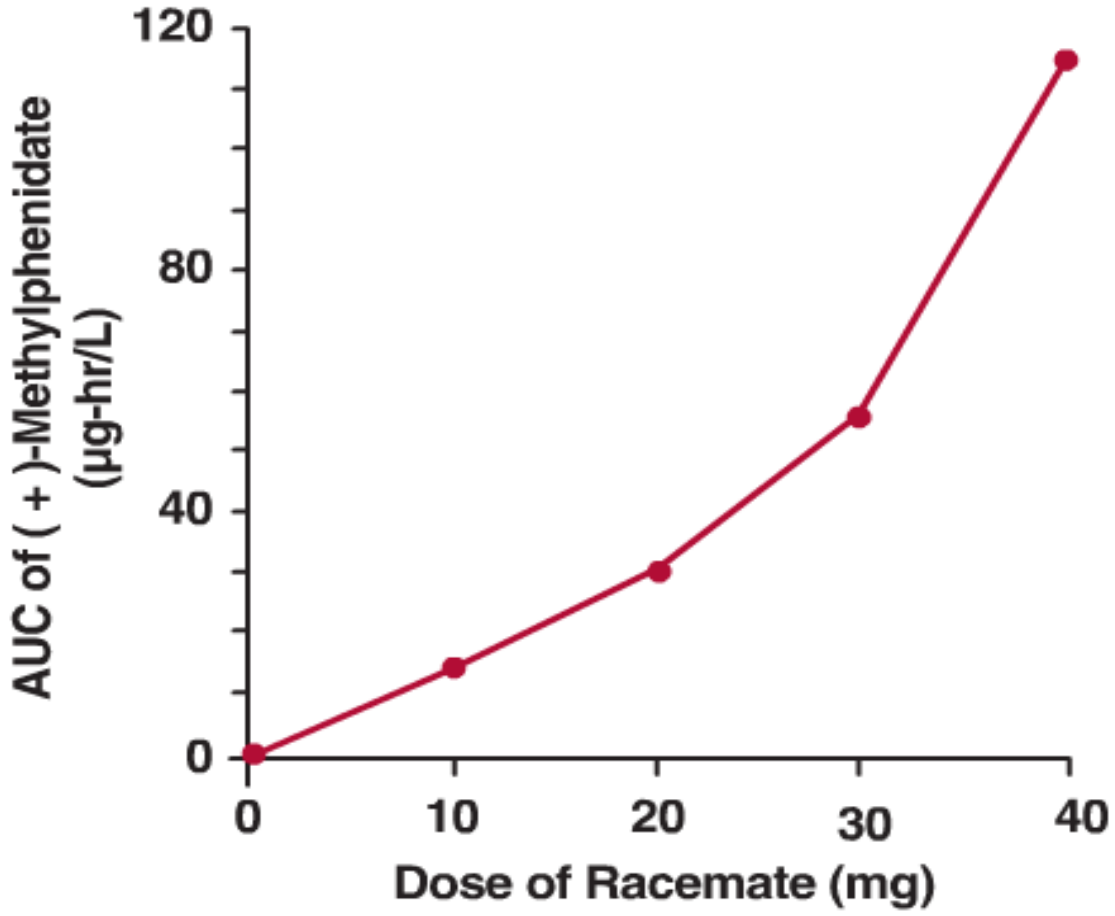
- holds for small enough doses (microdoses)
- linearity for large doses if transport, binding, and elimination remain first order

Linear vs Non-linear System

- Linear
  - single kinetic study + linearity $\Rightarrow$ can predict response to any input, including getting to SS

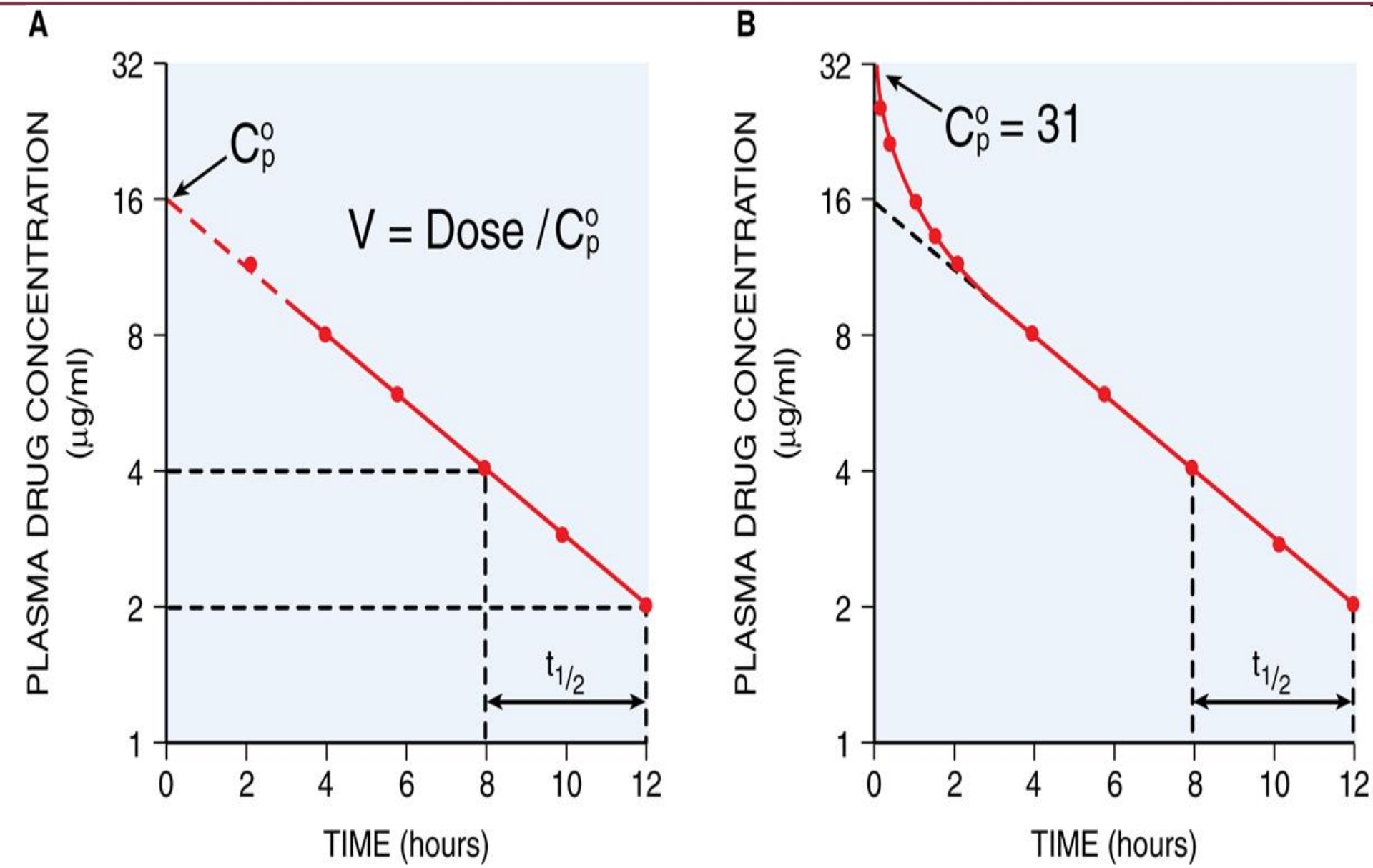
- NON-linear systems:
  - CL, V, etc. not constant; depend on C_{SS}, Dose
  - requires testing at different doses; models
  - time to SS not predicted by single dose study
- Common non-linearities
  - Saturation kinetics (Michaelis-Menten)
  - Saturable plasma protein, tissue binding
  - Threshold effects (e.g., glucose spilling)
  - Induction: Neuronal/hormonal regulation

“Non-linear Kinetics” Example



The relationship between the *AUC* of (+)-methylphenidate and dose following oral administration of 10, 20, 30, and 40 mg of the racemate to the same volunteer. No appreciable difference is seen for the metabolites. (From: Aoyama T, Kotaki H, Sasaki T. Nonlinear kinetics of threo-methylphenidate enantiomers in a patient with narcolepsy and in healthy volunteers. Eur J Clin Pharmacol 1993;44:79–84.)

Pharmacokinetics Half Life (t1/2)



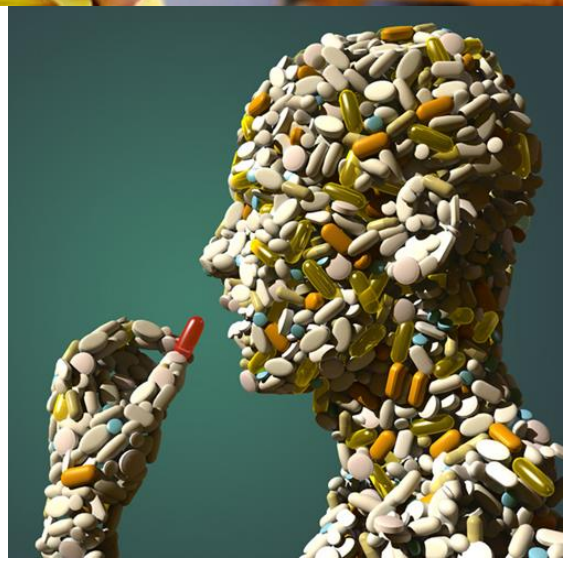
PK/PD Modeling

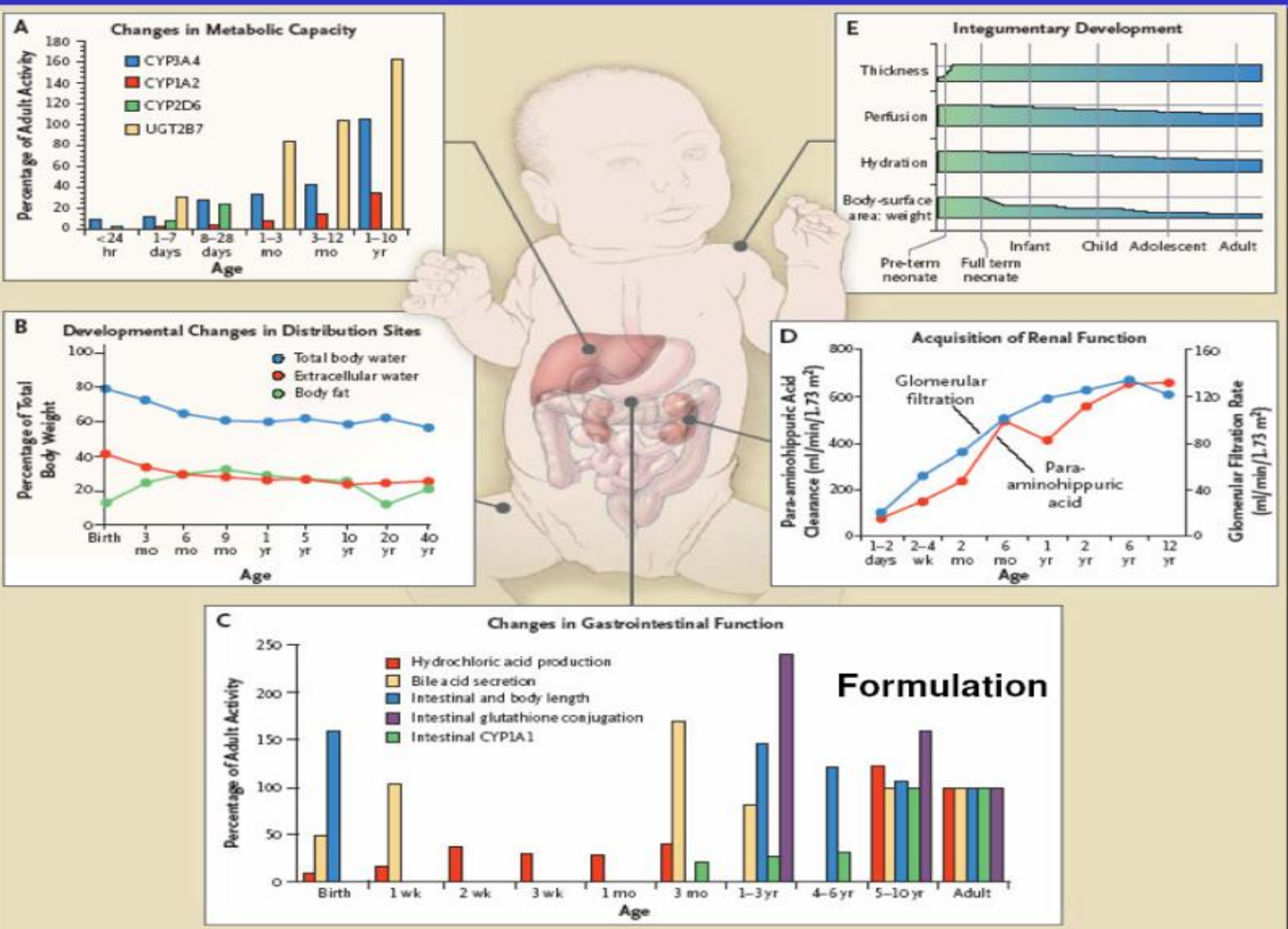
- Procedure:
  - Estimate exposure and examine correlation between PD other endpoints (including AE rates)
  - Use mechanistic models
- Purpose:
  - Estimate therapeutic window
  - Dose selection
  - Identify mechanism of action
  - Model probability of AE as function of exposure (and covariates)
  - Inform the label of the medicine

SPECIFIC CONDIDERATIONS

Specific considerations of PD/PK

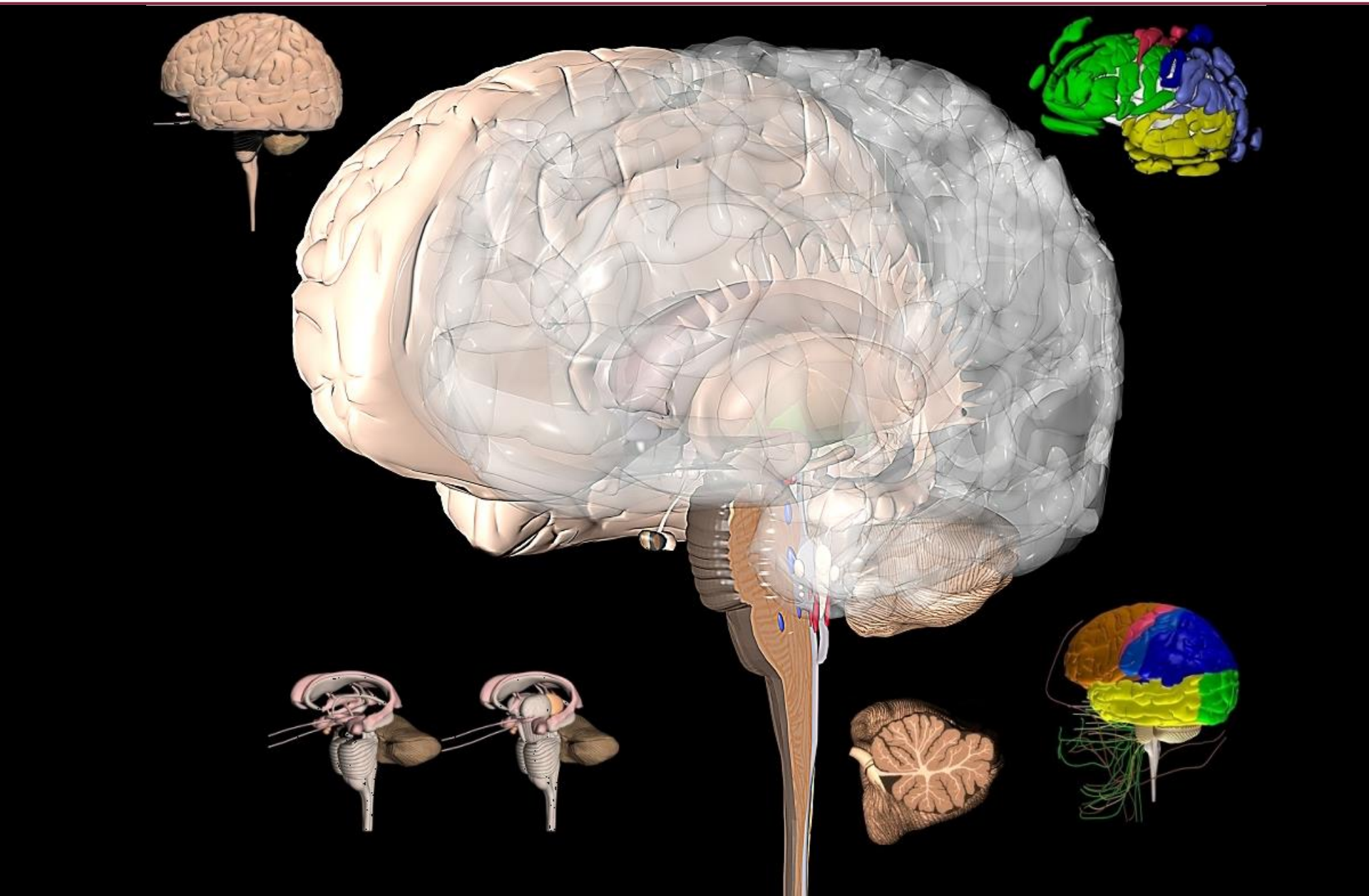
- Patient populations
  - Paediatric, gender, elderly
- Other medications and foods
  - Drug-drug
  - Drug-food
- Pharmacogenomics
  - Genetic polymorphism – Codeine Cyp2D6 ultrarapid
- Other diseases,
  - Co-infections, etc



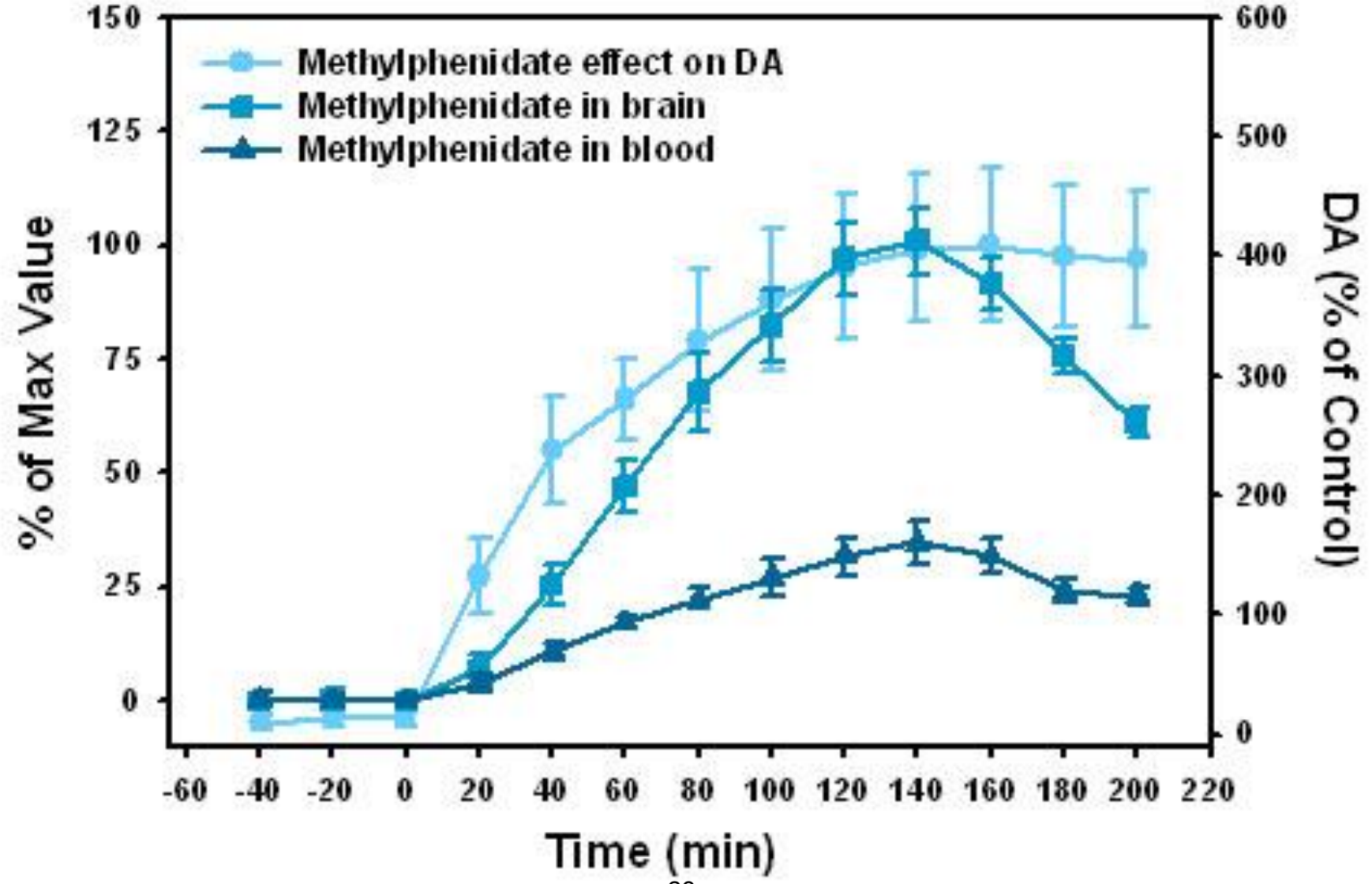


Ref: Kearns et al. NEJM 2003

The Brain - Challenges



Relationship Dynamics/Kinetics - Challenges



REGULATORY FRAMEWORK

Regulatory Control

- **Package insert (PI)**
  - Currently in South Africa the “package insert” (as defined by Act 101 1965 as amended in Regulation 9) is a scientific data sheet that is **intended first and foremost for the healthcare professional, viz. the prescriber / dispenser as an informative tool for the prescribing / dispensing** of medicine to the patient

Patient information leaflet (PIL)

  - The patient information leaflet on the other hand is **intended primarily for the patient (end user)** and imparts valuable information regarding the medicine in layman’s terms that can be easily understood (Regulation 10)

- **Evidence Based**
  - **Non-Clinical and Clinical studies (NCEs)**
  - **Literature support (Generics)**

MCC - PI Guideline Pharmacological Action

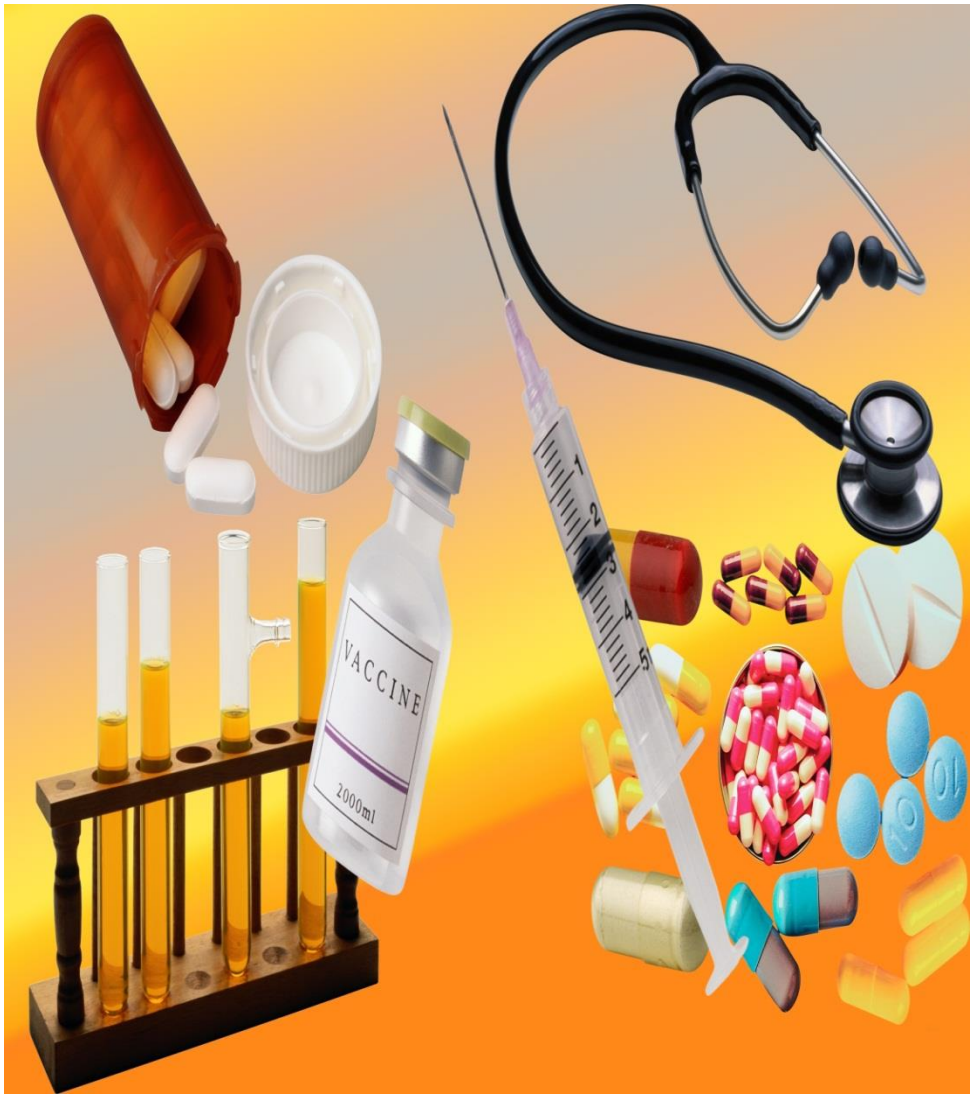
- **Pharmacodynamics**
  - Describe
    - mechanism of action (if known),
    - pharmacodynamic effects,
    - relevant clinical efficacy.
  - For antimicrobial agents:
    - Do not include antimicrobial sensitivity data derived from *in vitro* testing, but include data on *in vitro* resistance.
    - Include only *in vivo* data of organisms which have been shown to be eradicated in clinical trials which can be linked to the indications (See INDICATIONS).
    - When efficacy data are not available, *in vitro* sensitive organisms can be included.
      - This information should be accompanied by a statement that *in vitro* sensitivity does not necessarily imply clinical sensitivity.

MCC - PI Guideline Pharmacological Action

- **Pharmacokinetic properties**
  - relevant for the recommended dose and for the strength
    - absorption, distribution, protein binding, biotransformation, elimination and linearity/non-linearity, as appropriate for the product marketed.
  - intake of the product in relation to food intake (i.e. with or without food).
  - specific patient groups with respect to factors such as
    - age, gender, smoking, polymorphic metabolism and concomitant pathological situations such as renal impairment and hepatic insufficiency, when clinically relevant.
  - Information on pharmacokinetic and pharmacodynamic relationship(s) and the contribution (if any) of
    - metabolite(s)

MCC - PIL Guideline

- **NO** direct reference to Pharmacodynamics or –kinetics
  - What the medicine is used for?
    - Dynamics
  - How to take/use? Fatty meal etc.
    - Kinetics
  - How frequent?
    - Kinetics
  - How long is treatment?
    - Dynamics
  - What to do when the effect is too strong or too weak?
    - Dynamics
  - If you forgot to take?
    - Kinetics
  - When taken with other medication and or foods?
    - Interactions (dynamic/kinetics)
  - Aspects on safety



Additional Information

- **Web sites:**

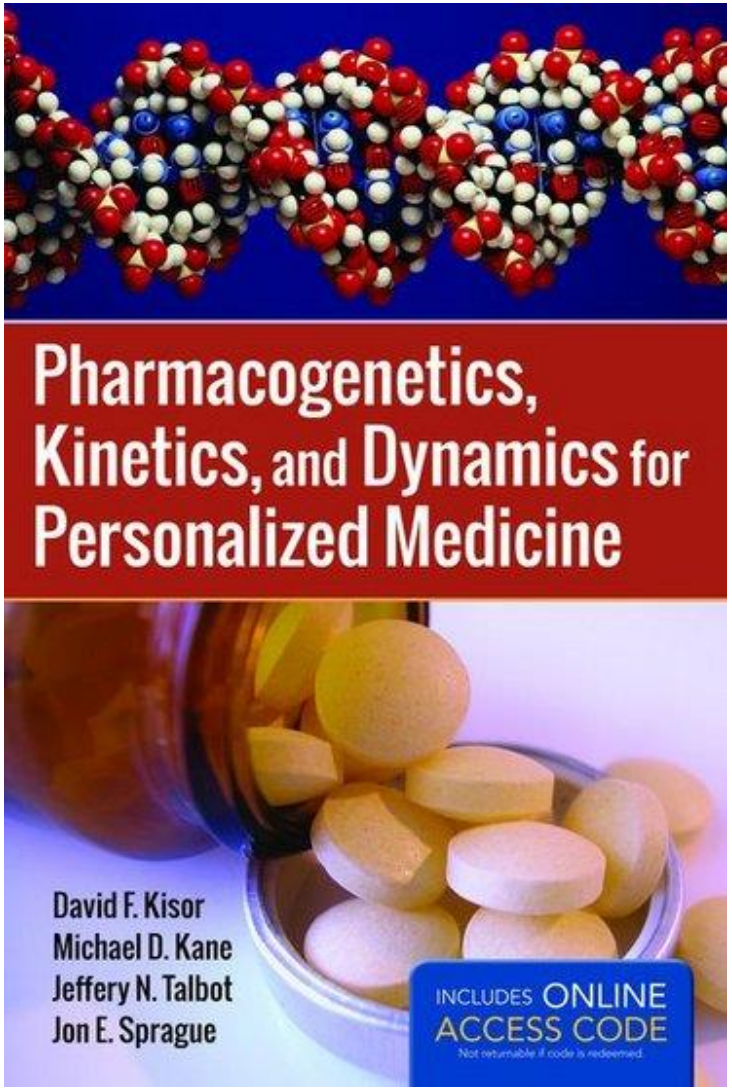
- **www.cc.nih.gov/ training/training/**
- **www.boomer.org/pkin**
- **www.icp.org.nz/**

CONCLUSIONS

Conclusions

PD/PK at the centre of any medicine:

- Label Claim
- Efficacy
- Safety
- Special populations
- Critical Information for the
  - Manufacturer
  - Prescriber
  - Dispenser
  - Patient
- Basis for rational drug use
- Basis of Pharmacovigilance



Thank You

www.wcp2014.org

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13-18 July 2014

17th World Congress of Basic and Clinical Pharmacology, 2014

South Africa

IUPHAR International union of basic and clinical pharmacology

South African Society for Basic and Clinical Pharmacology

PharfA Pharmacology for Africa
www.iuphar-africa.org

First ever in Africa!

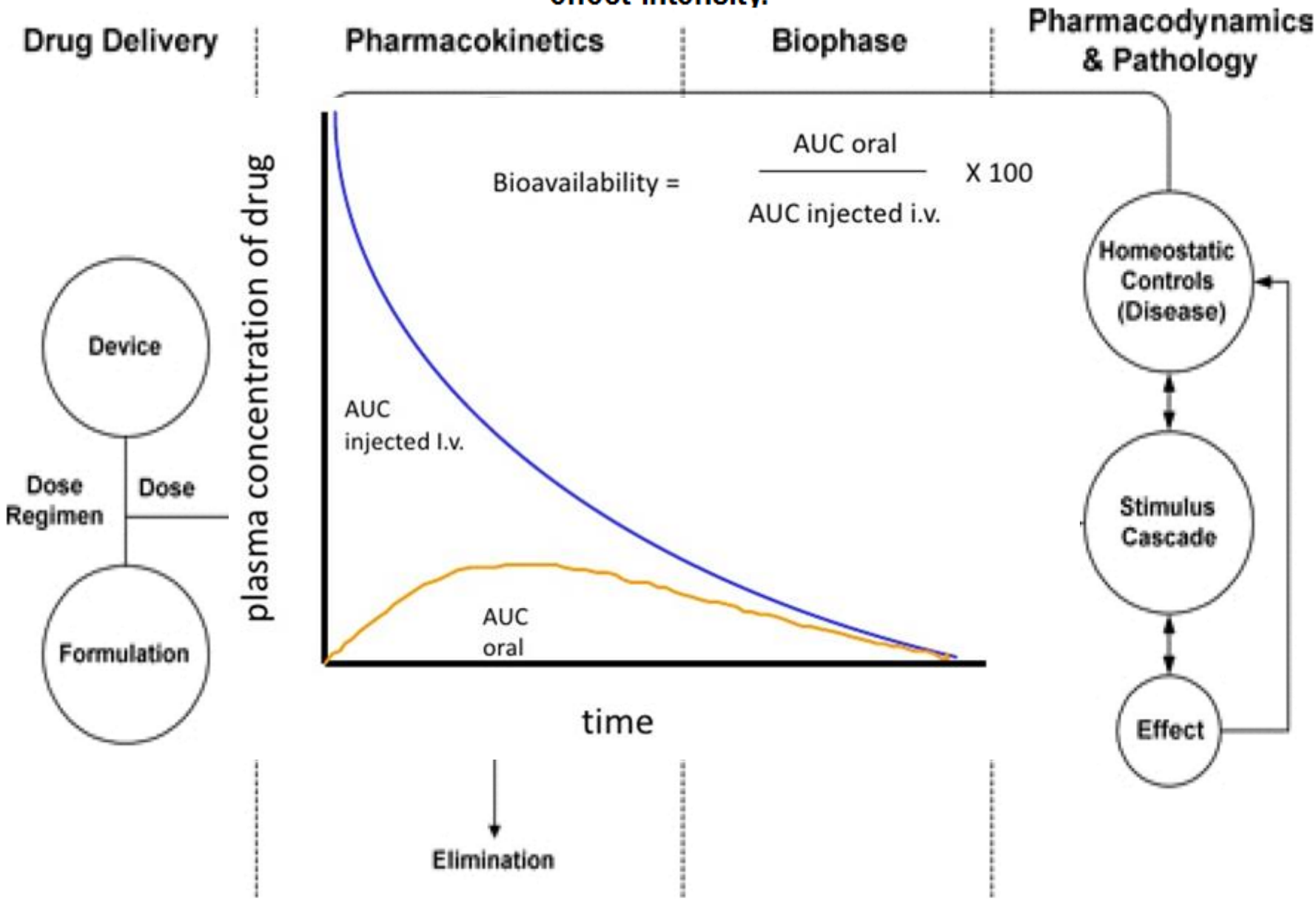
First ever in Africa!

Thank you

13-18 July 2014

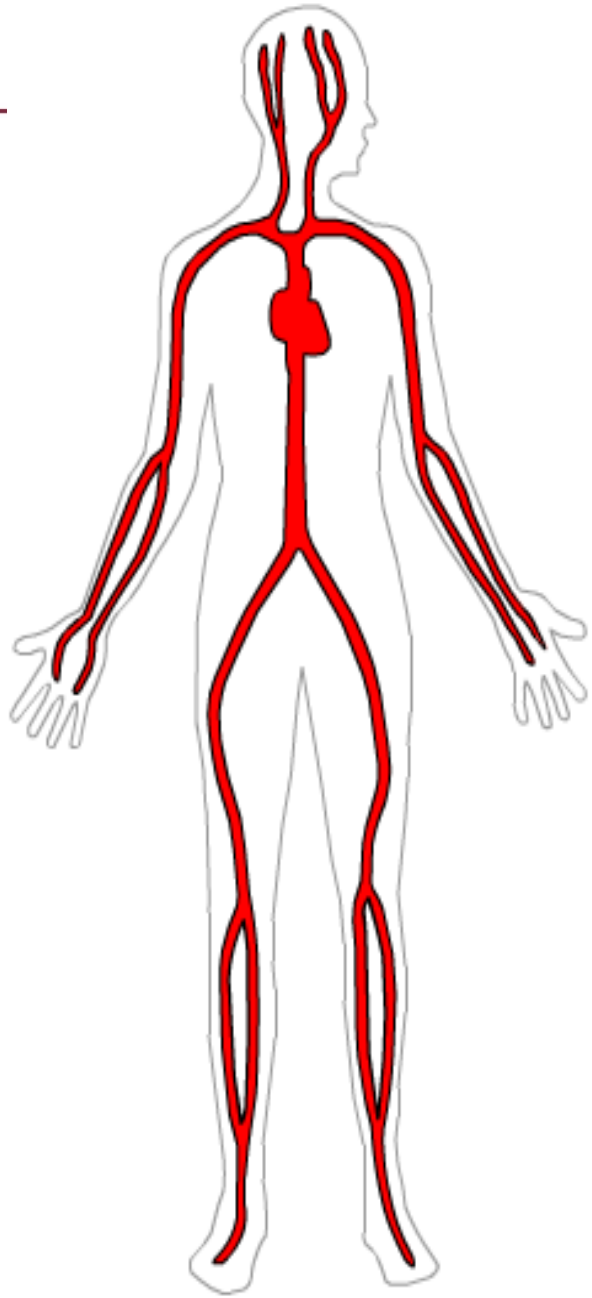
Cape Town South Africa

Schematic representation of the pharmacokinetic– pharmacodynamic processes and homeostasis that determine the relationship between the administered dose and the resulting effect intensity.



Huntjens D R H et al. Rheumatology 2005;44:846-859

Volume of Distribution



Vd

5 L

Drug concentrated in blood stream

Drug in blood and extracellular space

Drug equally distributed in blood and tissues

Drug moderately concentrated in tissues

Drug highly concentrated in tissues (usually adipose)

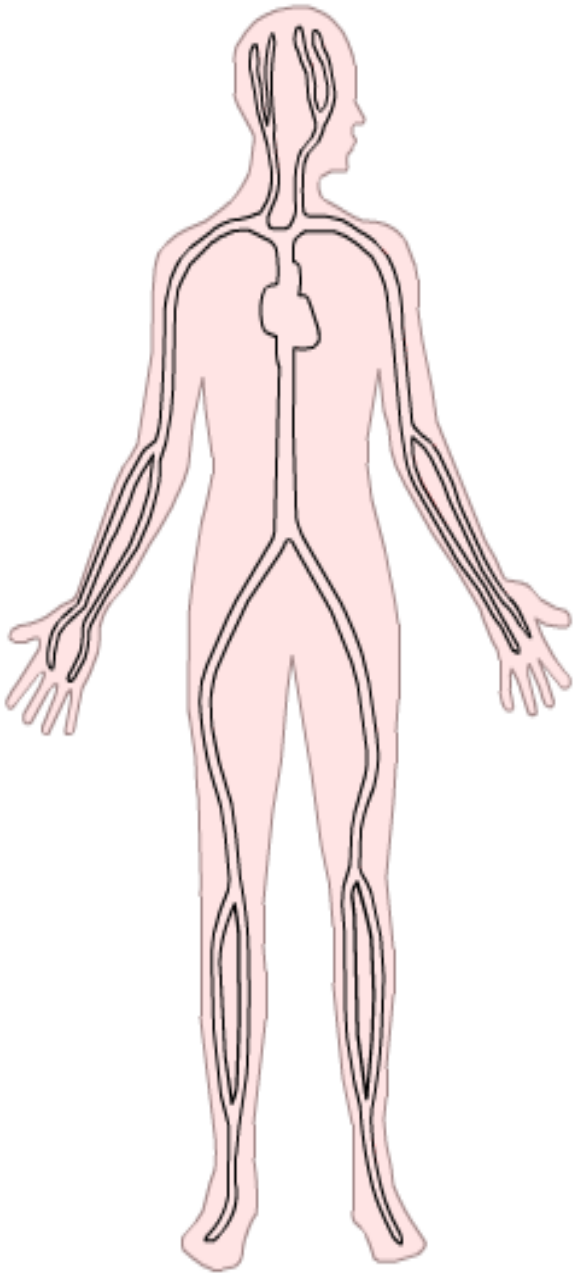
10,000 L

Amount in body = Vd x plasma concentration

$$Ab = Vd \times Cp$$

$$Vd = \frac{Ab}{Cp}$$

Volume of Distribution



Vd

5 L

Drug concentrated in blood stream

Drug in blood and extracellular space

Drug equally distributed in blood and tissues

Drug moderately concentrated in tissues

Drug highly concentrated in tissues (usually adipose)

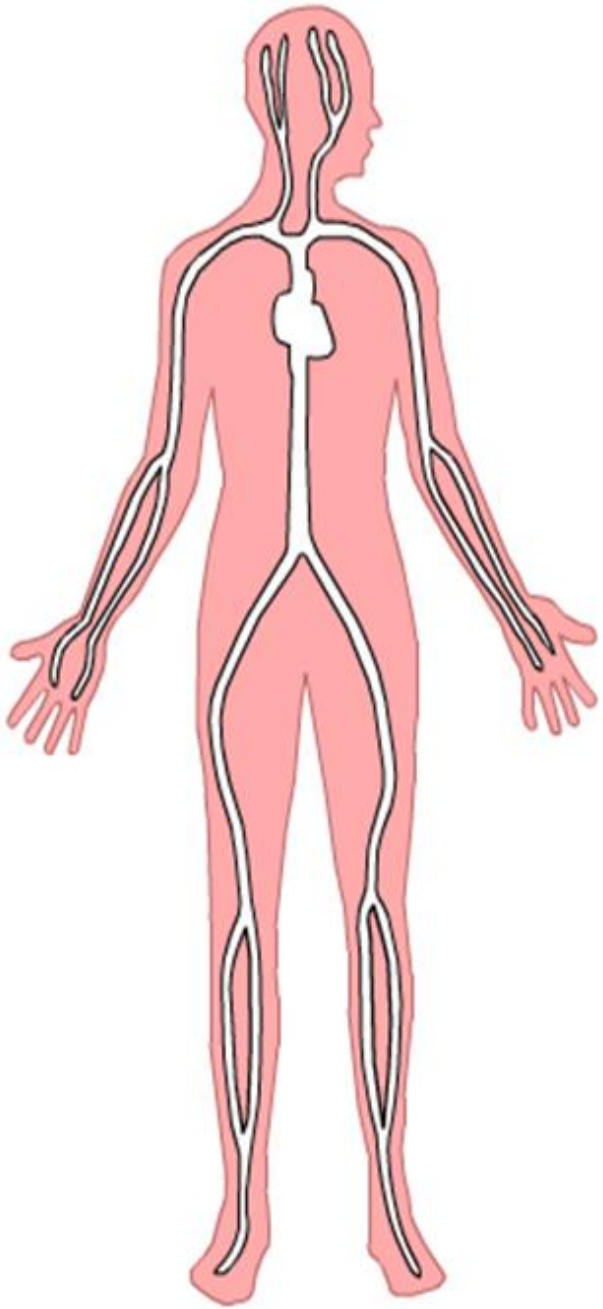
10,000 L

Amount in body = Vd x plasma concentration

$$Ab = Vd \times Cp$$

$$Vd = \frac{Ab}{Cp}$$

Volume of Distribution



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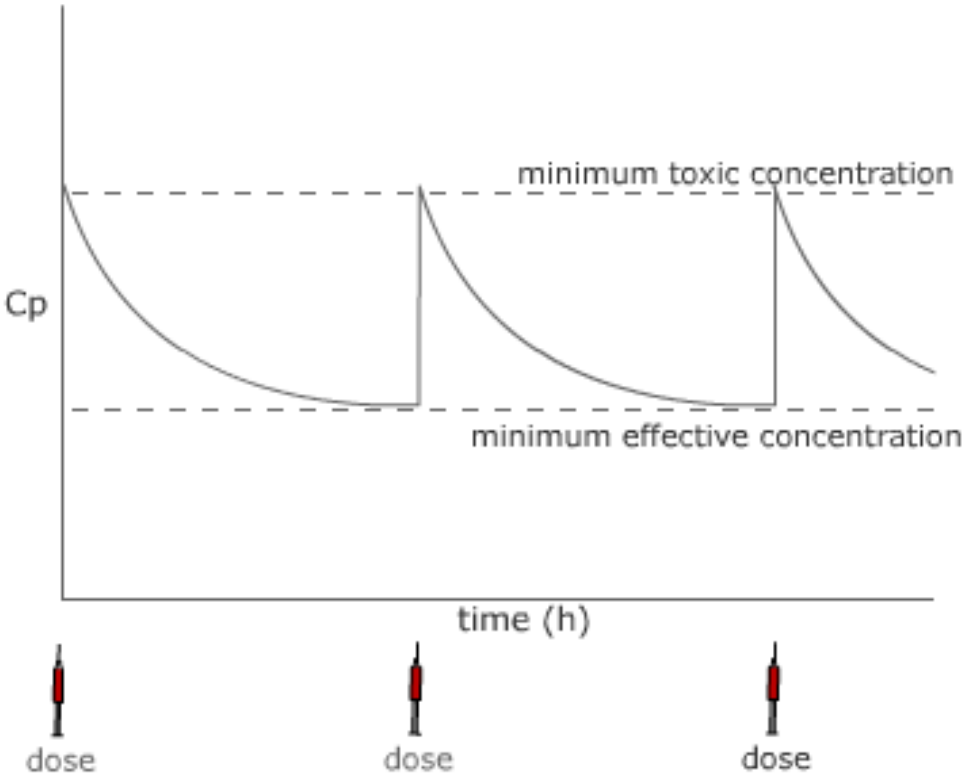
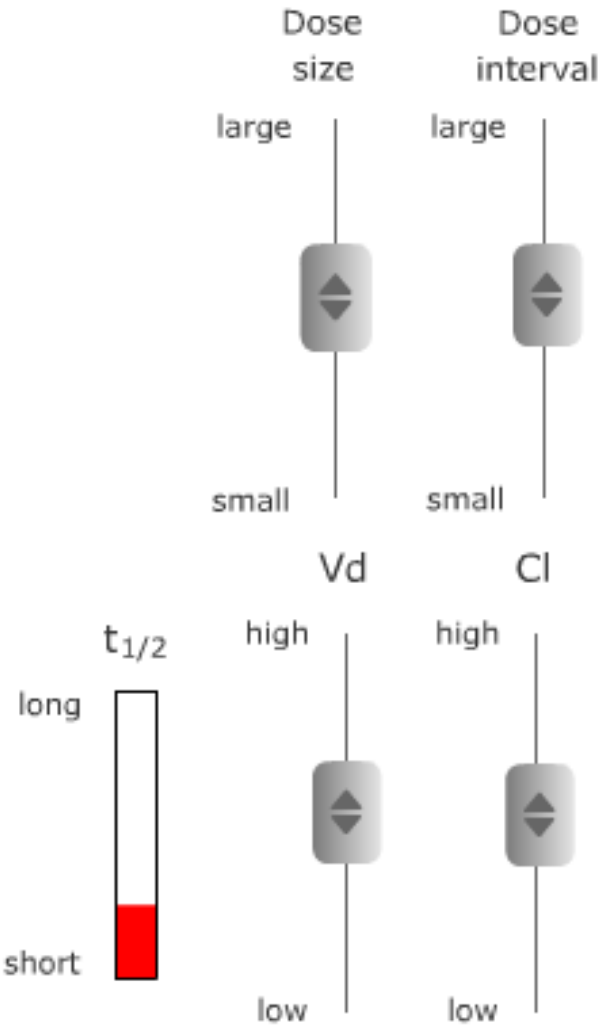
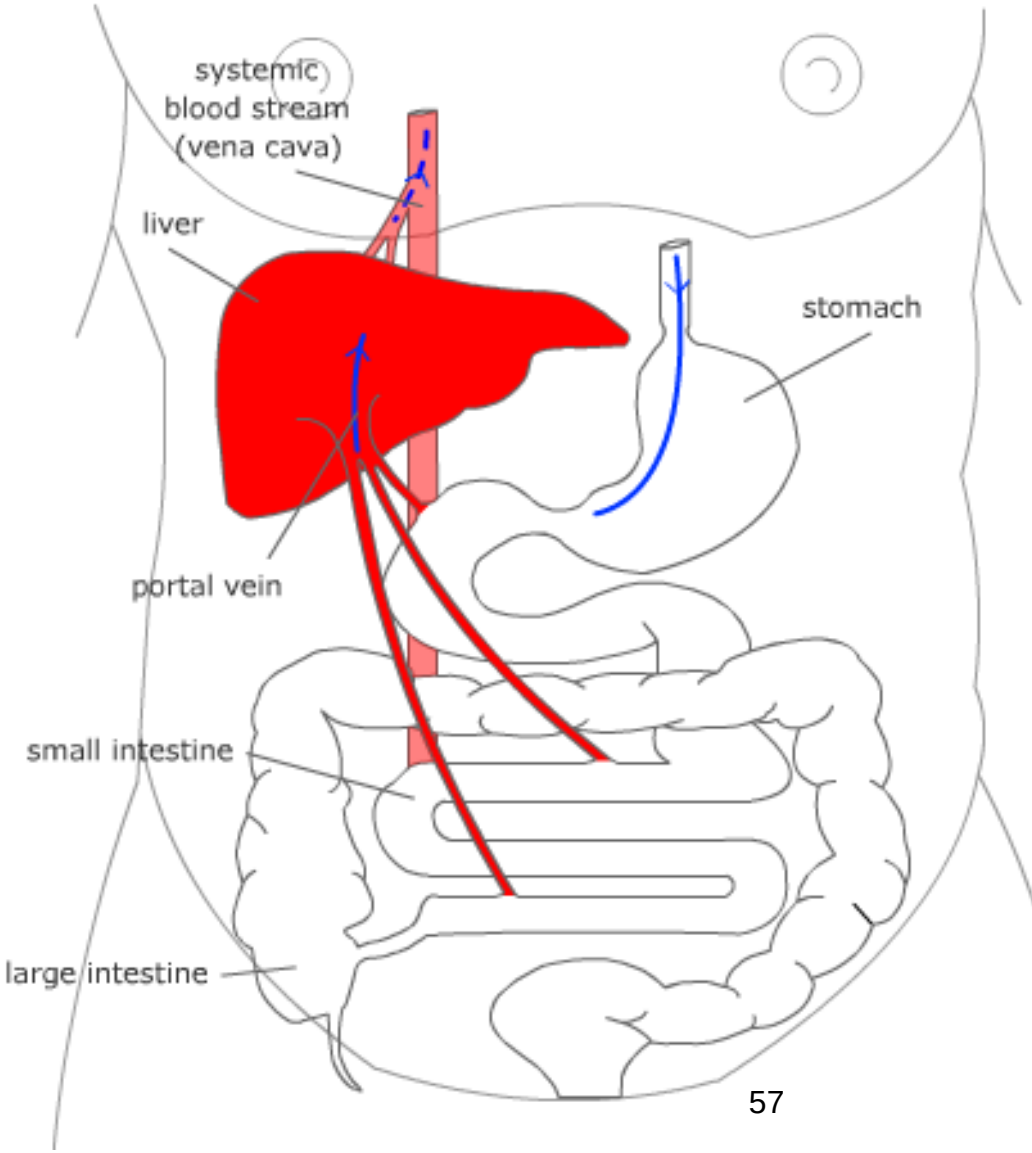
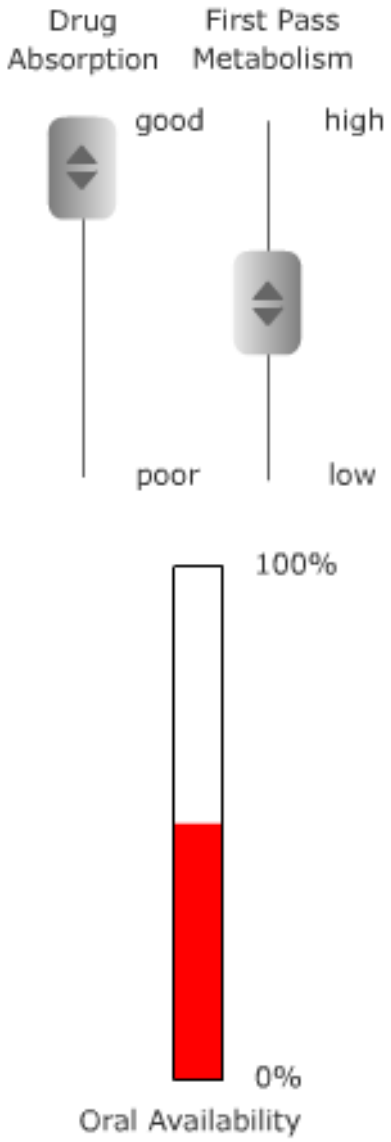
Kinetic Relationships

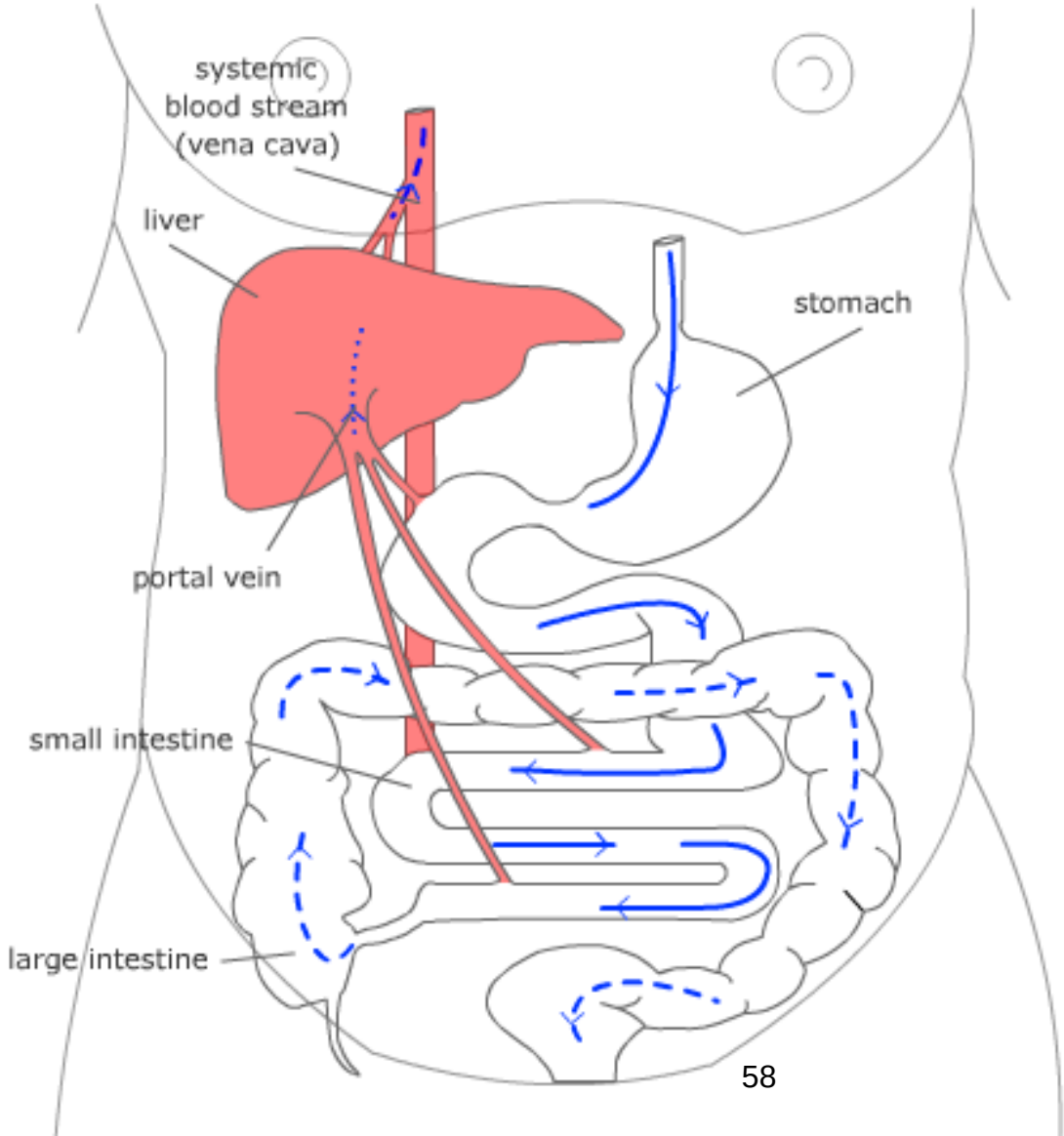


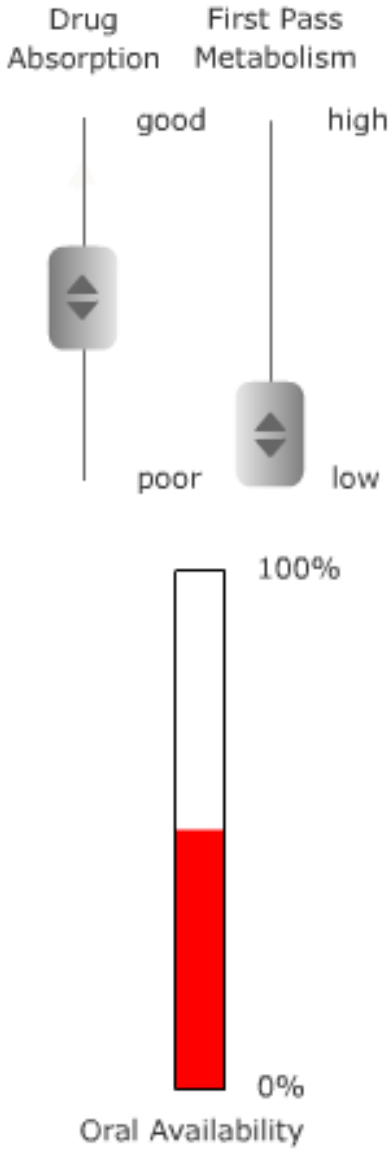


Metabolism - First Pass






systemic
blood stream
(vena cava)
liver
stomach
portal vein
small intestine
large intestine


Drug
Absorption
First Pass
Metabolism
good
high
poor
low
100%
0%
Oral Availability

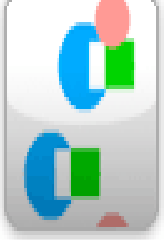
CTD Module 4: 3.Toxicology
SPC Relevant Scientific information

- 1.Single-Dose Toxicity
- 2.Repeat-Dose Toxicity
- 3.Genotoxicity
  - 1.*In vitro* Studies
  - 2.*In vivo* Studies
- 4.Carcinogenicity
- 5.Reproductive and Development Toxicity
  - 1.Fertility and Embryonic Development
  - 2.Embryo-Fetal Development
  - 3.Pre- and Post-natal Development & Maternal Function
  - 4.Offspring, Juvenile, Second & Third-Generation Studies
- 6.Local Tolerance
- 7.Other Toxicity Studies
  - 1.Antigenicity
  - 2.Immunogenicity
  - 3.Mechanistic Studies (not included elsewhere)
  - 4.Dependence
  - 5.Metabolites
  - 6.Impurities, 7. Other

	PHASE I	PHASE II	PHASE III	PHASE IV
OBJECTIVES:	Determine the metabolic and pharmacological actions and the maximally tolerated dose	Evaluate effectiveness, determine the short-term side effects and identify common risks for a specific population and disease	Obtain additional information about the effectiveness on clinical outcomes and evaluate the overall risk-benefit ratio in a demographically diverse sample	Monitor ongoing safety in large populations and identify additional uses of the agent that might be approved by the FDA
FACTORS TO BE IDENTIFIED:	-Bioavailability -Bioequivalence -Dose proportionality -Metabolism -Pharmacodynamics -Pharmacokinetics	-Bioavailability -Drug-disease interactions -Drug-drug interactions -Efficacy at various doses -Pharmakodynamics -Pharmakokinetics -Patient safety	-Drug-disease interactions -Drug-drug interactions -Dosage intervals -Risk-benefit information -Efficacy and safety for subgroups	-Epidemiological data -Efficacy and safety within large, diverse populations -Pharmacoeconomics
DATA FOCUS:	-Vital signs -Plasma and serum levels -Adverse events	-Dose response and tolerance -Adverse events -Efficacy	-Laboratory data -Efficacy -Adverse events	-Efficacy -Pharmacoeconomics -Epidemiology -Adverse events
DESIGN FEATURES:	-Single, ascending dose tiers -Unblinded -Uncontrolled	-Placebo controlled comparisons -Active controlled comparisons -Well-defined entry criteria	-Randomized -Controlled -2-3 treatment arms -Broader eligibility criteria	-Uncontrolled -Observational
DURATION:	Up to 1 month	Several months	Several years	Ongoing (following FDA approval)
POPULATION:	Healthy volunteers or individuals with the target disease (such as cancer or HIV)	Individuals with target disease	Individuals with target disease	Individuals with target disease, as well as new age groups, genders, etc.
SAMPLE SIZE:	20 to 80	200 to 300	Hundreds to thousands	Thousands
EXAMPLE:	Study of a single dose of Drug X in normal subjects	Double-blind study evaluating safety and efficacy of Drug X vs. placebo in patients with hypertension	Study of Drug X vs. standard treatment in hypertension study	Study of economic benefit of newly-approved Drug X vs. standard treatment for hypertension

Drug Clearance

The most important pharmacokinetic parameter. Determines maintenance dose.



Saturable Drug Metabolism

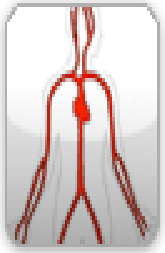
When drug concentrations exceed the capacity of metabolism.

Drug Elimination

Drug clearance and dose requirements vary markedly throughout life.

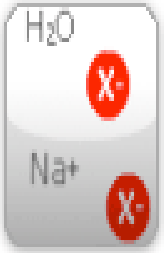
Protein Binding

Only important in interpreting measured drug concentrations.



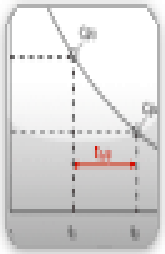
Volume of Distribution

The volume into which a drug appears to be distributed. Determines loading dose.



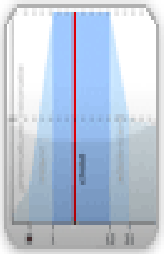
PH and Pharmacokinetics

Acids are ionized in basic media.
Bases are ionized in acidic media.



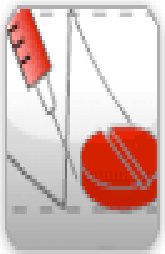
The Half-life

The time for the concentration of the drug to halve.



Dosing and Age

Drug clearance and dose requirements vary markedly throughout life.



Dosing Variations

The route of drug administration influences pharmacokinetics.

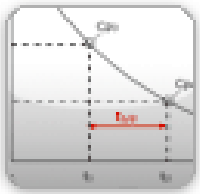
Drugs in Pregnancy

Effect of drugs on the pregnancy.
Effect of pregnancy on the drugs.

requirements vary markedly throughout life.

Volume of Distribution

The volume into which a drug appears to be distributed. Determines loading dose.



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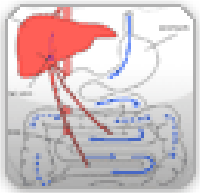
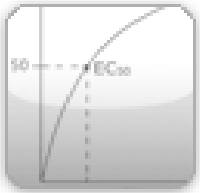


Oral Availability

The fraction of drug that reaches the systemic circulation after oral ingestion.



Pharmacodynamics

The action of the drug on the body.

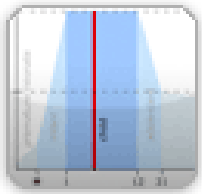
Pharmacogenetics

How genes determine drug concentrations.

measured drug concentration

PH and Pharmacokinetic

Acids are ionized in basic me
Bases are ionized in acidic m



Dosing and Age

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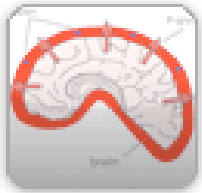
Effect of drugs on the pregna
Effect of pregnancy on the dru

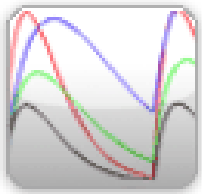
Drug Interactions

How one drug affects the con
actions of another.



Drug Transport

Active transporters can help p
drug toxicities and aid uptake



Graph Plotter

Vary your dose regimen for di
settings.