INTRODUCTION TO PHARMACOKINETICS (PK)

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21-February-2019

Outline

- Definition & Relevance of Pharmacokinetics & Pharmacodynamics (PK/PD)
- Small v/s Large Molecules
- Fundamental Concepts of PK
- Q&A

Drug Label – Sections Informed by PKPD Information

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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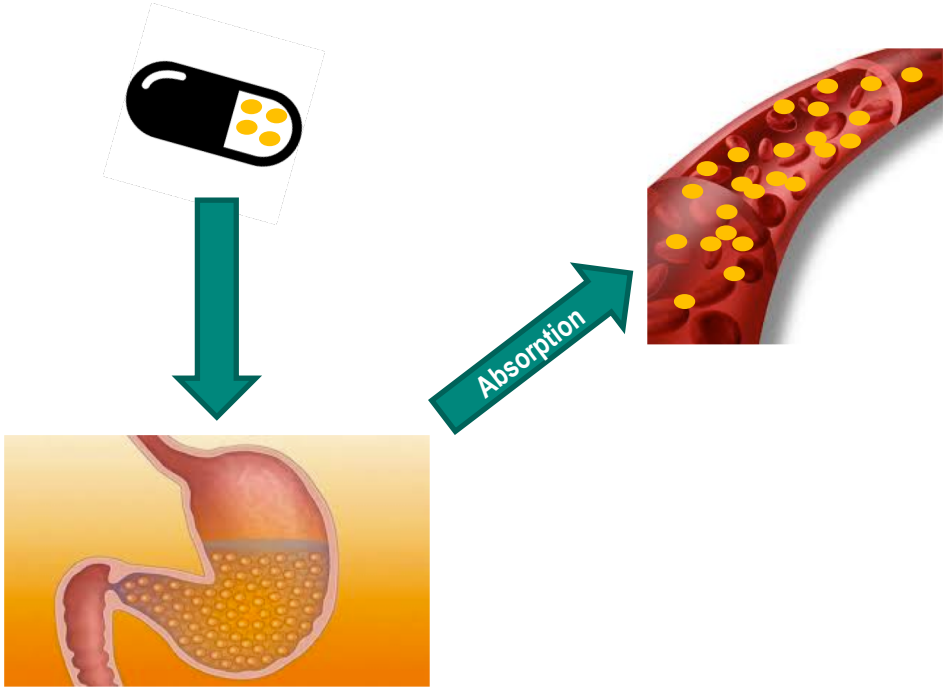
What is Pharmacokinetics?

Pharmacokinetics (PK)

- What the body does to the drug



Parent Drug

Metabolite

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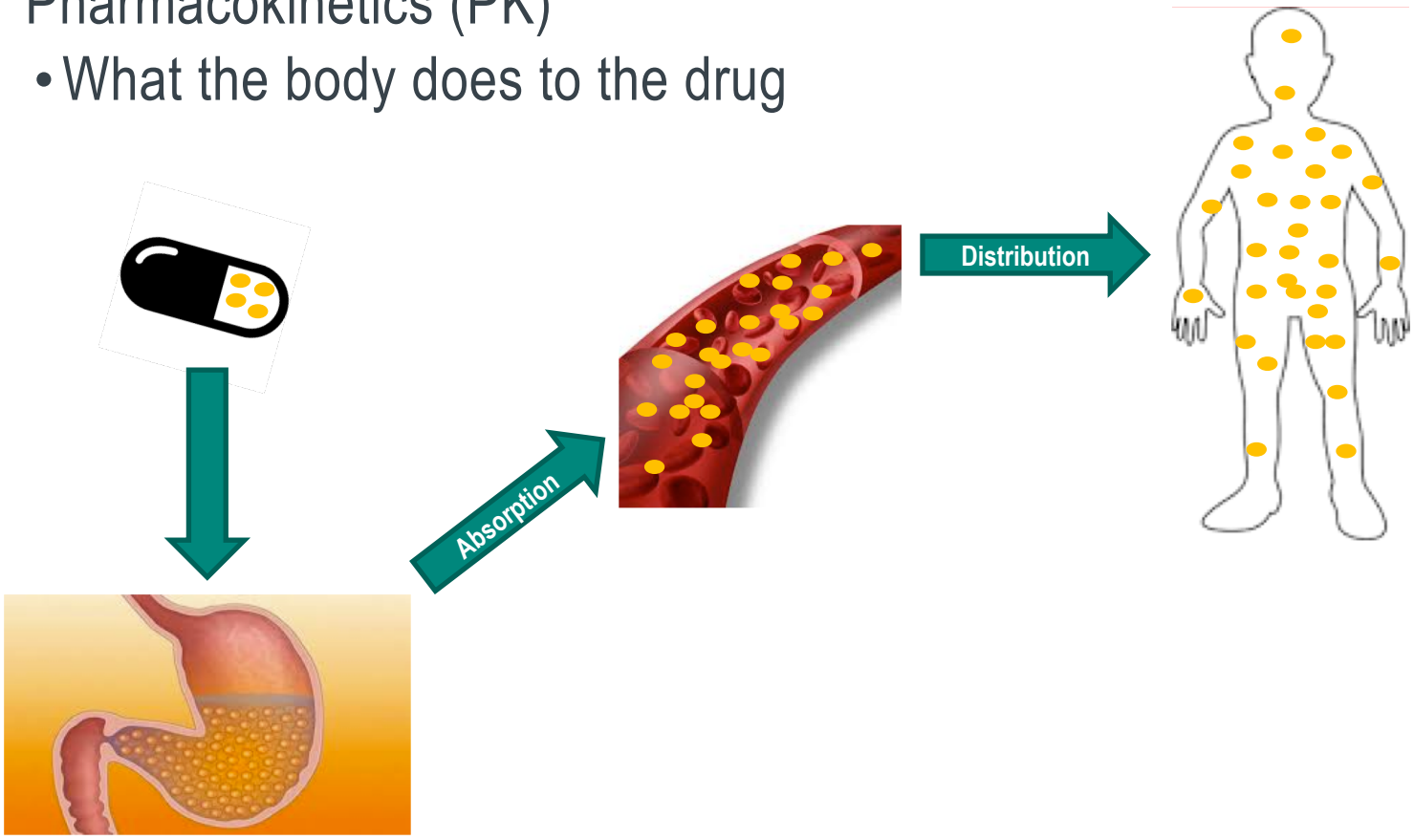

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What is Pharmacokinetics?

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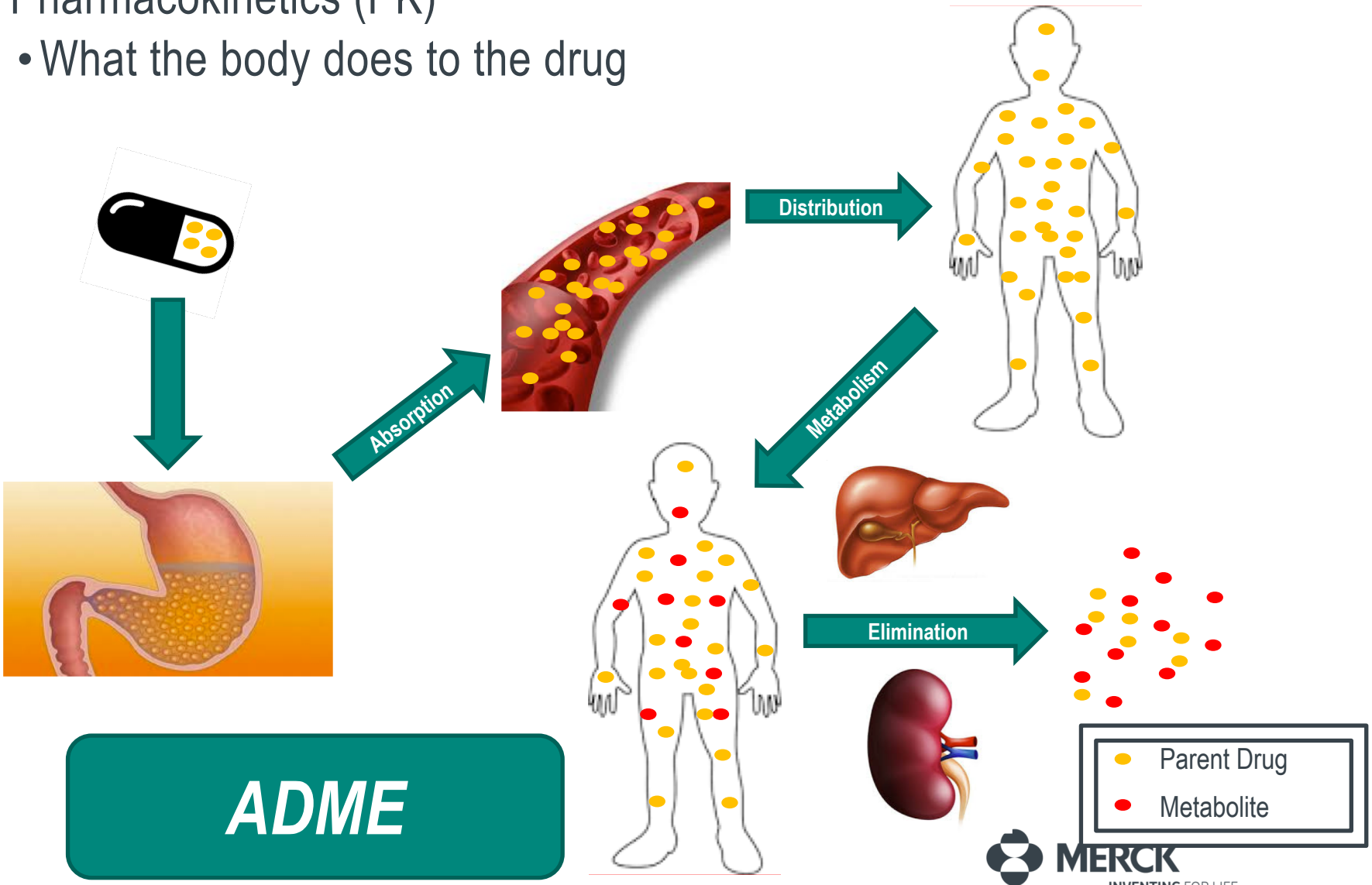
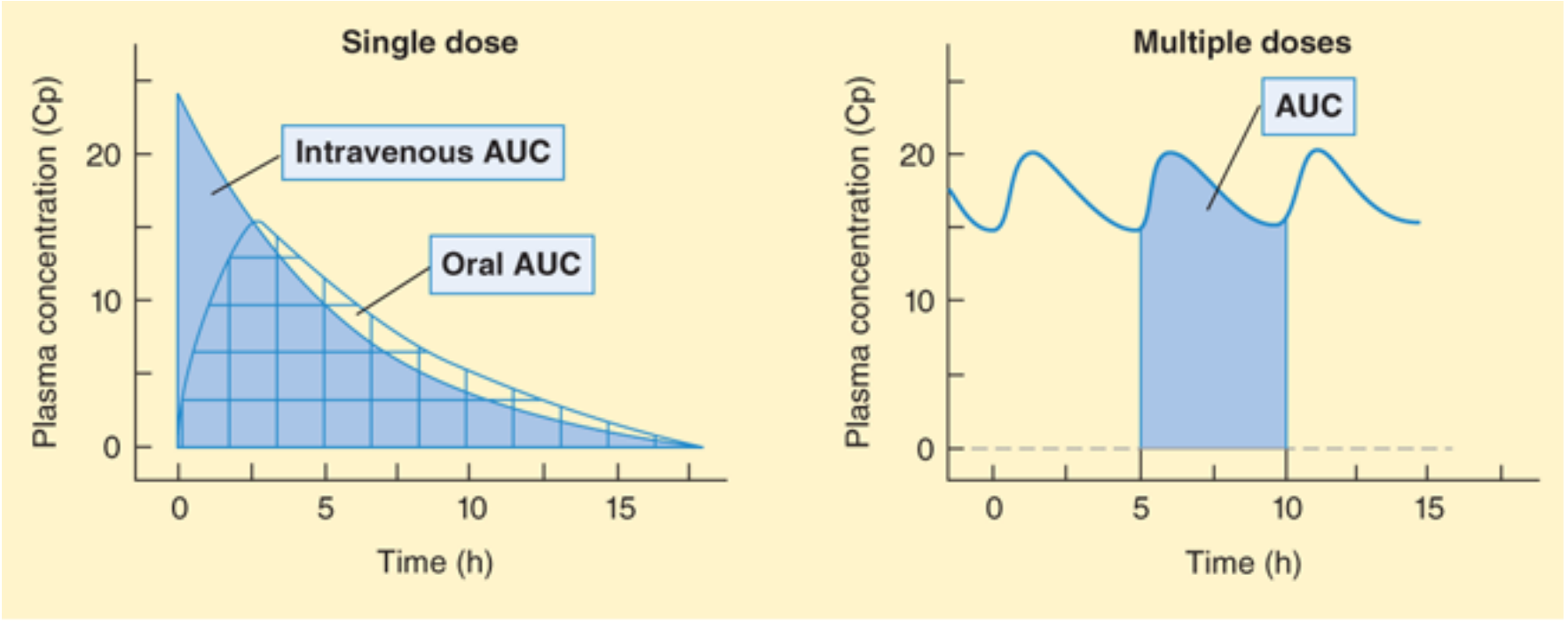


PK Profiles Based on Route of Administration & Multiple Dosing

AUC: Area Under the Curve (measure of drug exposure)



Source: A.J. Trevor, B.G. Katzung, M. Kruidering-Hall: Katzung & Trevor's Pharmacology: Examination & Board Review, 11th Ed.
www.accesspharmacy.com

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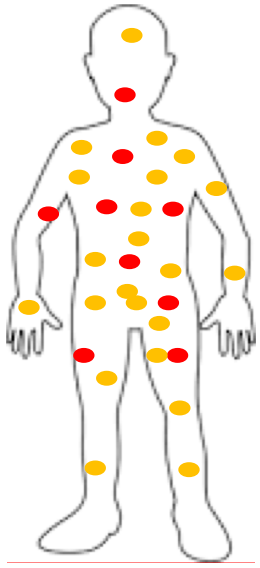
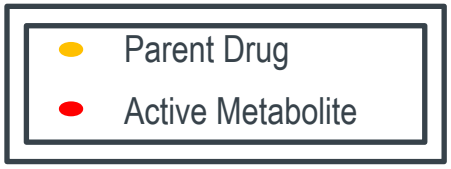
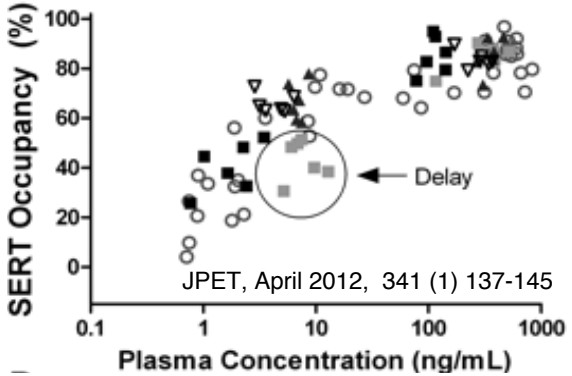
What is Pharmacodynamics?

Pharmacodynamics (PD)

- What the drug does to the body





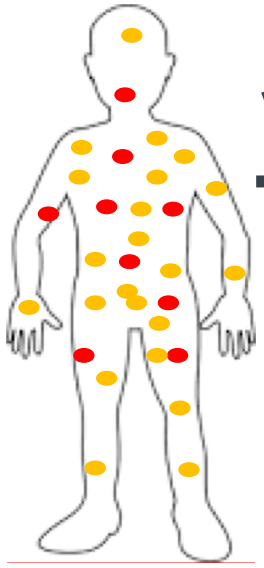


Transporter Occupancy of Duloxetine

What is Pharmacodynamics?

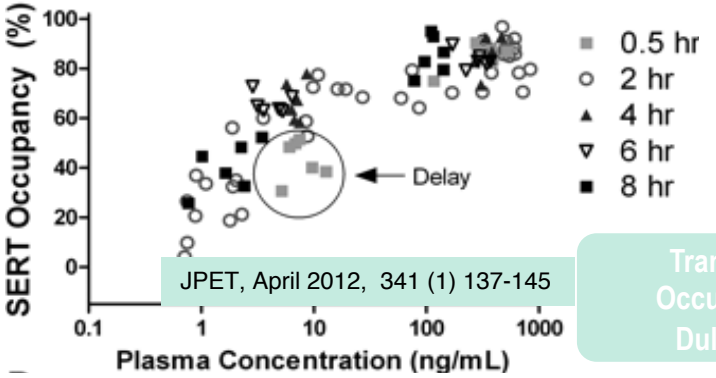
Pharmacodynamics (PD)

- What the drug does to the body



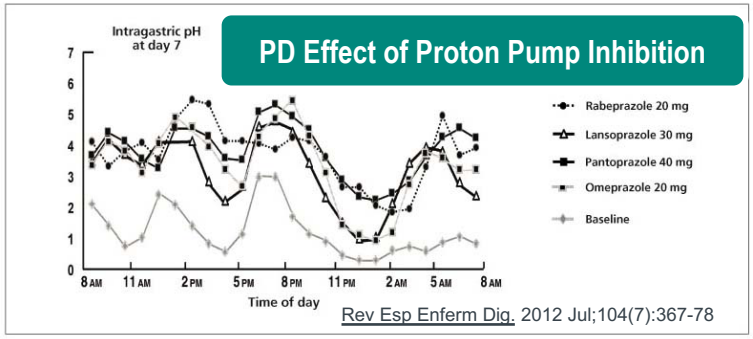
Parent Drug

Active Metabolite



JPET, April 2012, 341 (1) 137-145

Transporter Occupancy of Duloxetine



Rev Esp Enferm Dig. 2012 Jul;104(7):367-78

Fig. 1. Comparison of the intragastric pH profile of different PPIs. Mean 24-h intragastric pH with 4 PPIs *versus* baseline (49).

What is Pharmacodynamics?

Pharmacodynamics (PD)

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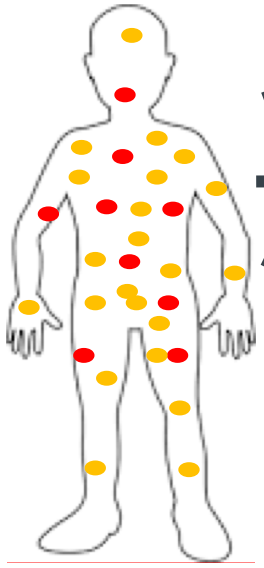

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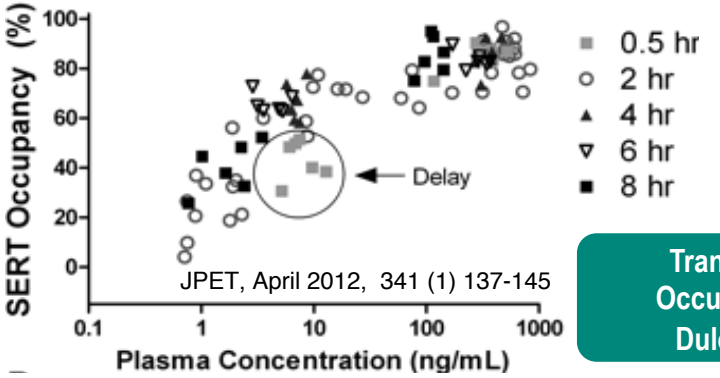

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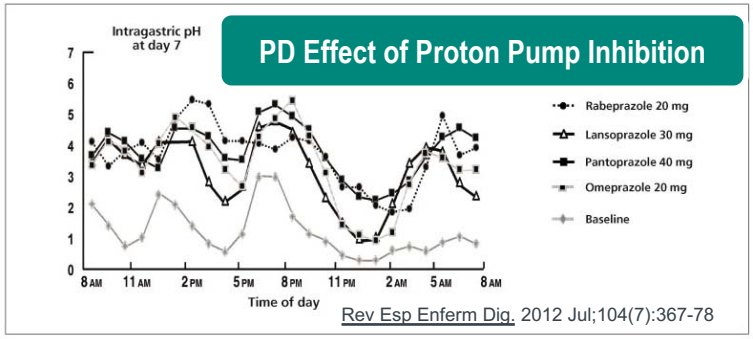

PD Effect of Proton Pump Inhibition

Rev Esp Enferm Dig. 2012 Jul;104(7):367-78

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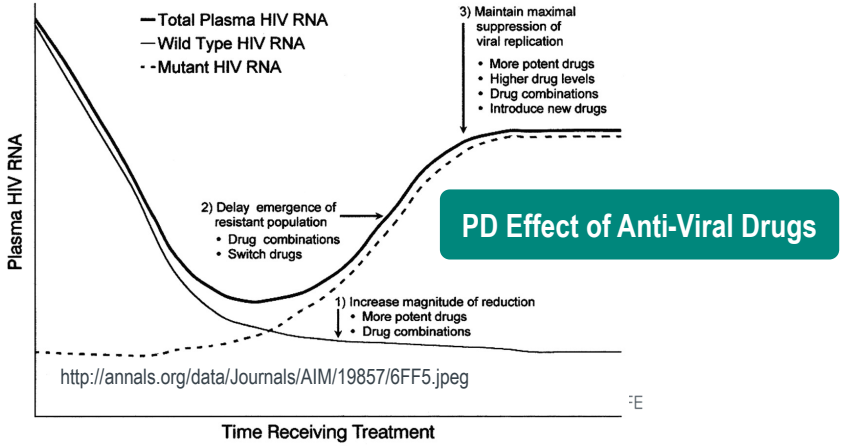
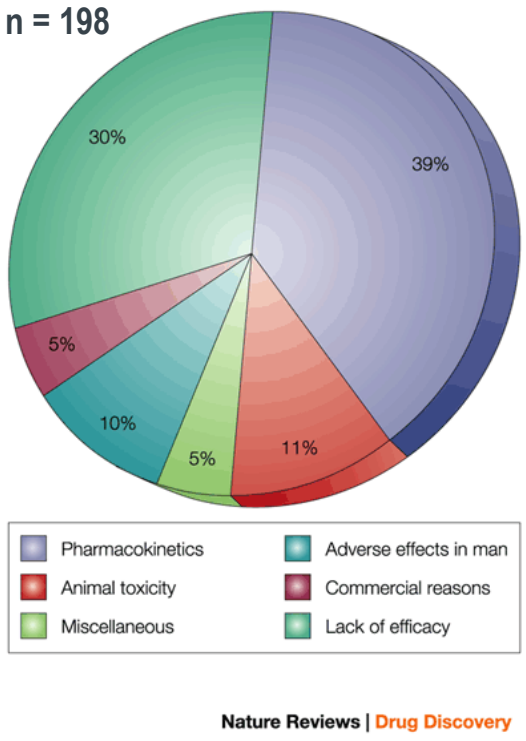


PD Effect of Anti-Viral Drugs

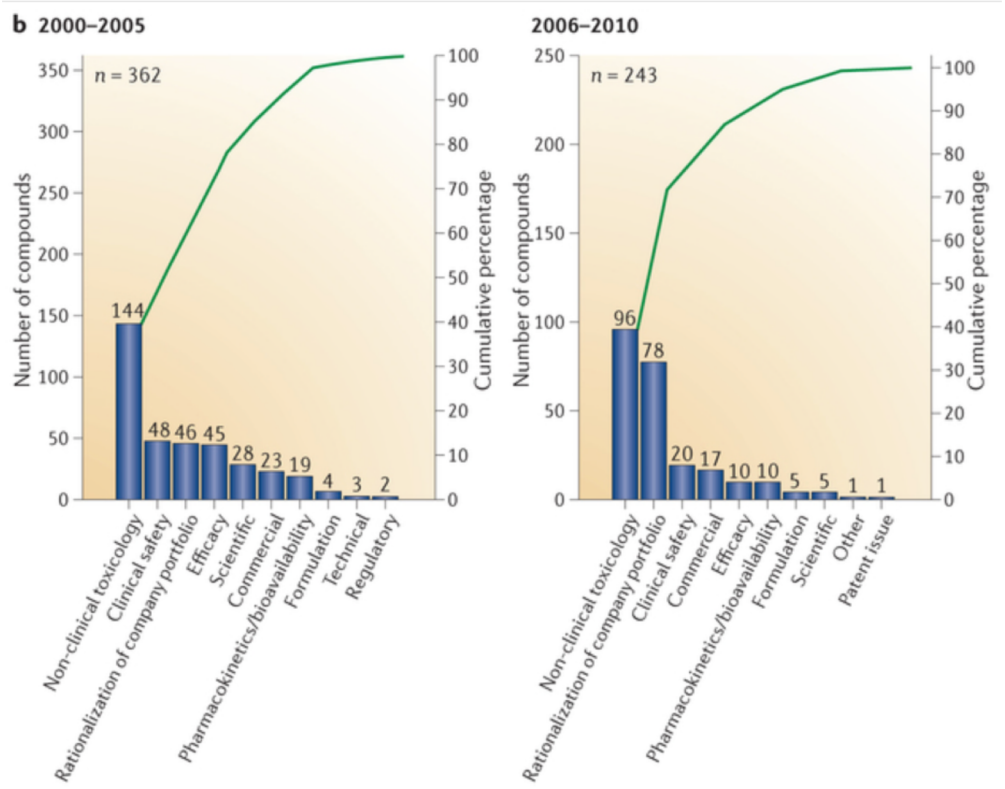
http://annals.org/data/Journals/AIM/19857/6FF5.jpeg

Has an Increased Understanding of PK/PD Helped?

Attrition of drug candidates



Nature Reviews Drug Discovery **2**, 192-204 (March 2003)



Nature Reviews Drug Discovery 14, 475–486 (2015)

Better understanding of PK/PD principles seems to have shifted the drug attrition profile

Why is PK/PD Important? A Recent Example

Selecting the right Drug and Dose in the right Population

Right Drug

Right Dose & Regimen

Right Population

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Why is PK/PD Important? A Recent Example

Selecting the right Drug and Dose in the right Population

KEYTRUDA® (pembrolizumab) Injection 100 mg

Right Drug

Right Dose & Regimen

Right Population

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Why is PK/PD Important? A Recent Example

Selecting the right Drug and Dose in the right Population

KEYTRUDA® (pembrolizumab) Injection 100 mg

Right Drug

Right Dose & Regimen

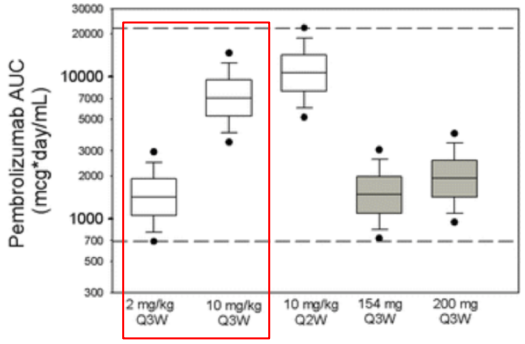
Keytruda Approved for Any Solid Tumor With a Specific Genetic Marker

Keytruda (pembrolizumab) was granted an accelerated approval by the Food and Drug Administration (FDA) for the treatment of both adult and pediatric patients who have unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors.

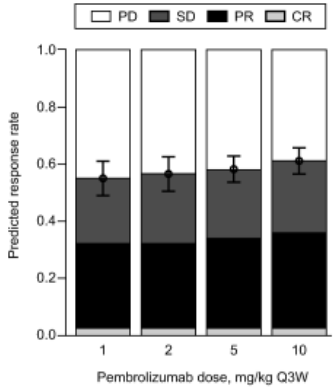
JASON M. BRODERICK @jasoncology
PUBLISHED: MAY 23, 2017

Right Population

Recent Example from PD-1 Inhibitors in Oncology



PK -> PD



Journal for ImmunoTherapy of Cancer, 2017, **5**:43

http://onlinelibrary.wiley.com/doi/10.1002/psp4.12140/full#psp412140-fig-0003

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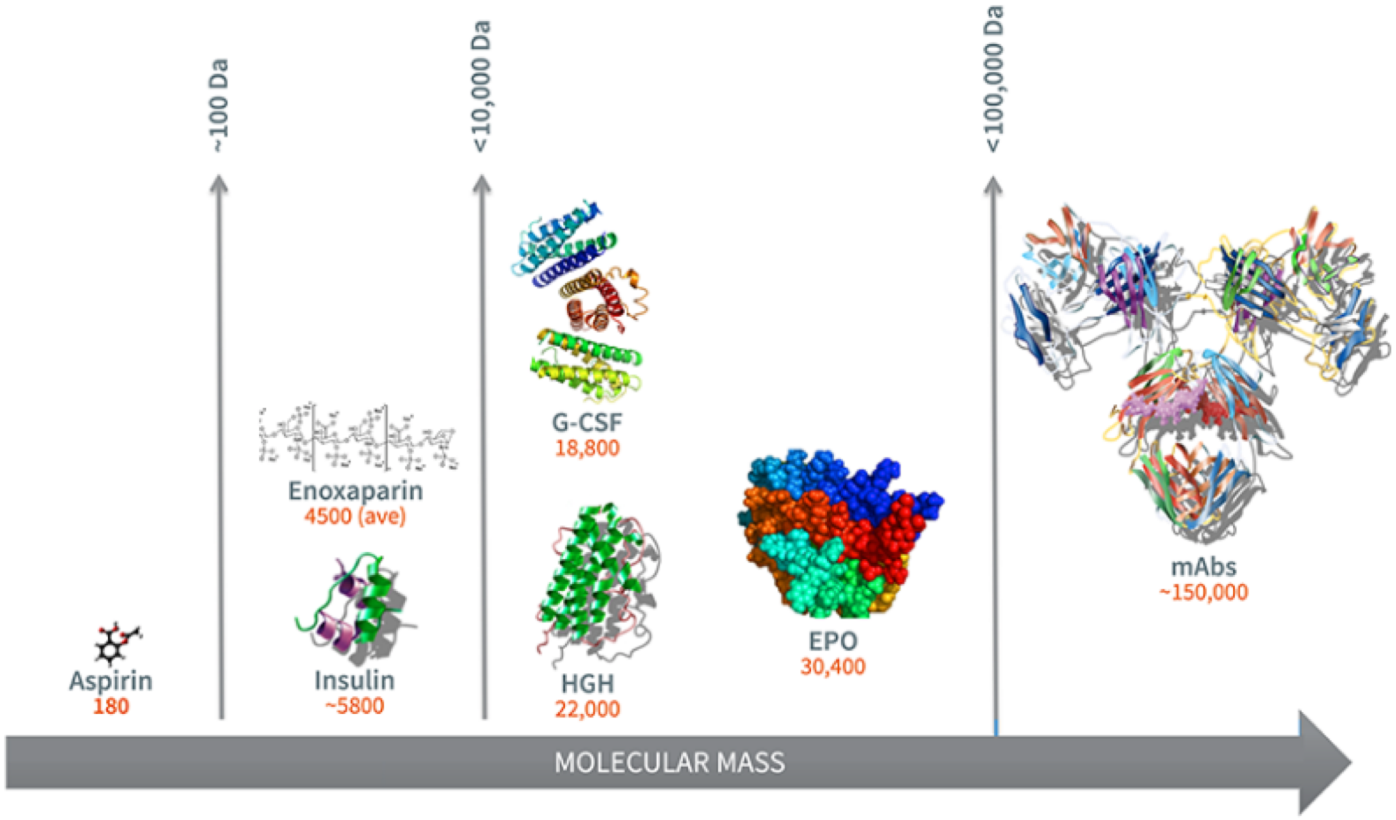
Small vs Large Molecule

Comparison of Molecular Mass of Small-Molecule (Chemical) Drugs Versus Large Biologics[7-13]



Ave=average; **DA**=Daltons; **EPO**=erythropoietin;
G-CSF=granulocyte colony-stimulating factor; **HGH**=human growth hormone; **mAbs**=monoclonal antibodies.

ttp://www.amgenbiosimilars.com/the-basics/the-power-of-biologics/

Small vs Large Molecule

For matters related to PK/PD, molecular size and structure is important!!!

Small Molecule:

- Oral dosing route is generally preferred
- Half-life in body is typically in hours
- Additional PK considerations
  - Absorption characteristics from gut after oral dosing
  - First-pass metabolism (liver)
  - Potential for drug-drug interactions
  - Renal elimination
- No immunogenicity concerns
- Can access intra-cellular targets

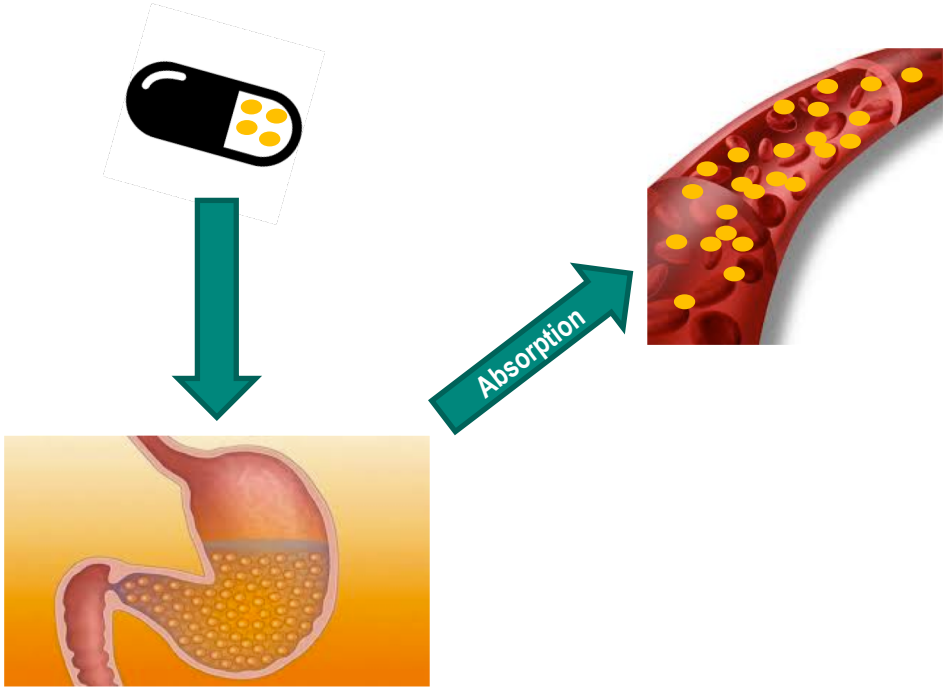
Large Molecule:

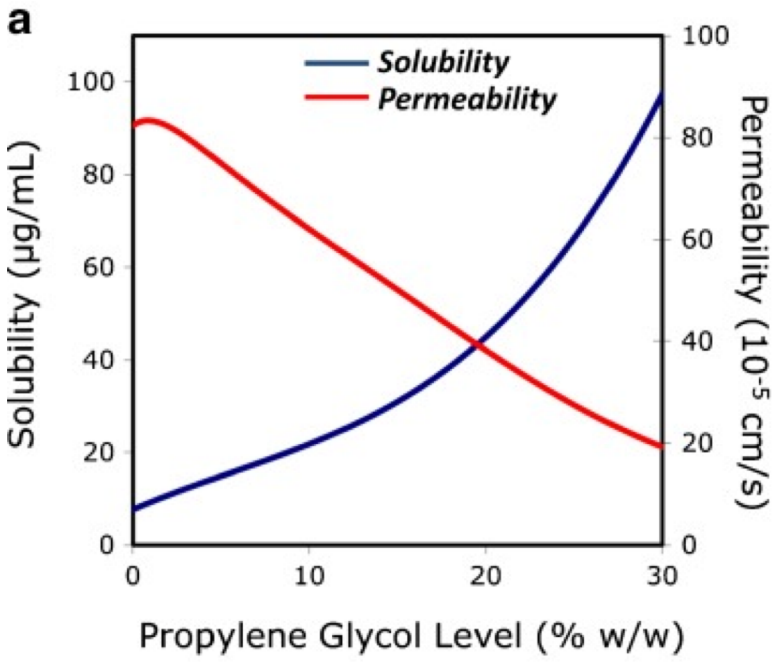
- IV/SC/IM dosing routes e.g. palivizumab (IM)
- Half-life in body is typically in days
- Additional PK considerations
  - Absorption characteristics from skin after SC dosing
  - No first-pass metabolism (liver)
  - Minimal potential for drug-drug interactions
  - Non-renal elimination mechanisms
- Immunogenicity concerns i.e. body can generate an immune response
- Primarily binds to extracellular targets

ADME - Absorption

Absorption is dependent on various physicochemical and physiological factors. The key parameters are

- Solubility in the GIT
- Permeability across the GI membrane





AAPS J. 2012 Jun; 14(2): 244–251

Parent Drug

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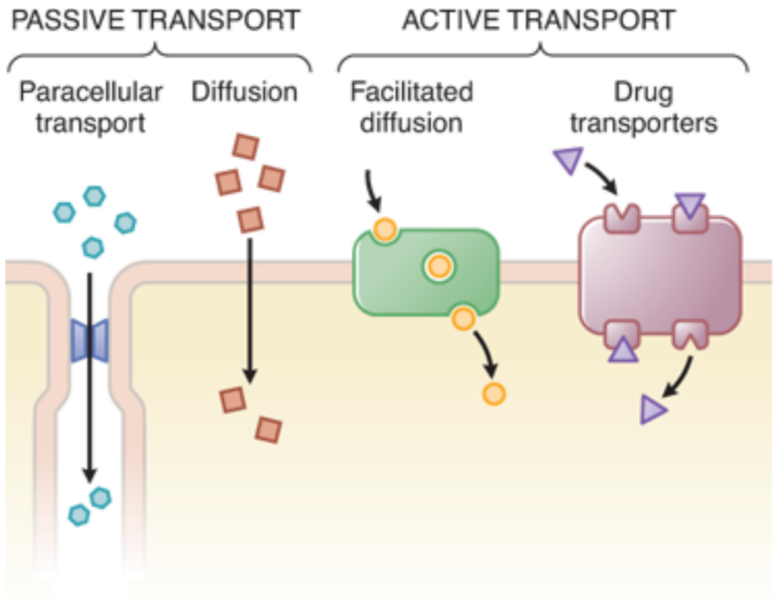
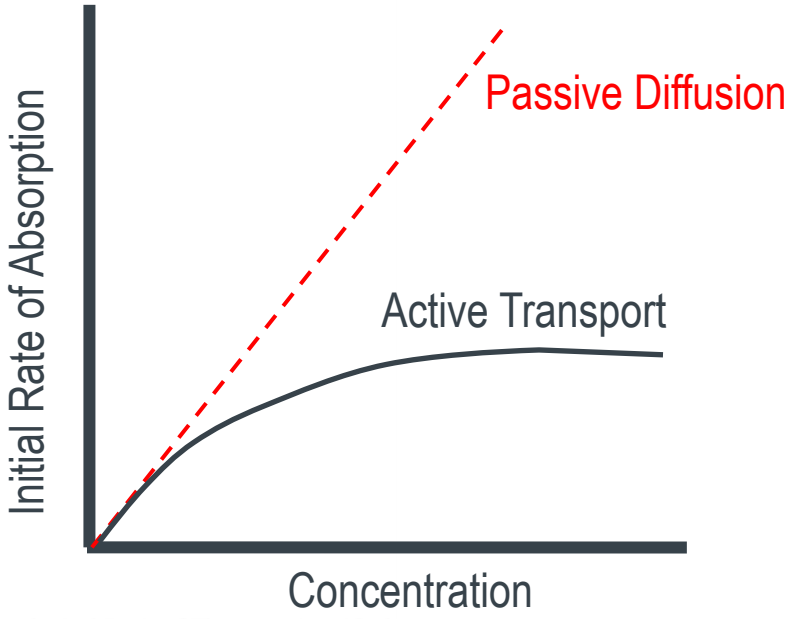
ADME - Absorption

Passive Diffusion v/s Active Transport

- Passive diffusion occurs based on a concentration gradient between intestinal lumen and portal vein concentrations
- Active transport of drug molecules is mediated through transporter proteins with potential for capacity limitation (e.g. glucose & β-lactams)





Source: L. L. Brunton, B. A. Chabner, B. C. Knollmann: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12ed.
www.accesspharmacy.com

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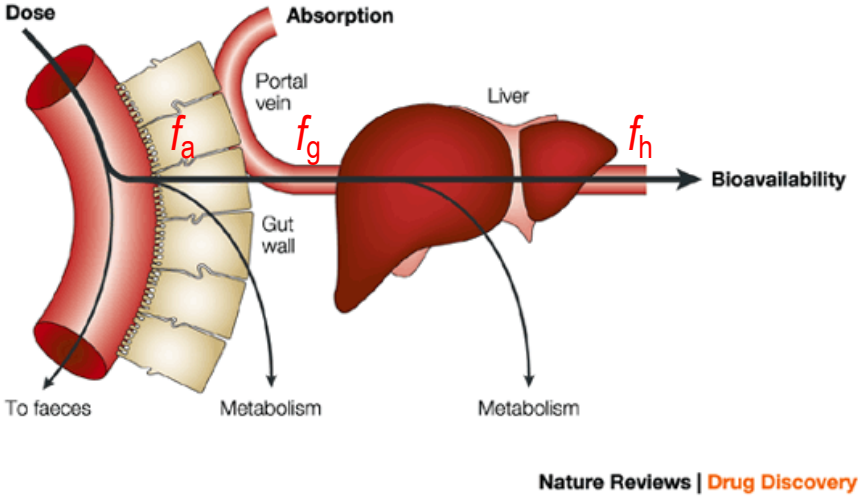
Extent of Absorption (Small Molecules Oral Dosing)

Extent of absorption i.e. Bioavailability (*F*)

- Fraction absorbed from lumen (f_a): Fraction of drug in the GI lumen that enters gut tissues
- Fraction absorbed from gut wall (f_g): Fraction of drug in gut wall that enters the portal vein i.e. fraction escaping gut metabolism
- Hepatic fraction absorbed (f_h): Fraction of drug in the portal vein that enters systemic circulation
- Hepatic Extraction Ratio (*ER*): Fraction of the drug that is extracted by the liver



$$F = f_a \cdot f_g \cdot f_h$$

$$f_h = (1 - ER)$$

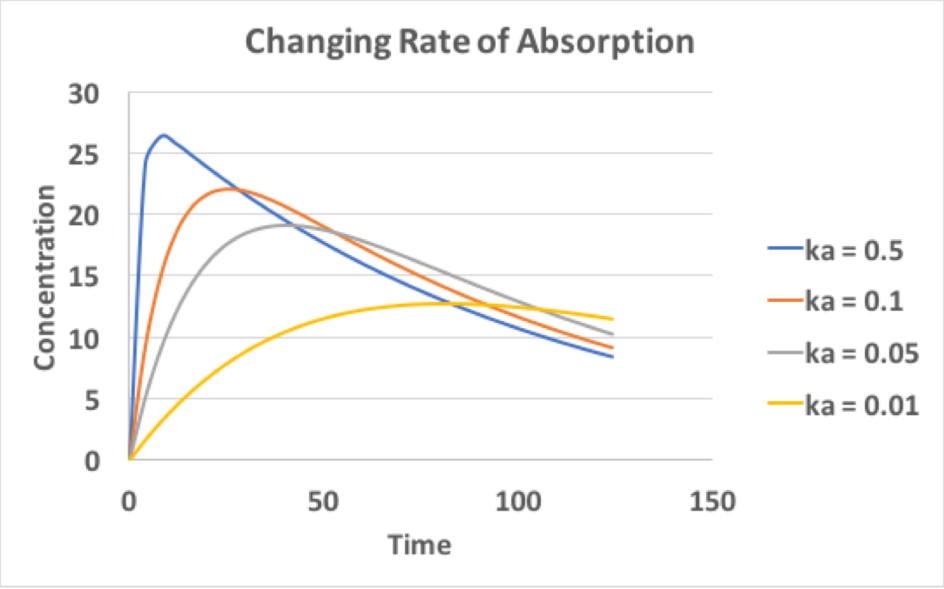
F is relevant for SC or IM injections as well

Nature Reviews Drug Discovery **2**, 192-204 (March 2003)

Rate of Absorption (Small Molecules)

Rate of absorption i.e. how fast the drug enters systemic circulation

- Determines the time (t_{max}) to maximum concentration (C_{max})
- For orally absorbed drugs, rate of absorption is generally described by a first-order rate constant, k_a. Units of k_a is 1/time
- Inverse relationship of k_a with t_{max}



Question 1

If the fraction of drug absorbed at each stage i.e. f_a, f_g, and f_h is 50%, then what the bioavailability (F)?

- A: 2500.0%
- B: 25.5%
- C: 12.5%

HINT:

$$F = f_a \cdot f_g \cdot f_h$$

Question 1 Solution

If the fraction of drug absorbed at each stage i.e. f_a, f_g, and f_h is 50%, then what the bioavailability (F)?

- **C: 12.5%**

$$F = f_a \cdot f_g \cdot f_h$$

Explanation: F = 0.5 x 0.5 x 0.5 = 0.125 x 100 = 12.5%

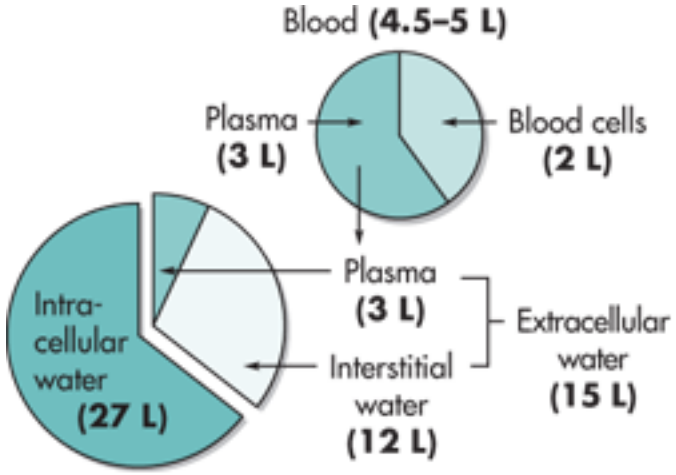
- Drugs like vancomycin and gentamycin are polar with MWT >400 g/mole. These drugs have low F due to low f_a

ADME - Distribution

Volume of distribution (V) of a drug is an apparent volume that correlates amount and concentration of drug in the body

$$Concentration = \frac{Amount}{Volume}$$

Typical physiological volumes include:

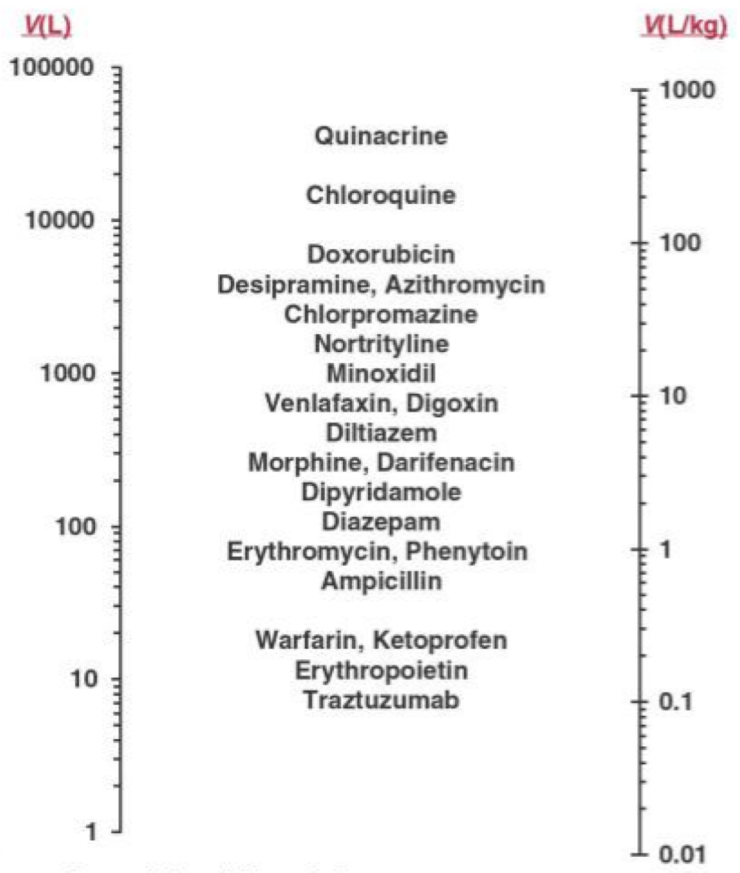


Source: Leon Shargel, Andrew B.C. Yu: Applied Biopharmaceutics & Pharmacokinetics, 7th Ed.
www.accesspharmacy.com

Why is “V” an Apparent Volume of Distribution?

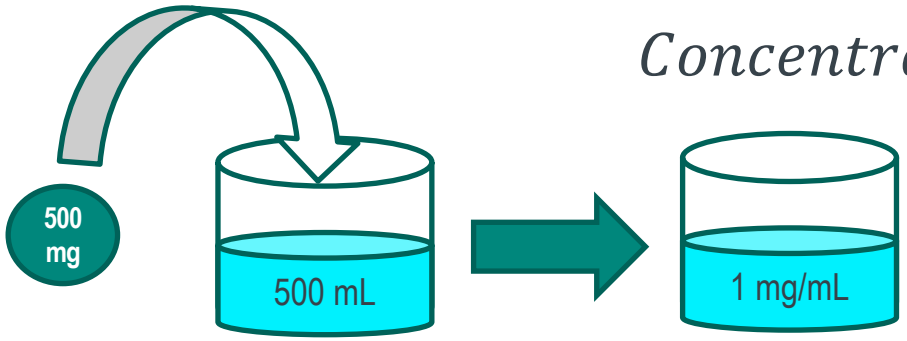
Reported volumes greatly exceed physiological volumes

Apparent “V” is determined by factors such as polarity, lipophilicity, and ionization state (pKa)



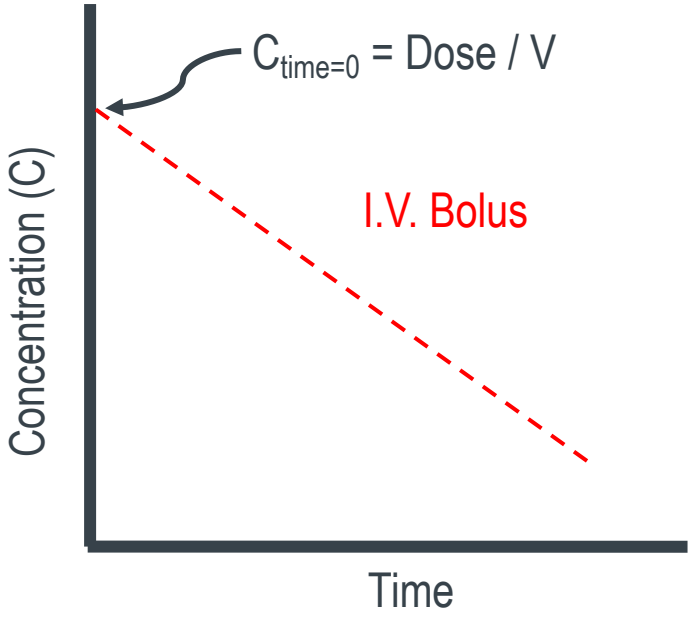
Rowland, M., Tozer, T. N., & Rowland, M. (2011). *Clinical pharmacokinetics and pharmacodynamics: Concepts and applications*. Philadelphia: Wolters Kluwer Health/Lippincott William & Wilkins.

Volume of Distribution (V or V_d)

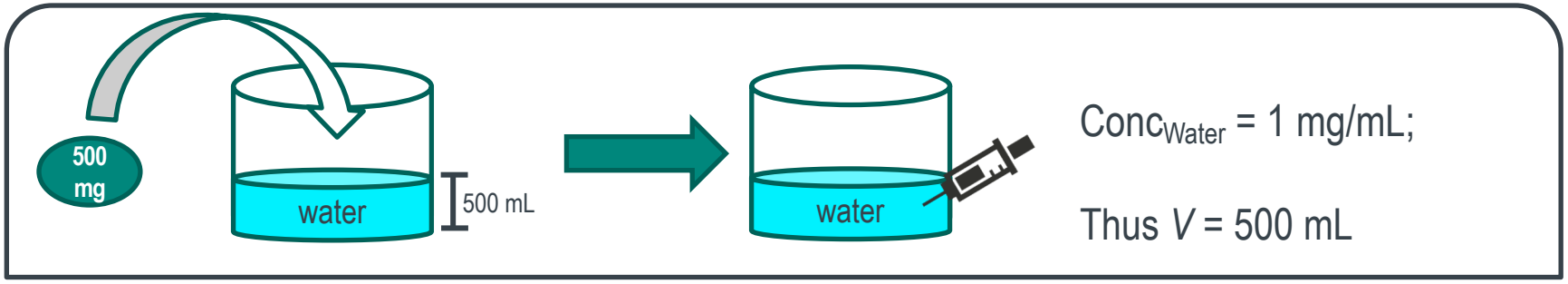


$$Concentration = \frac{Amount}{Volume}$$

Volume of distribution is useful to calculate a loading dose



Volume of Distribution is Apparent



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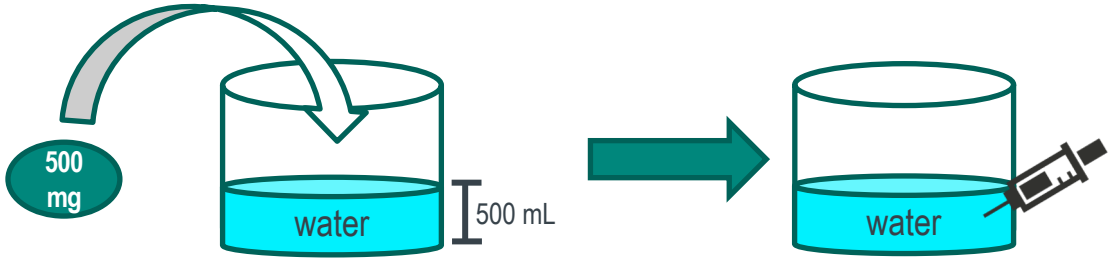
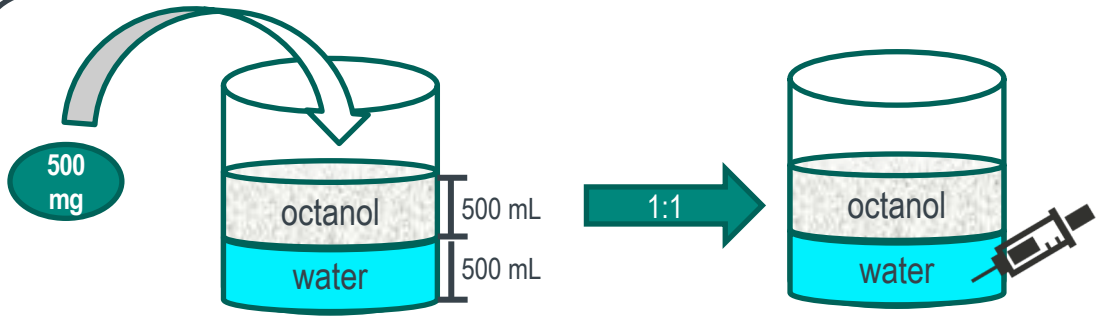


$Conc_{Water}$ = 1 mg/mL;

Thus V = 500 mL

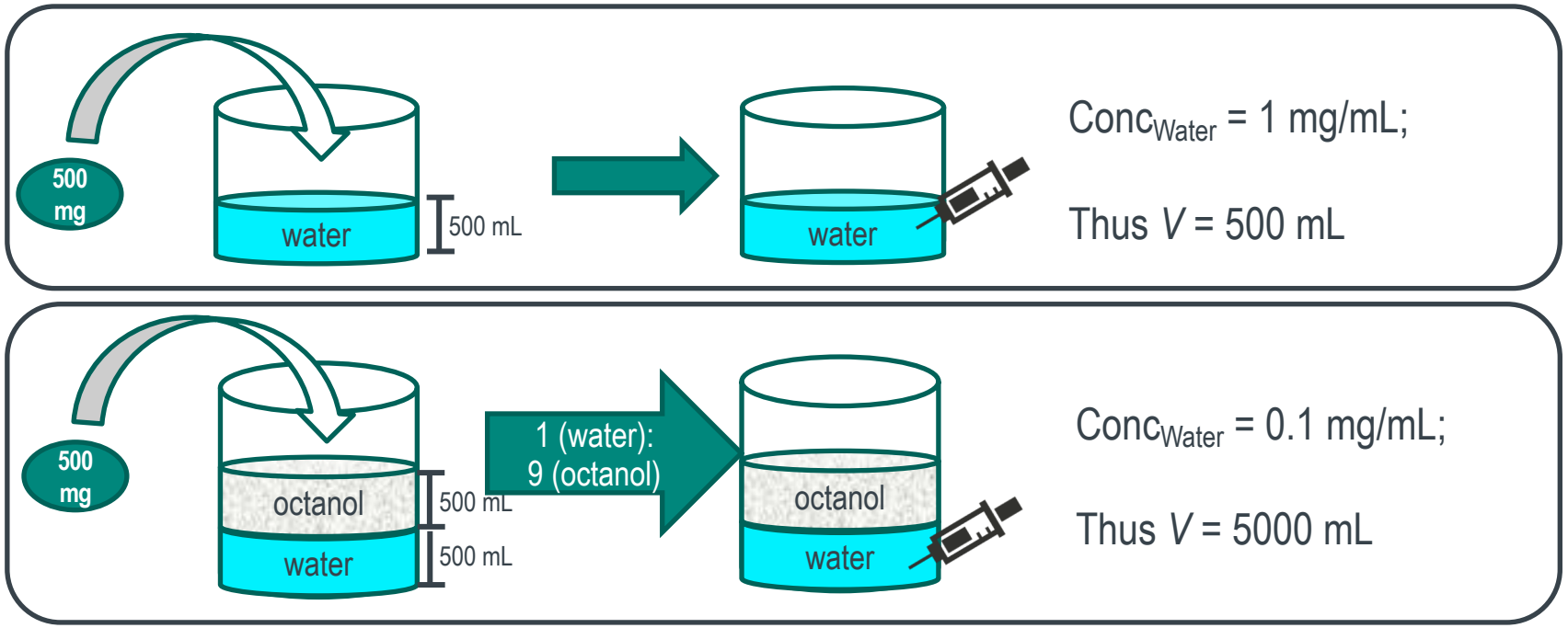


$Conc_{Water}$ = 0.5 mg/mL;

Thus V = 1000 mL

$$Volume = \frac{Amount}{Concentration}$$

Volume of Distribution is Apparent



Partitioning contributes to an increase in apparent volume of distribution

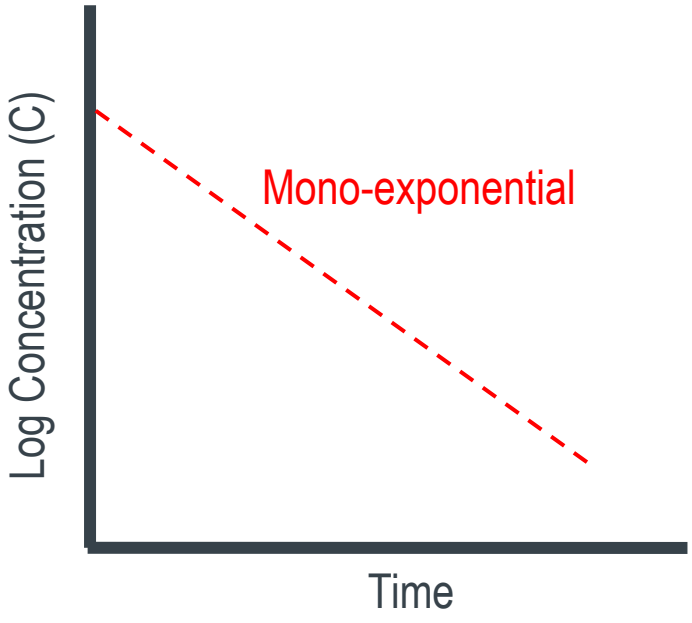
- Lipophilic drugs that distribute extensively into tissues *e.g.* diazepam (V = 168 L)
- V may approach physiological volumes *e.g.* monoclonal antibodies at high doses

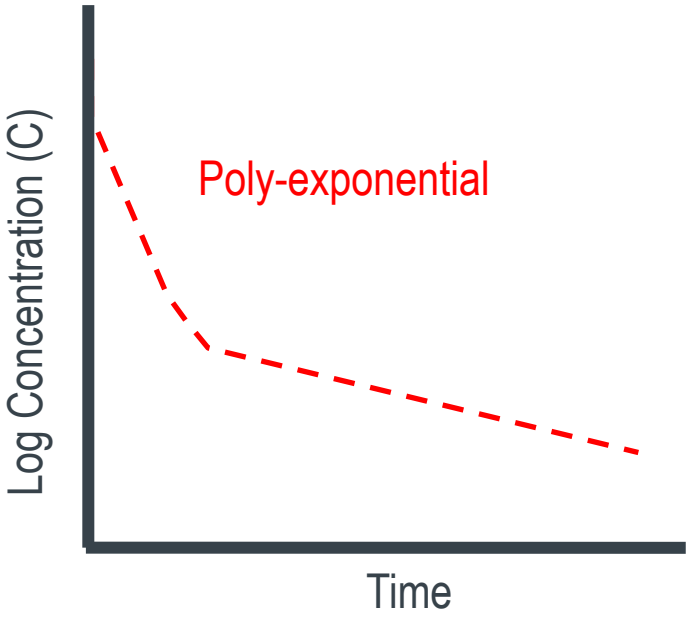
[1]Gibaldi, M. 1984 "Biopharmaceutics and Clinical Pharmacokinetics", 3rd ed., Lea & Febiger, Chapter 12, page 214

PK Models – One or More Compartments

Poly-exponential PK indicates distribution phenomenon (non-specific or target-related)

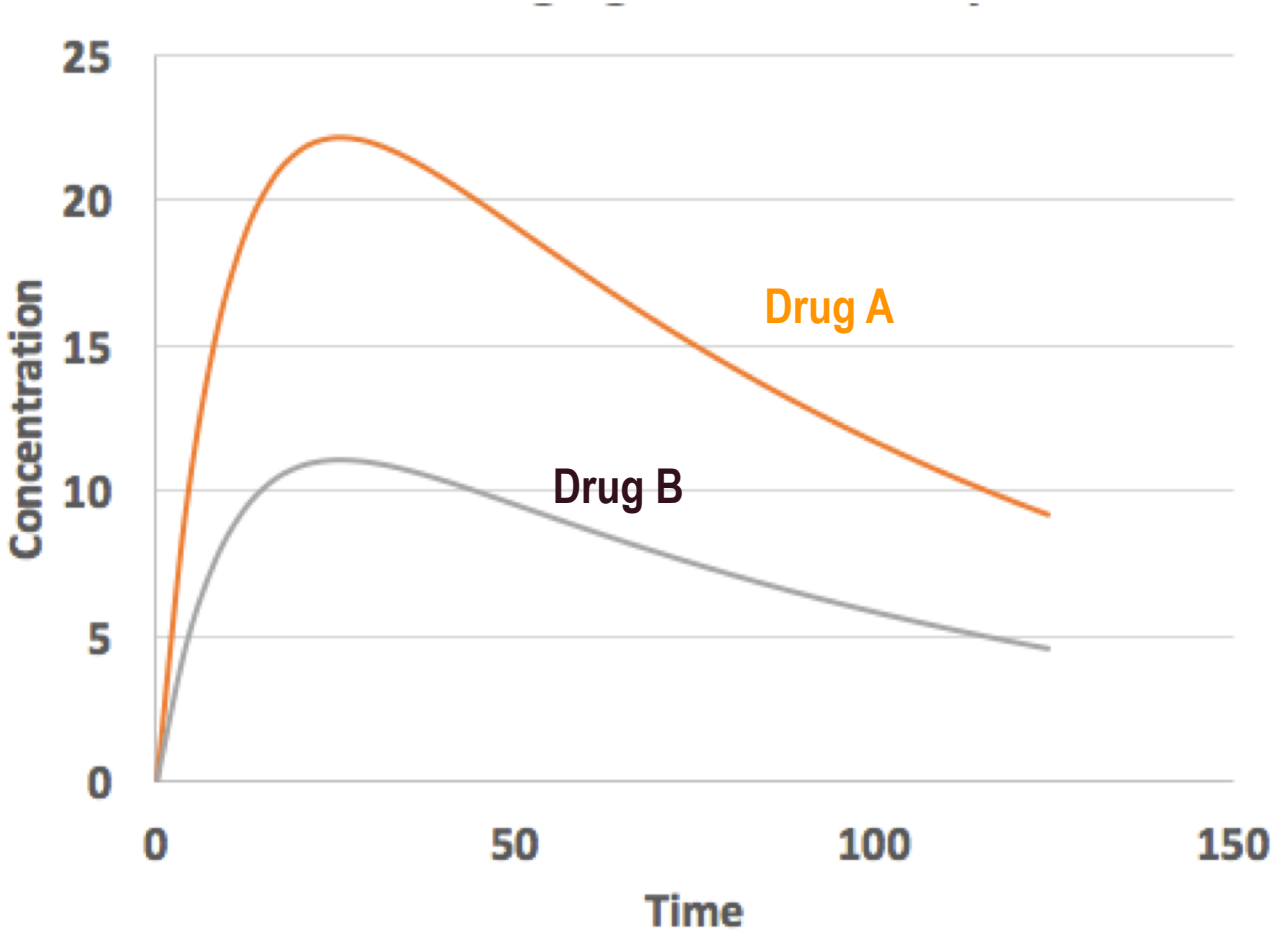
A poly-exponential PK curve will required two or more compartments for adequate characterization of data





Question 2

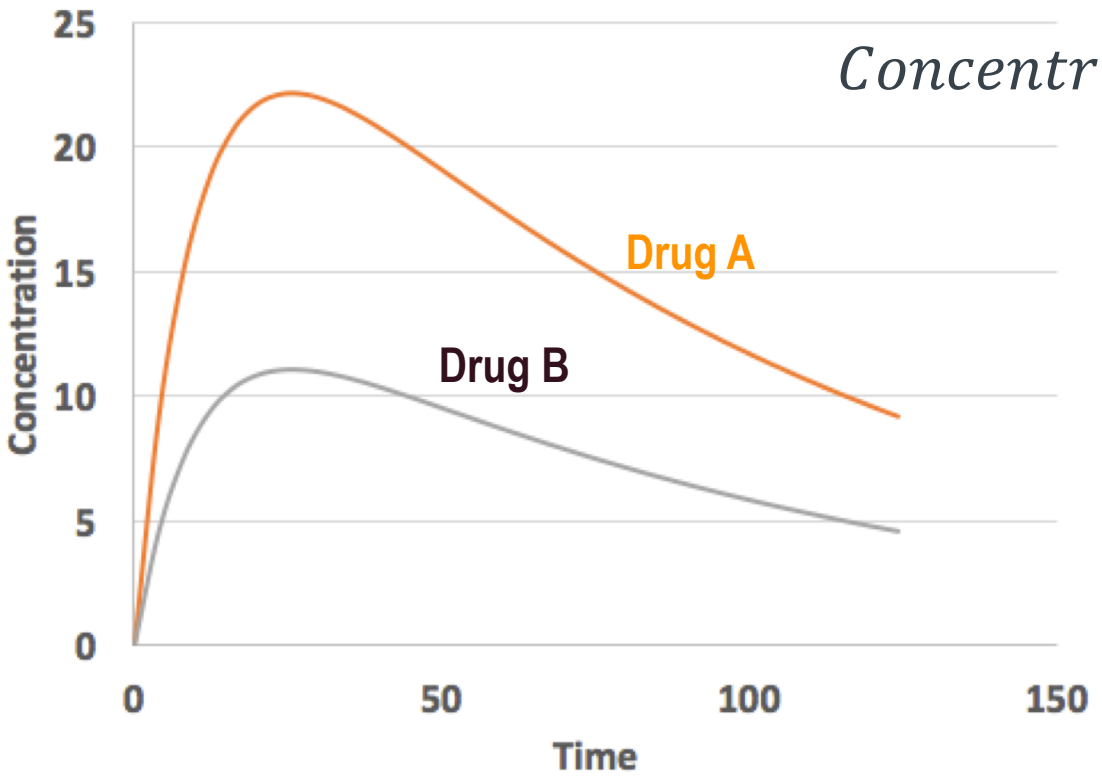
Which drug has a larger volume of distribution?



Question 2: Solution

Which drug has a larger volume of distribution?

- Answer: Drug B



$$Concentration = \frac{Amount}{Volume}$$

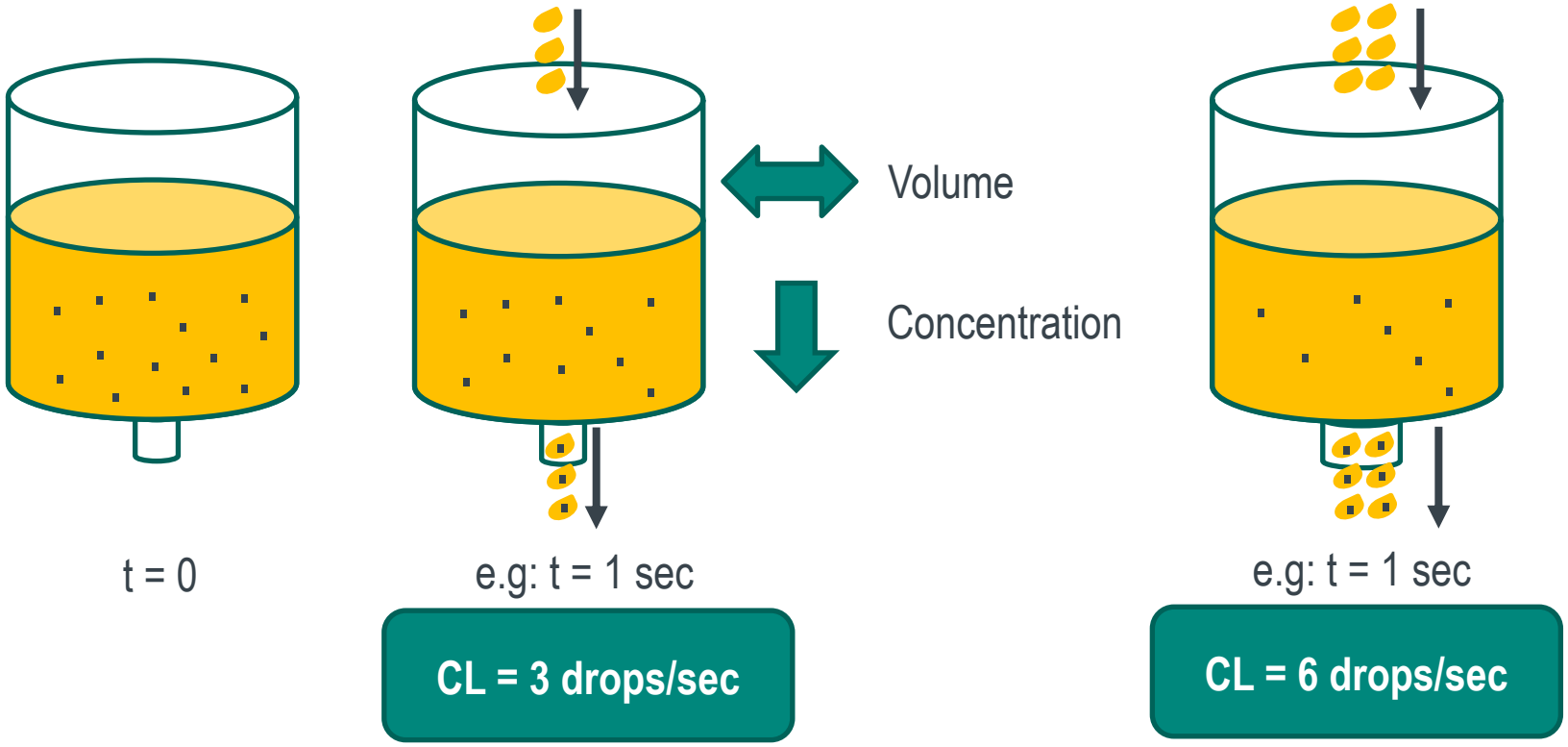
For any drug, a large apparent V is not necessarily a disadvantage. The absolute value of V is indicative of where the drug is distributed as well as physicochemical properties of the drug

ADME – Metabolism & Elimination

- Hepatic & Gut Metabolism
  - CYP, UGT, etc… enzymes
- Renal Elimination
- Various terms referring to Elimination
  - Clearance i.e. CL (Units: volume/time)
  - For an organ, the maximal clearance is equal to blow flow to that organ
    - Liver blood flow = 1.5 L/min
    - Kidney blood flow = 1.2 L/min
    - Glomerular Filtration Rate i.e. GFR = 0.1 L/min
  - Elimination Rate Constant *i.e.* k_{el} (Units: 1/time)
  - Elimination half-life *i.e.* t_{half} (Units: time)

Clearance (CL)

Drug CL is the volume that is cleared of a drug per unit of time



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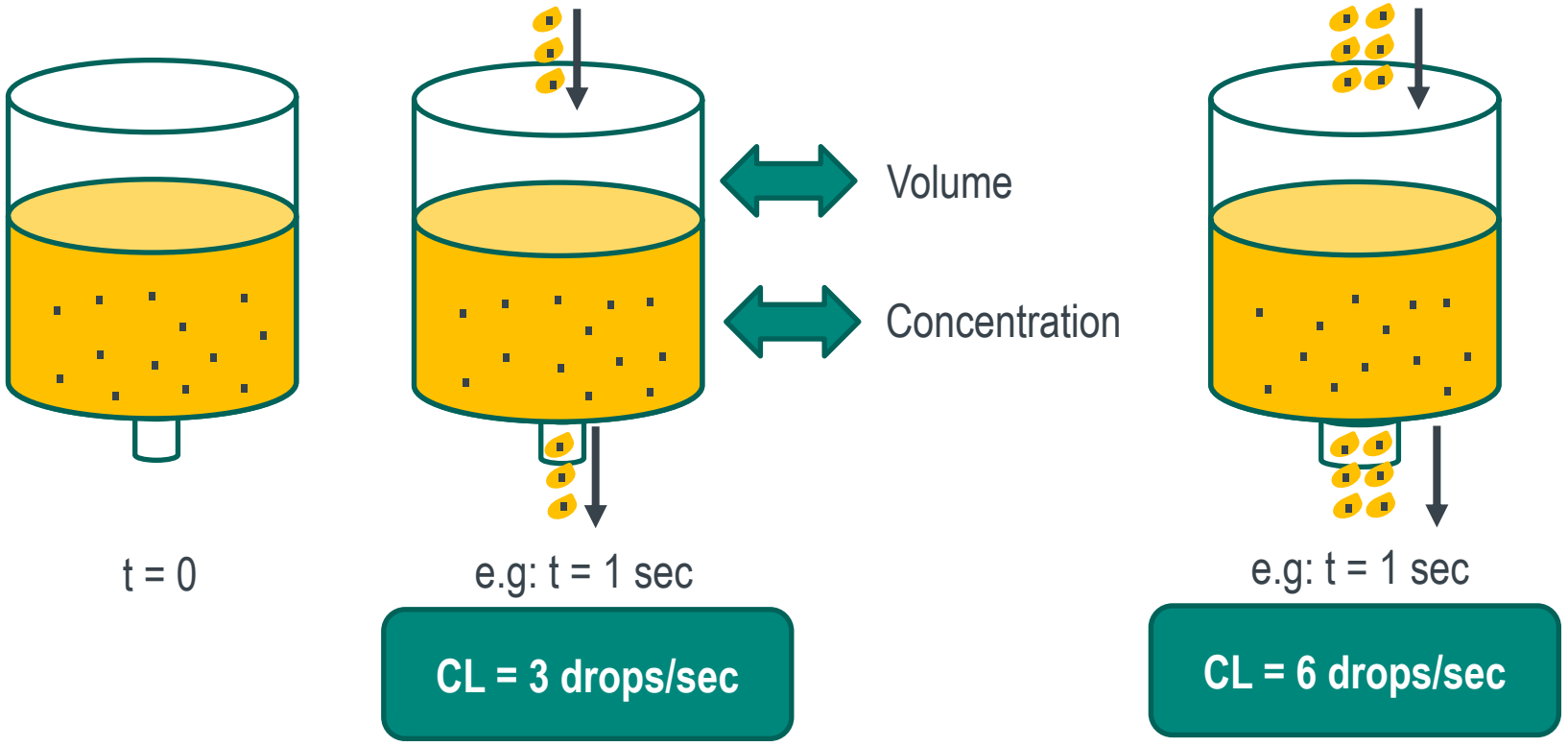
Clearance at Steady-State(CL)

At steady-state, *Rate In* = *Rate Out*

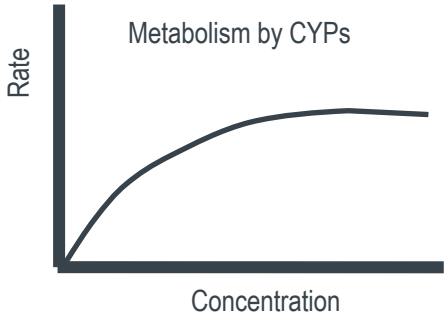


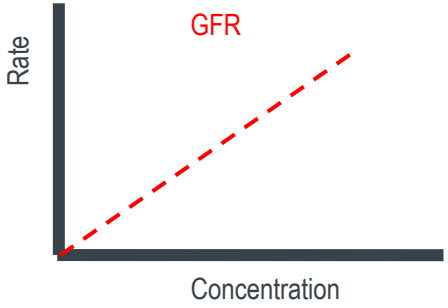
For IV infusions, the dosing rate can be calculated using CL and required steady state concentration

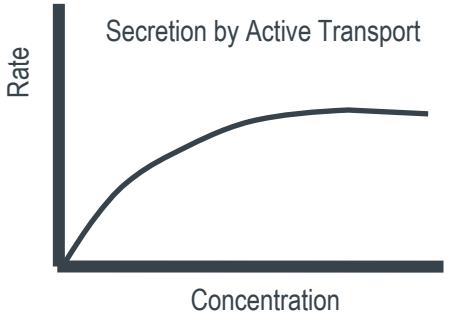
$$Infusion_{rate} = CL \cdot Conc_{ss}$$

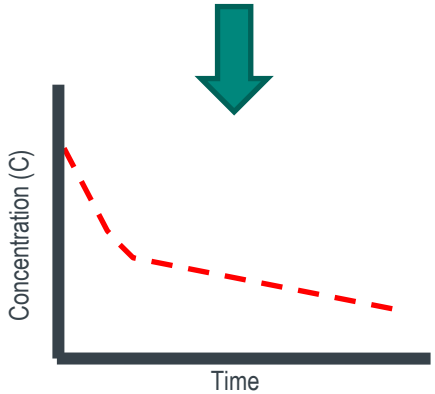
Total Clearance

Total CL is representative of the sum of all clearance mechanisms and organs





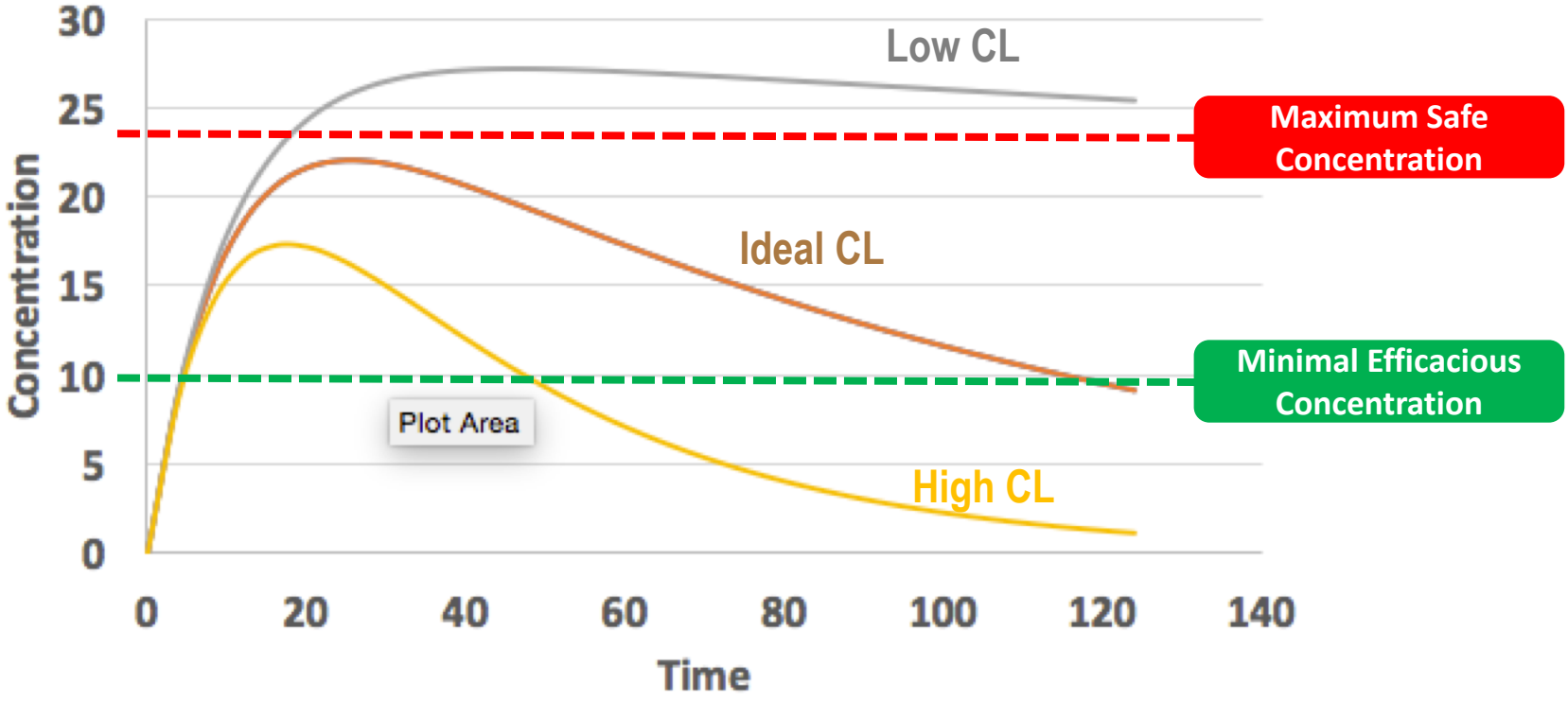




$$CL = CL_{gut} + CL_{liver} + CL_{kidney}$$

Impact of Clearance on PK

$$CL = \frac{Dose.F}{AUC_{0-inf}}, where\ F = 1\ for\ IV$$



CL is a determinant of drug exposure (AUC)

Metabolism

- Primarily impacts small molecules
- Four common type of reactions include:
  - Oxidation: Majorly mediated through cytochrome P450 (CYP) enzymes
  - Hydrolysis: Aspirin to salicylic acid and acetic acid
  - Reduction
  - Conjugation: Phase 2 reactions such as glucuronidation
- Metabolites are typically more polar and water soluble. Hence, lower reabsorption
- In some cases, metabolites may also be active
  - Prodrug: Codeine to morphine
- Characterizing metabolic profile of drugs is important to predict drug-drug interactions

Question 3a

Two drugs (A & B) are co-administered simultaneously. Drug A is known to **induce** the CYP3A4 enzyme. Drug B is primarily metabolized by CYP3A4 to an inactive metabolite. What is the impact on the PK (exposure) for both drugs compared to when these drugs are administered alone?

A. AUC of Drug B is lower
B. AUC of both drugs A & B is lower
C. No impact on AUC
D. AUC of Drug B is higher

Question 3a: Solution

Two drugs (A & B) are co-administered simultaneously. Drug A is known to **induce** the CYP3A4 enzyme. Drug B is primarily metabolized by CYP3A4 to an inactive metabolite. What is the impact on the PK (exposure) for both drugs compared to when these drugs are administered alone?

A. **AUC of Drug B is lower (efficacy may be compromised)**
B. AUC of both drugs A & B is lower
C. No impact on AUC
D. AUC of Drug B is higher

Drug-drug interactions (DDI) are a major concern for drugs that are eliminated via the metabolic pathway. Enzyme induction may result in sub-therapeutic doses of drug.

Question 3b

Two drugs (A & B) are co-administered simultaneously. Drug A is known to **inhibit** the CYP3A4 enzyme. Drug B is primarily metabolized by CYP3A4 to an inactive metabolite. What is the impact on the PK (exposure) for both drugs compared to when these drugs are administered alone?

A. AUC of Drug B is lower
B. AUC of both drugs A & B is lower
C. No impact on AUC
D. AUC of Drug B is higher

Question 3b: Solution

Two drugs (A & B) are co-administered simultaneously. Drug A is known to **inhibit** the CYP3A4 enzyme. Drug B is primarily metabolized by CYP3A4 to an inactive metabolite. What is the impact on the PK (exposure) for both drugs compared to when these drugs are administered alone?

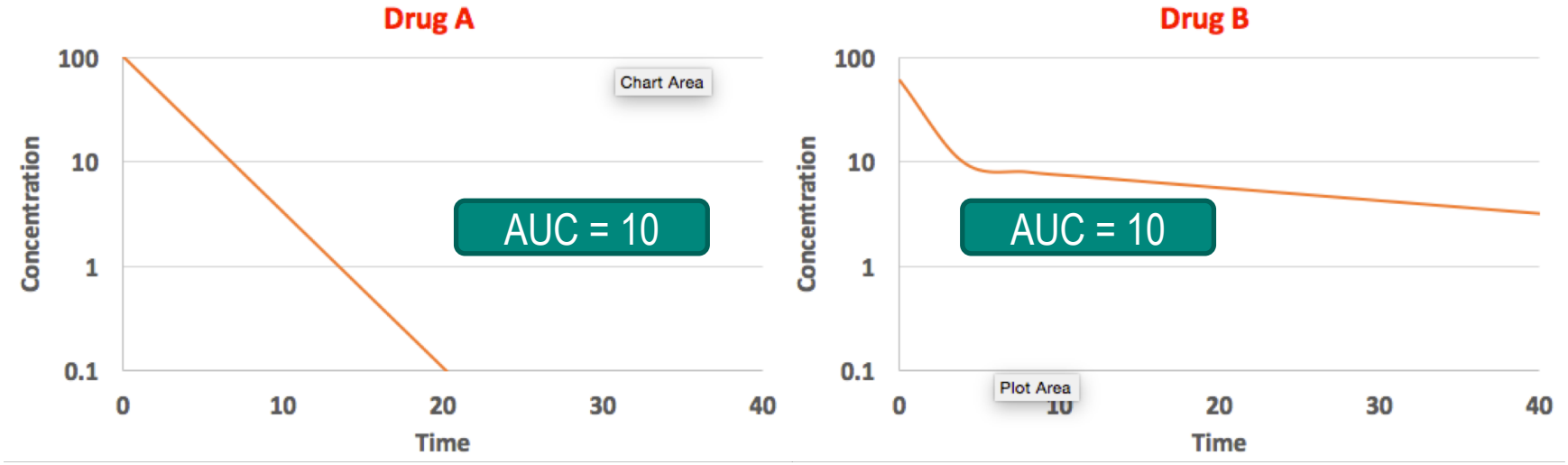
A. AUC of Drug B is lower
B. AUC of both drugs A & B is lower
C. No impact on AUC
D. AUC of Drug B is higher (potential safety concern)

Drug-drug interactions (DDI) are a major concern for drugs that are eliminated via the metabolic pathway. This is especially true for drugs with a narrow therapeutic index.

An ideal drug candidate would have multiple elimination pathways, such that inhibiting any one pathway does not significantly impact exposures.

ADDITIONAL SLIDES

Final Questions

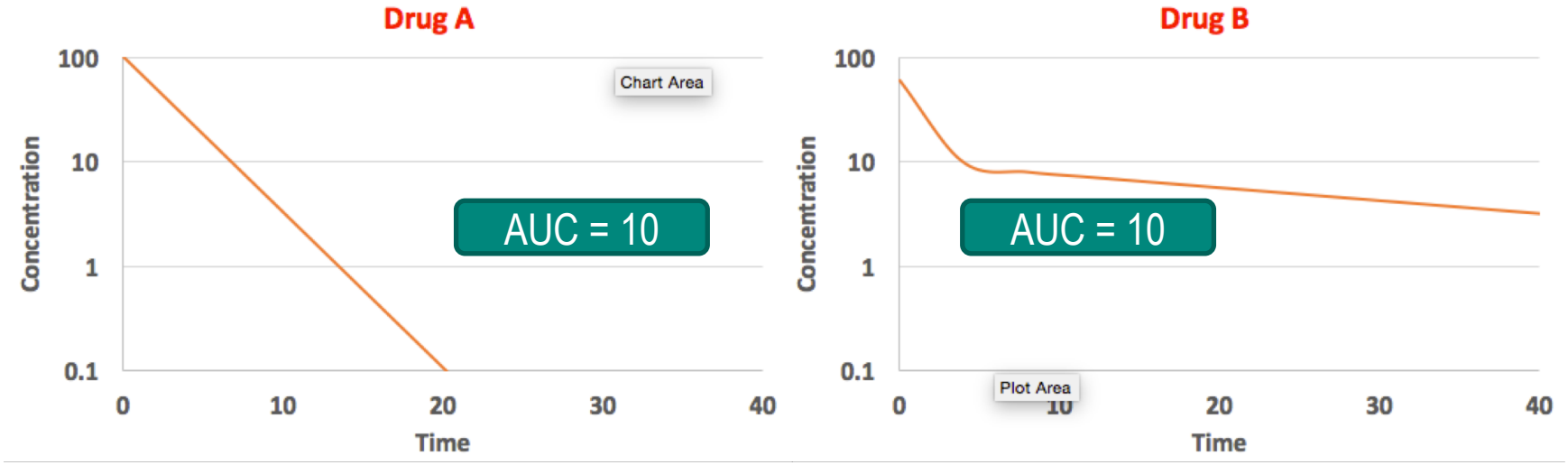


Assume same IV dose for drugs A & B

Q1: Which drug has higher CL?

1. A
2. B
3. A = B

Final Questions



Assume same IV dose for drugs A & B

Q1: Which drug has higher CL?

1. A
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$$CL = \frac{Dose.F}{AUC_{0-inf}}, where\ F = 1\ for\ IV$$

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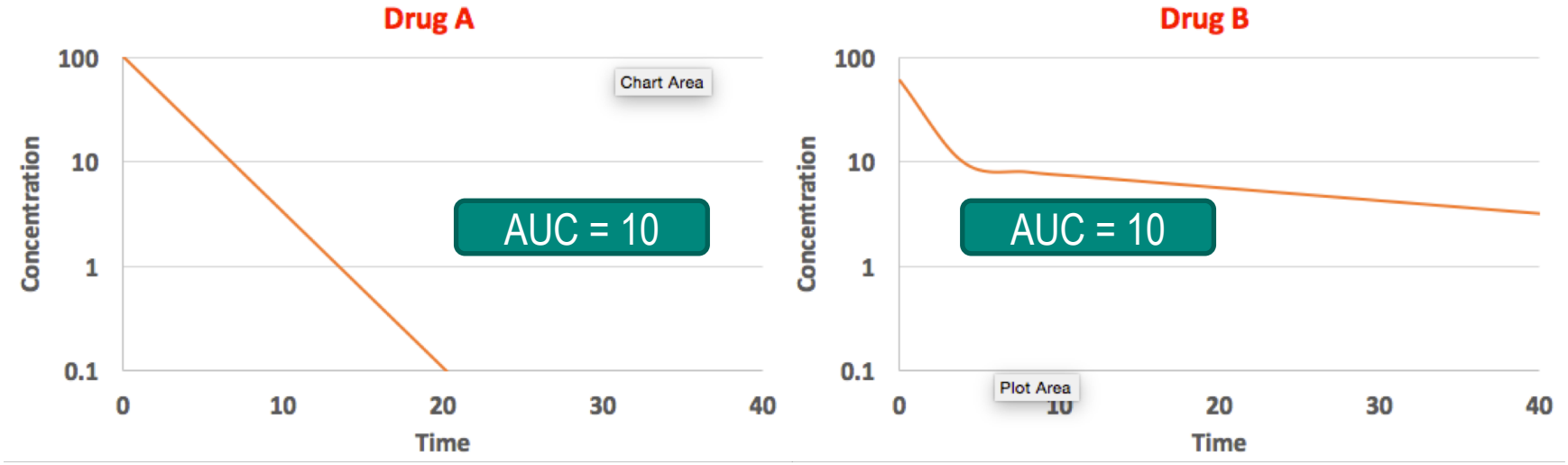
Final Questions



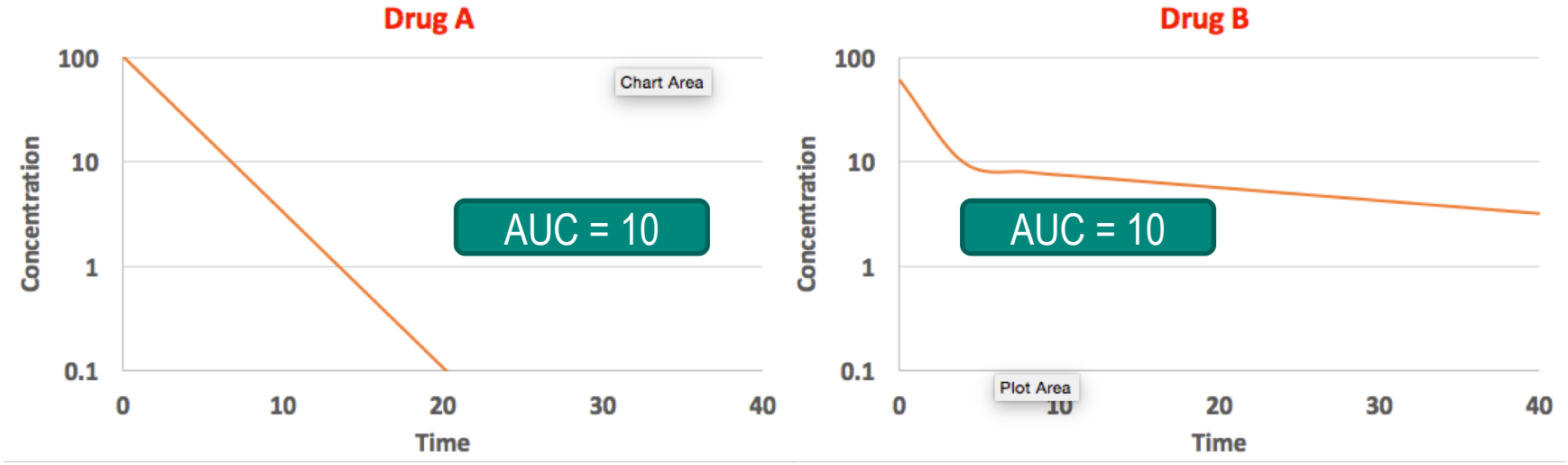
Assume same dose for drugs A & B

CL = 1.5 L/min

Q2: Which compound has greater tissue distribution?

1. A
2. B

Final Questions



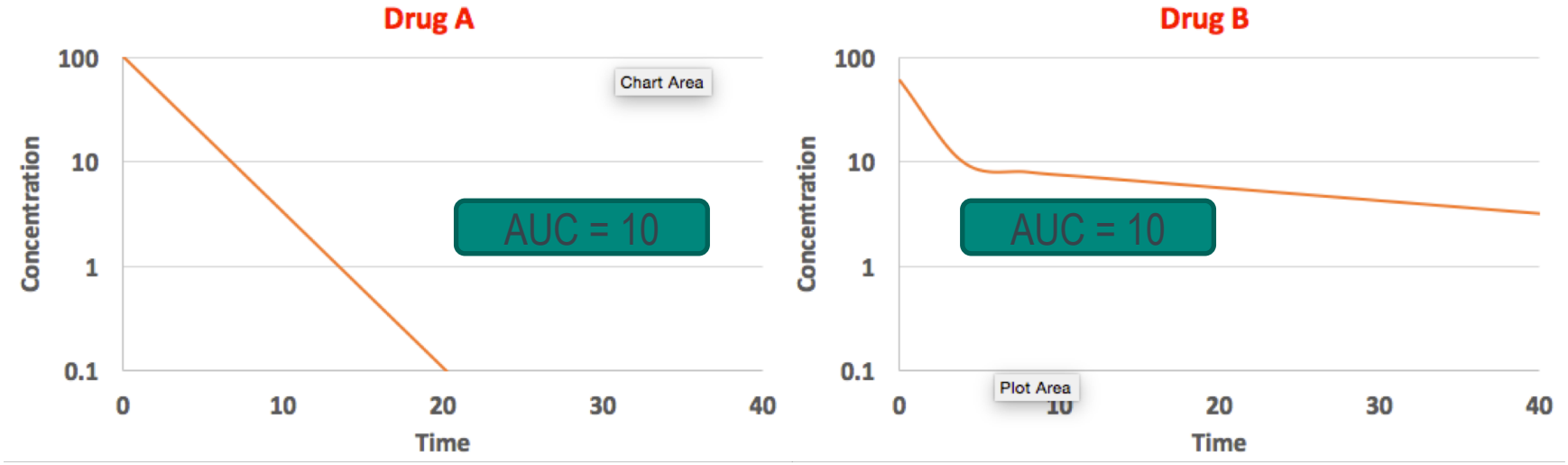
Assume same dose for drugs A & B

CL = 1.5 L/min

Q2: Which compound has greater tissue distribution?

1. A
2. **B**

Final Questions



Assume same dose for drugs A & B

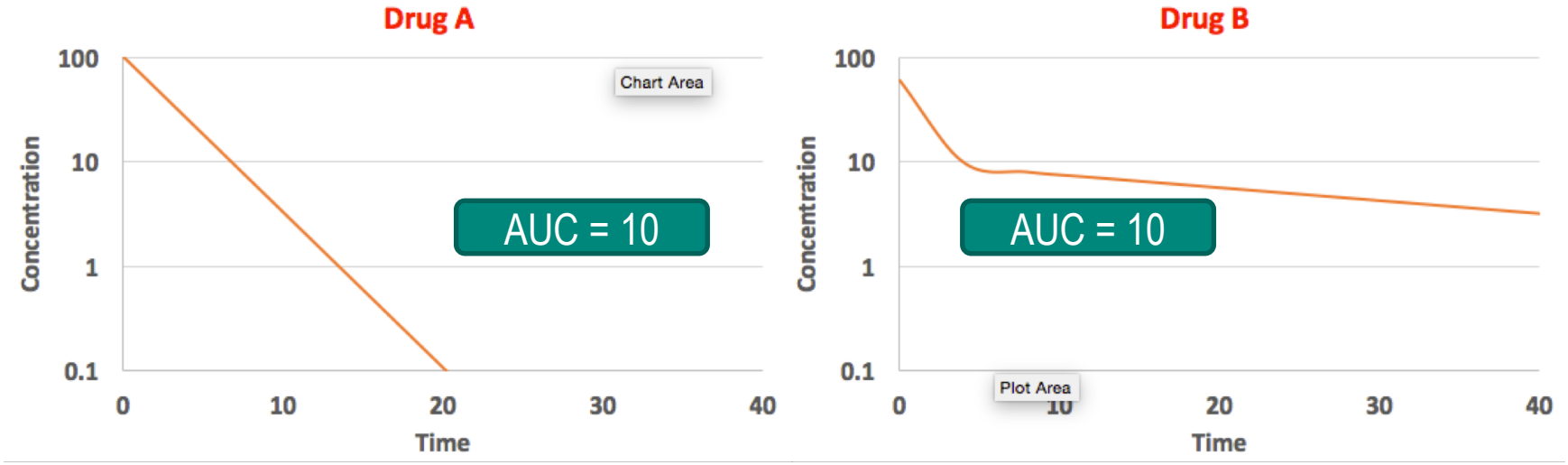
CL = 1.5 L/min

Q3: Is glomerular filtration the sole mechanism of elimination?

1. Yes
2. No

Hint: GFR is ~0.1 L/min

Final Questions



Assume same dose for drugs A & B

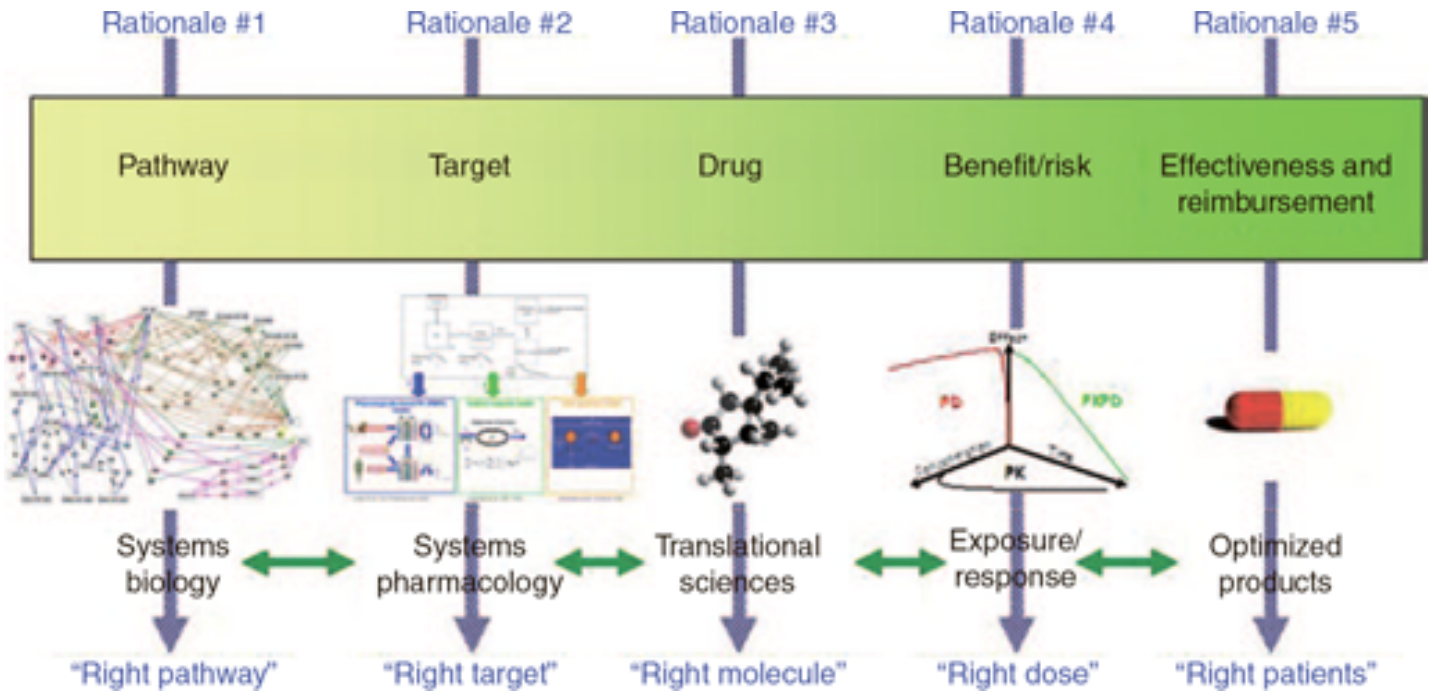
CL = 1.5 L/min

Q3: Is glomerular filtration the sole mechanism of elimination?

1. Yes
2. **No**

Hepatic metabolism could be a major and sole elimination pathway as well.

Model-Based Drug Development: A Rational Approach to Efficiently Accelerate Drug Development



Clinical Pharmacology & Therapeutics
Volume 93, Issue 6, pages 502-514, 14 MAR 2013 DOI: 10.1038/clpt.2013.54
http://onlinelibrary.wiley.com/doi/10.1038/clpt.2013.54/full#cptclpt201354-fig-0001

Examples Where Model-Based Analysis Has Helped Speed Up Drug Development

Table III. Time savings of 2 to 18 months in phase II or III studies (6 out of 11 projects)

Clin. Pharmacokinet. 1997 Aug; 33 (2)

Project	Method/gain	Time saving
Immu #1	The relationships between pharmacokinetic and safety/efficacy were investigated in a phase I study conducted in patients. These results helped to skip phase II and were used to design the pivotal phase III study	12-18 months
ID #2	The selection of doses for a phase II study was based on a pathophysiological/pharmacokinetic-pharmacodynamic model. Without this model, another study (exploratory phase II) would have been necessary to ensure that the selected doses were well tolerated in this patient population	9-15 months
CVS #4	One higher dose concentration was added in the phase II study based on pharmacodynamic results in healthy volunteers. The results of the phase II study showed that, without this additional higher dose concentrations, the phase II study would have had to be repeated because of the inappropriate selection of doses	12 months

Indication	MBDD approach adopted	Efficiencies gained over historical designs and analysis
Thromboembolism[a]	Omit phase IIa, model-based dose–response relationship, adaptive phase IIb design	2,750 Fewer patients, 1 year shorter study duration
Hot flashes	Model-based dose–response relationship	1,000 Fewer patients
Fibromyalgia	Prior data supplementation, model-based dose–response relationship, sequential design	760 Fewer patients, 1 year shorter study duration
Type 2 diabetes	Prior data supplementation, model-based dose–response relationship	120 Fewer patients, 1 year shorter study duration
Gastroesophageal reflux	Model-based dose–response relationship	1,025 Fewer patients
Rheumatoid arthritis	Model-based dose–response relationship	437 Fewer patients, increased probability of success
Global anxiety disorder	Omit phase IIb	260 Fewer patients, 1 year shorter study duration
Lower urinary tract symptoms	Meta-analysis	Increased probability of success
Urinary incontinence	Meta-analysis	Increased probability of success

MBDD, model-based drug development.

[a]This application is discussed further in the text as example 4, "Adaptive dose-finding phase II study designed using clinical trial simulations."

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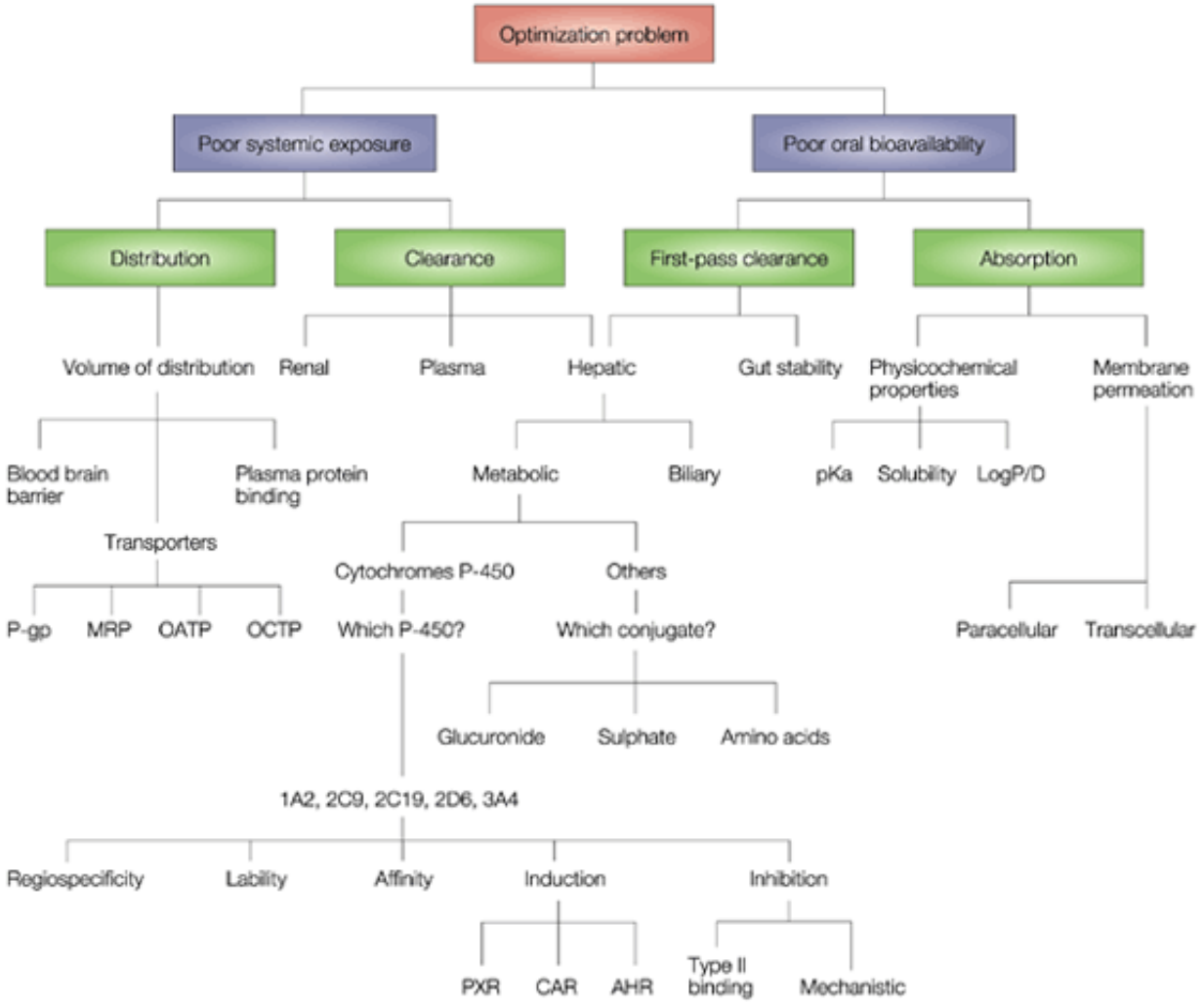
Volume 93, Issue 6, pages 502-514, 14 MAR 2013

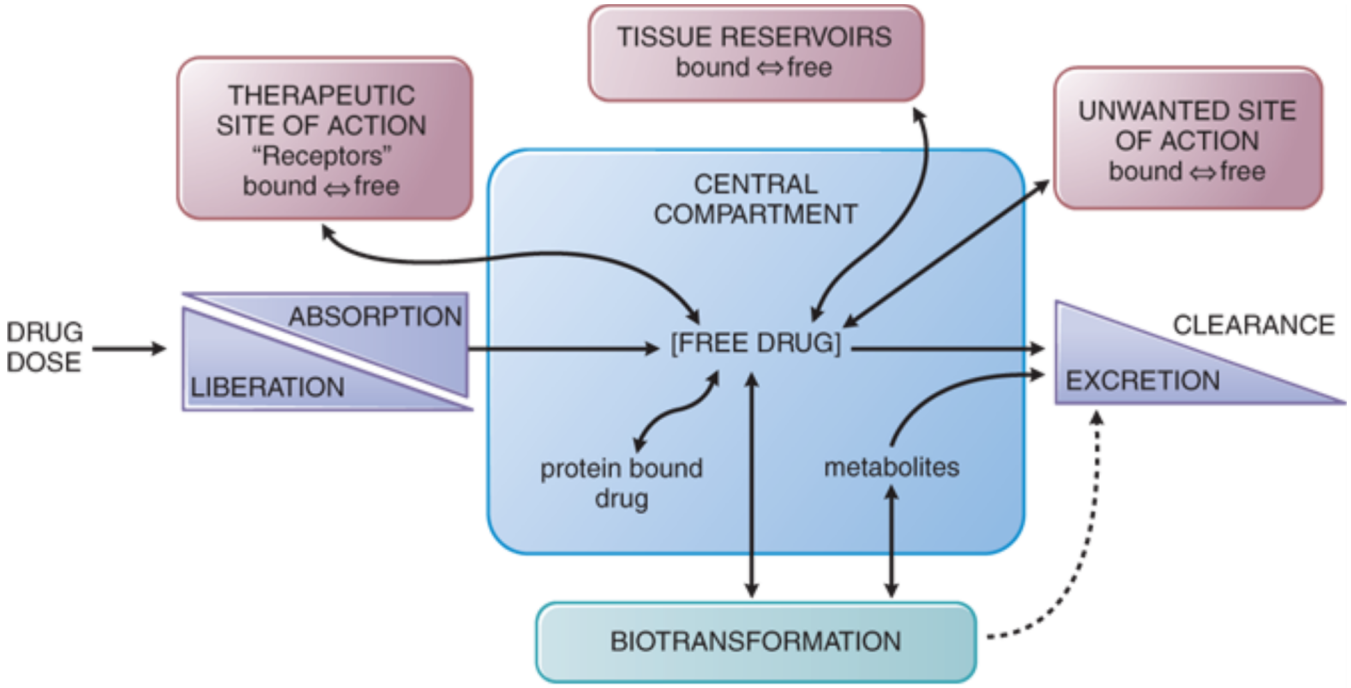
PK Optimization in Drug Development



Nature Reviews | Drug Discovery

Nature Reviews Drug Discovery **2**, 192-204 (March 2003)

PK in a Nutshell – Use Free Drug Concentrations



Source: L. L. Brunton, B. A. Chabner, B. C. Knollmann: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12ed.
www.accesspharmacy.com

The interrelationship of the absorption, distribution, binding, metabolism, and excretion of a drug and its concentration at its sites of action. Possible distribution and binding of metabolites in relation to their potential actions at receptors are not depicted.

Source: Pharmacokinetics: The Dynamics of Drug Absorption, Distribution, Metabolism, and Elimination, *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12e*

Citation: Brunton LL, Chabner BA, Knollmann BC. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12e*; 2011 Available at: http://accesspharmacy.mhmedical.com/content.aspx?bookid=1613&sectionid=102157226 Accessed: June 02, 2017

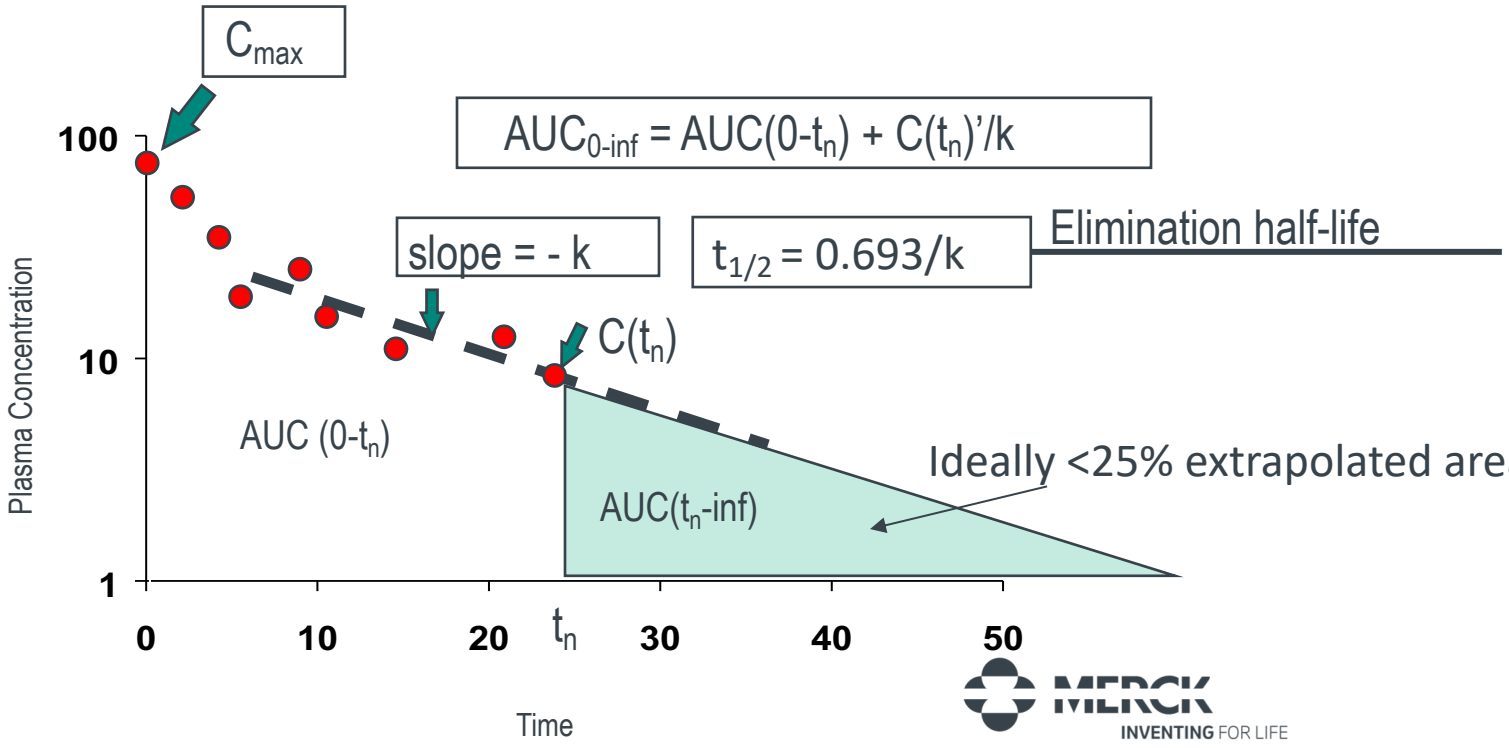
PK Analysis - NCA

Non-Compartmental Analysis

- Slope (k)
- Height (C_{max})
- Area Under the Curve (AUC)

$$CL = \frac{Dose.F}{AUC_{0-inf}}, where\ F = 1\ for\ IV$$

$$F = \frac{AUC_{po}}{Dose_{po}} \cdot \frac{Dose_{iv}}{AUC_{iv}}$$



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PK Analysis – Compartmental Evaluation

One compartment body model with first order absorption (e.g. Oral dose)

$$C_p = \frac{Dose \cdot F \cdot k_a}{V \cdot (k_a - k_{el})} (e^{-k_{el} \cdot t} - e^{-k_a \cdot t})$$

Goal: Estimate model parameters using non-linear regression

THANK YOU

MERCK