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Pharmacokinetics: The Basics

July 2020 MRC2.PSY.D.00125

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Objectives

- Explain the concept and clinical relevance of pharmacokinetics
- Describe drug bioavailability and the factors that affect systemic drug concentrations
- Elucidate the processes involved in the absorption, distribution, metabolism, and elimination of drugs
- Discuss the clinical application of the elimination rate constant and elimination half-life

Pharmacokinetics[1]

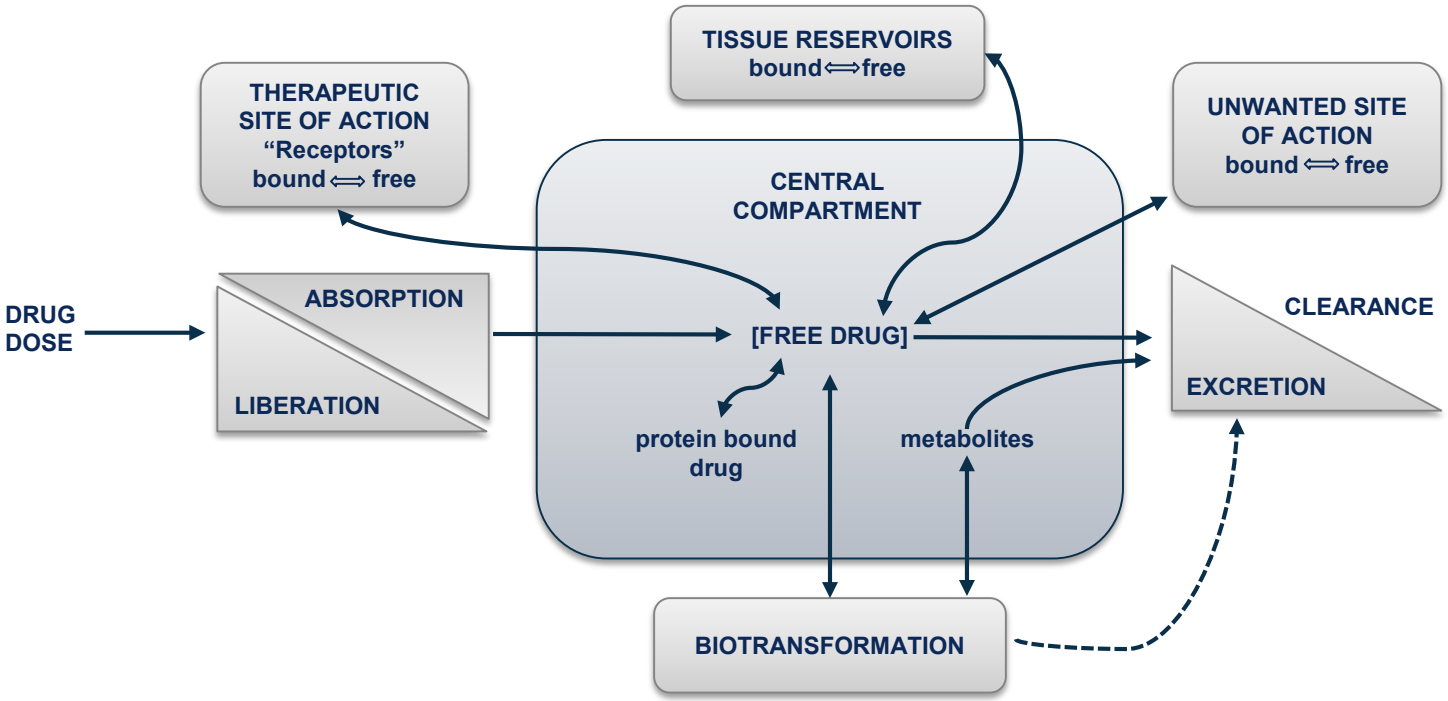


Image from: Brunton LL, et al; 2005[1]

1. Brunton LL, et al (eds). *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. McGraw-Hill; 2005.

Bioavailability

- Bioavailability is defined as the fraction of the administered dose that reaches systemic circulation[1]
- The factors that influence bioavailability include[1]:
  - Dissolution rate
  - Dosage form
  - Route of administration
  - Chemical stability of the active ingredient
  - Metabolism

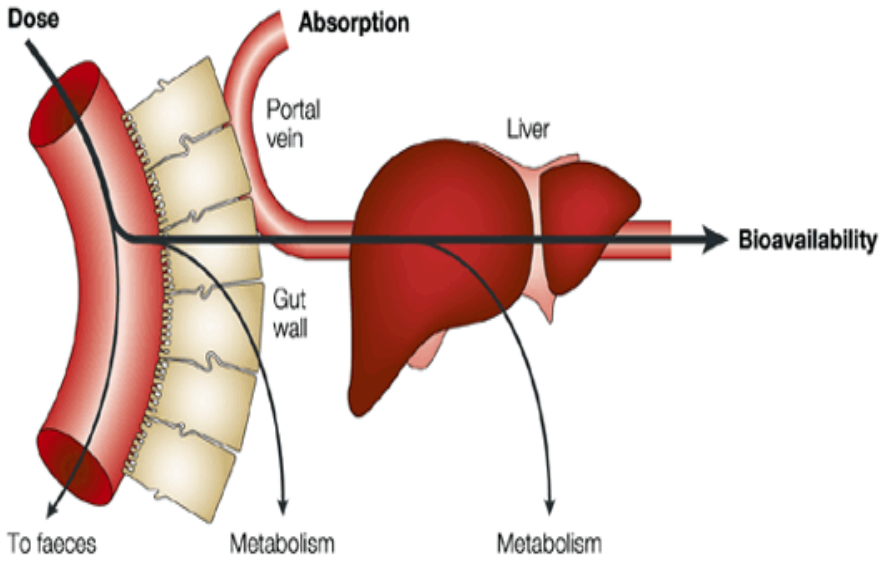


Image from: van de Waterbeemd H, et al;. 2003[2]

1. Winter ME (ed). Basic Clinical Pharmacokinetics. 5th ed. Lippincott Williams & Wilkins; 2010.
2. van de Waterbeemd H, et al. *Nat Rev Drug Discov*. 2003;2(3):192-204.

Pharmacokinetics[1]

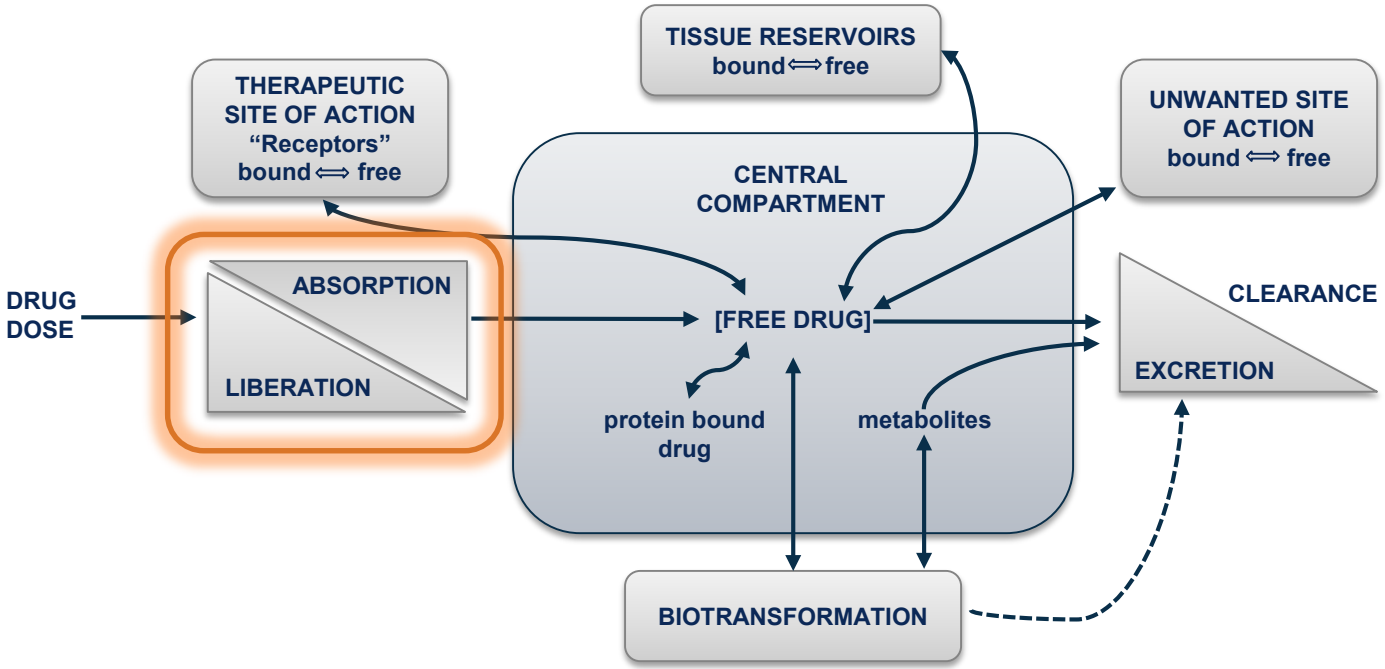


Image from: Brunton LL, et al; 2005[1]

1. Brunton LL, et al (eds). *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. McGraw-Hill; 2005.

Absorption

Sites of Drug Administration and Absorption

Administration[1]	Site of Absorption[1]	Factors Influencing Absorption
Mouth	Oral cavity	Solubility, ionization state, molecular weight[2]
	Sublingual	Solubility, ionization state, molecular weight[2]
Oral	Stomach	Dosage form, lipophilicity, ionization state[3]
	Small intestine	Dosage form, lipophilicity, ionization state[3]
	Large intestine	Dosage form, lipophilicity, ionization state[3]
Inhalation	Lungs	Solubility and permeability[4]
Topical	Skin	Lipophilicity[3]
Intramuscular	Muscle	Solubility[3]
Subcutaneous	Skin/muscle	Solubility[3]
Intravenous	Not applicable	Not applicable[3]

1. Alavijeh MS, et al. *NeuroRx*. 2005; 2(4): 554–571.
2. Narang N, et al. *Int J Pharm Pharm Sci*. 2011;3(2):18–22.
3. Brunton LL, et al (eds). *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. McGraw-Hill; 2005.
4. Ruge CA, et al. *Lancet Respir Med*. 2013;1(5):402–413.

Pharmacokinetics[1]

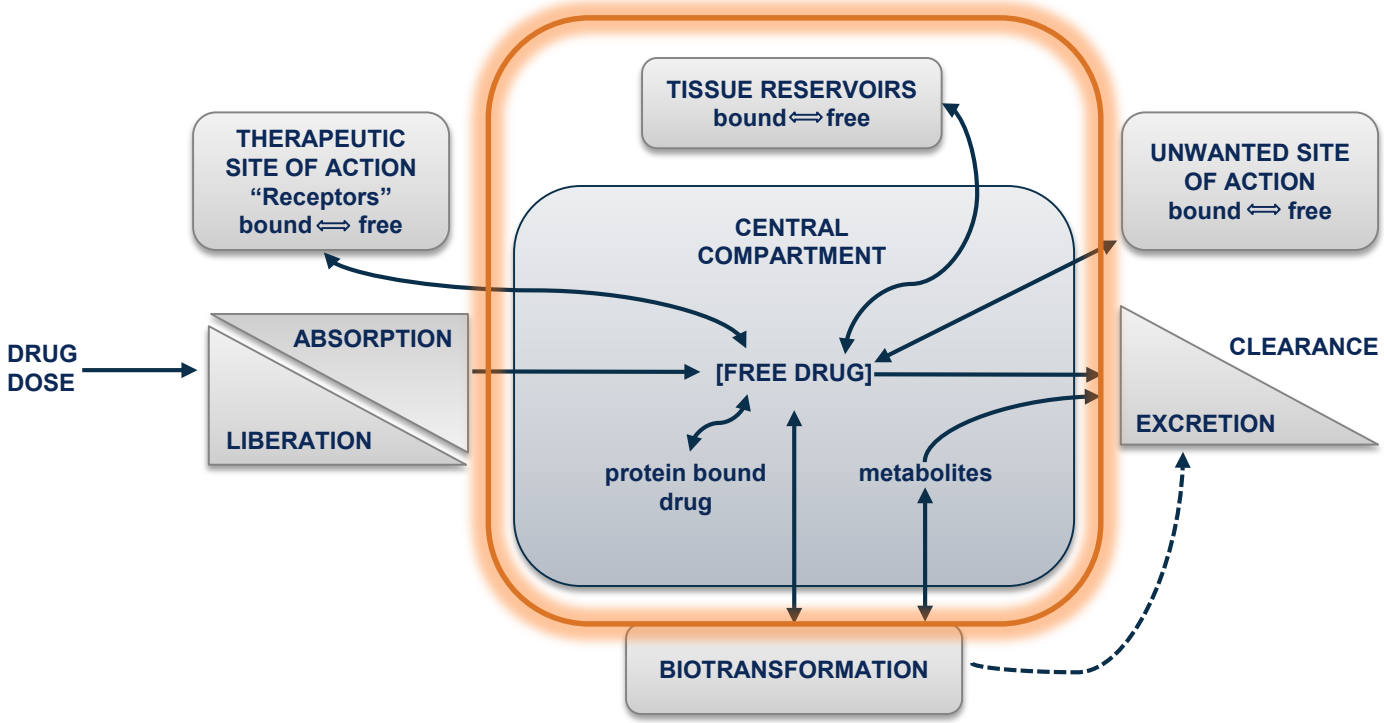


Image from: Brunton LL, et al; 2005[1]

1. Brunton LL, et al (eds). *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. McGraw-Hill; 2005.

Distribution

- Distribution is defined as the movement of drug from the site of absorption to the rest of the body (eg, plasma/tissues)[1,2]
- Drugs may distribute into the following fluid compartments[3,4]:
  - Plasma
  - Interstitial fluid
  - Intracellular fluid
- Volume of distribution is defined as the relationship between the amount of drug in the body and the plasma concentration of the drug[4]
  - Depends on lipid solubility and plasma/tissue protein binding properties[5]

$$\text{Volume of distribution}^{5} = \frac{Amount\ of\ drug\ in\ the\ body}{Plasma\ drug\ \text{concentration}}$$

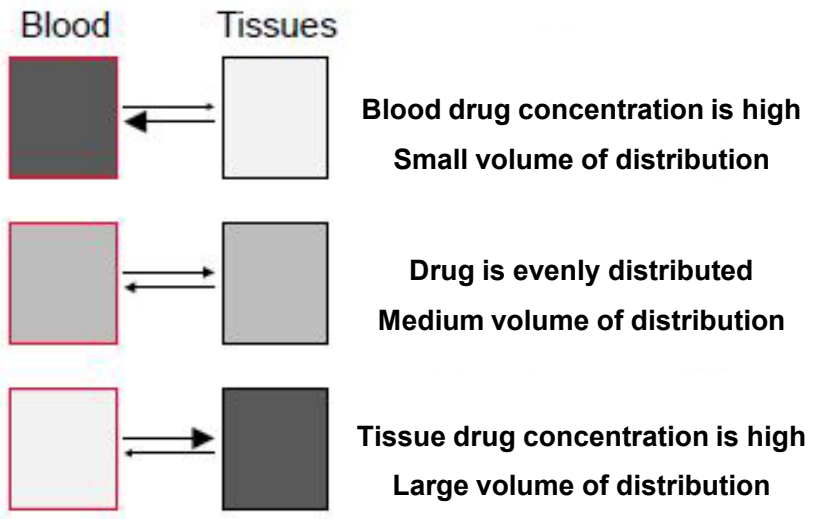


Image based on: Brunton LL, et al; 2005[4] and Winter ME, et al; 2010[5]

1. Wooten JM. *South Med J*. 2012; 105(8):437–445.
2. Gad SC (ed). *Preclinical Development Handbook: ADME and Biopharmaceutical Properties*. 1st ed. John Wiley & Sons, Inc.; 2008.
3. Rhoades RA, Bill DR (eds). *Medical Phyisiology: Principles for Clinical Medicine*. 4th ed. Lippincott Williams & Wilkins; 2012.
4. Brunton LL, et al (eds). *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. McGraw-Hill; 2005.
5. Winter ME (ed). *Basic Clinical Pharmacokinetics*. 5th ed. Lippincott Williams & Wilkins; 2010.

Pharmacokinetics[1]

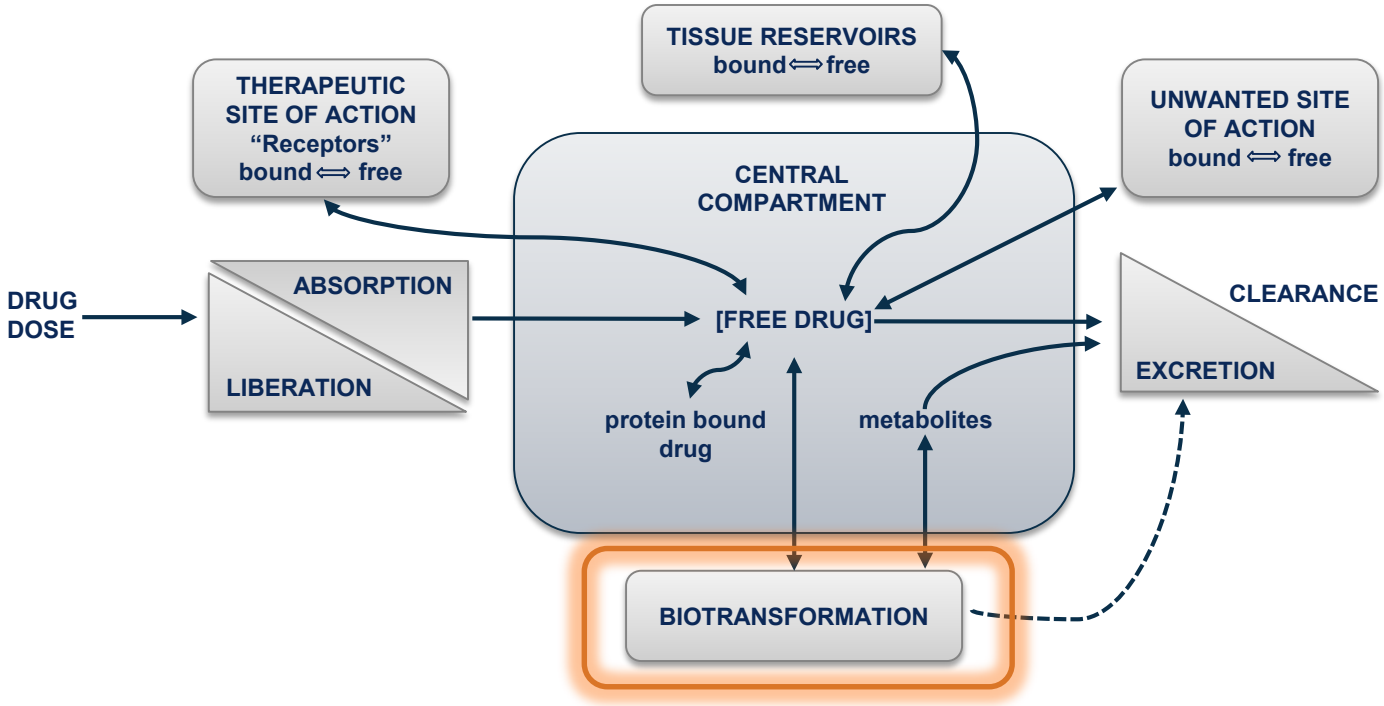


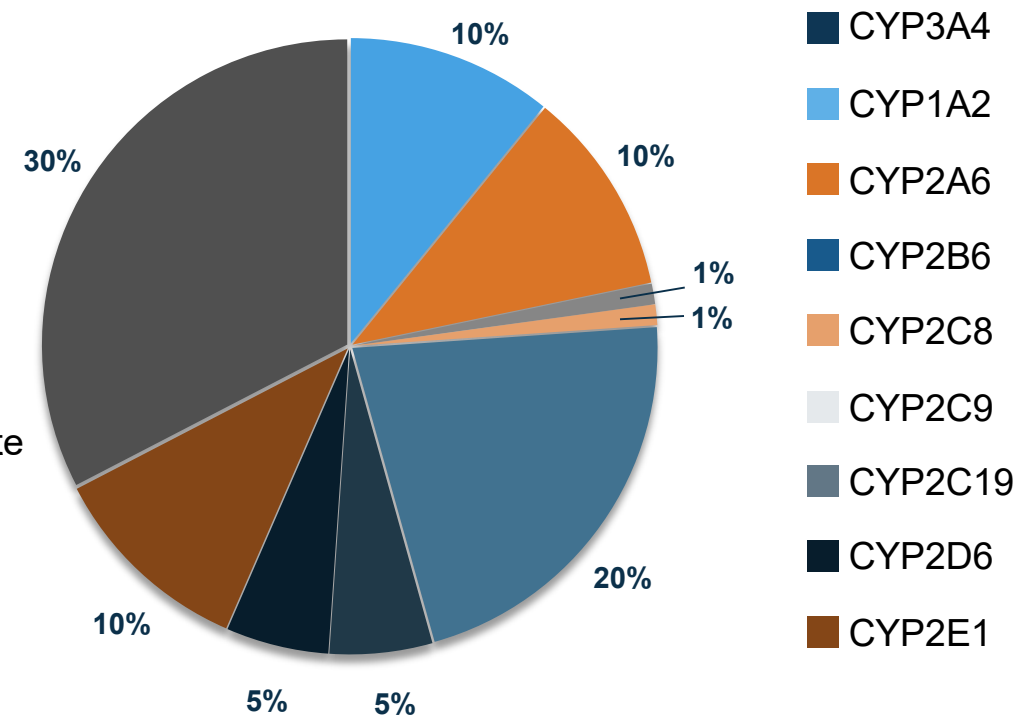
Image from: Brunton LL, et al; 2005[1]

1. Brunton LL, et al (eds). *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. McGraw-Hill; 2005.

Metabolism

- Metabolism—enhances water solubility and excretion of drugs[1]
- Two phases of drug metabolism[2]:
  - Phase I—functionalization:
    - Prodrug activation
    - Drug inactivation
    - Generate less active metabolites
  - Phase II—conjugation:
    - Enhance the hydrophilicity of the drug/phase I metabolites to facilitate elimination
- Cytochrome P450 enzymes are responsible for 75% of total drug metabolism[3]

Cytochrome P450 Isoform Relative Amounts in the Liver[1]



1. Alavijeh MS, et al. *NeuroRx*. 2005; 2(4):554–571.
2. Brunton LL, et al (eds). *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. McGraw-Hill; 2005.
3. Wang JF, et al. *Current drug metabolism*. 2010;11(4):342-346.

Pharmacokinetics[1]

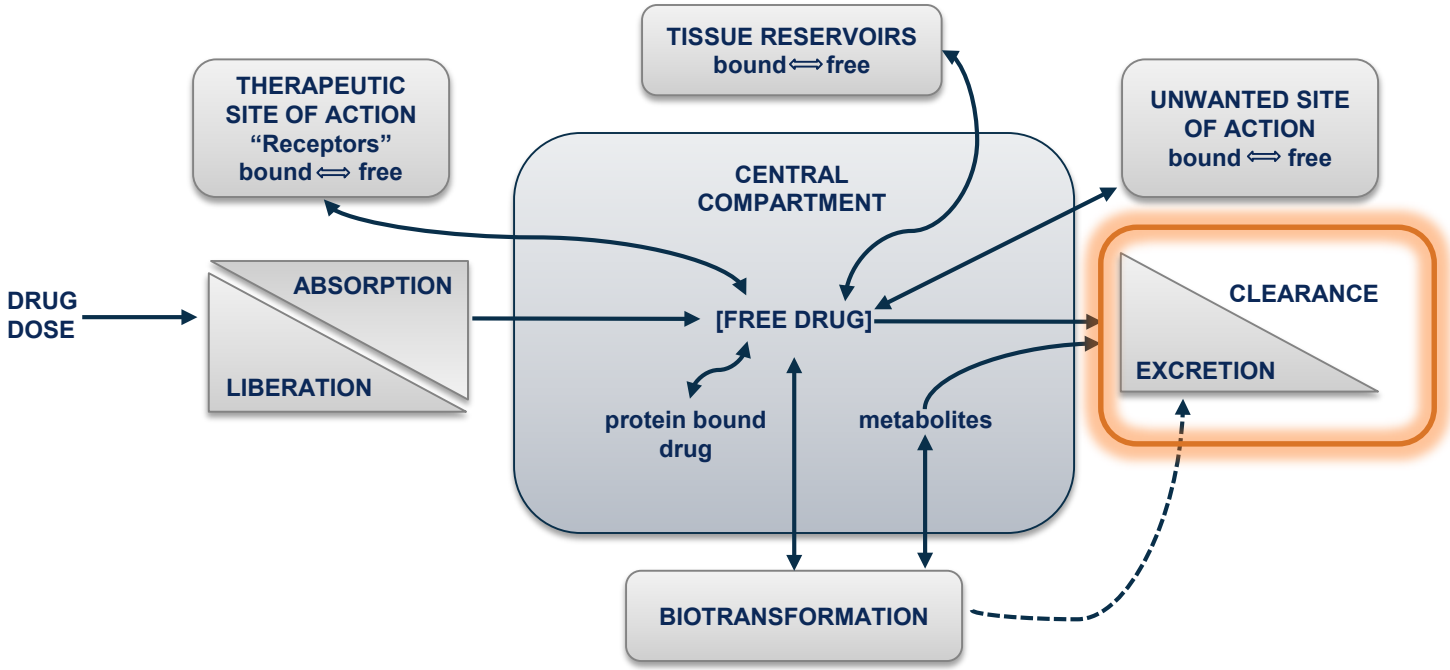


Image from: Brunton LL, et al; 2005[1]

1. Brunton LL, et al (eds). *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. McGraw-Hill; 2005.

Clearance

- Clearance is the theoretical volume of blood/plasma completely cleared of drug in a given time period[1]
- The bathtub provides a physical model to explain how clearance determines the rate of drug elimination[2]

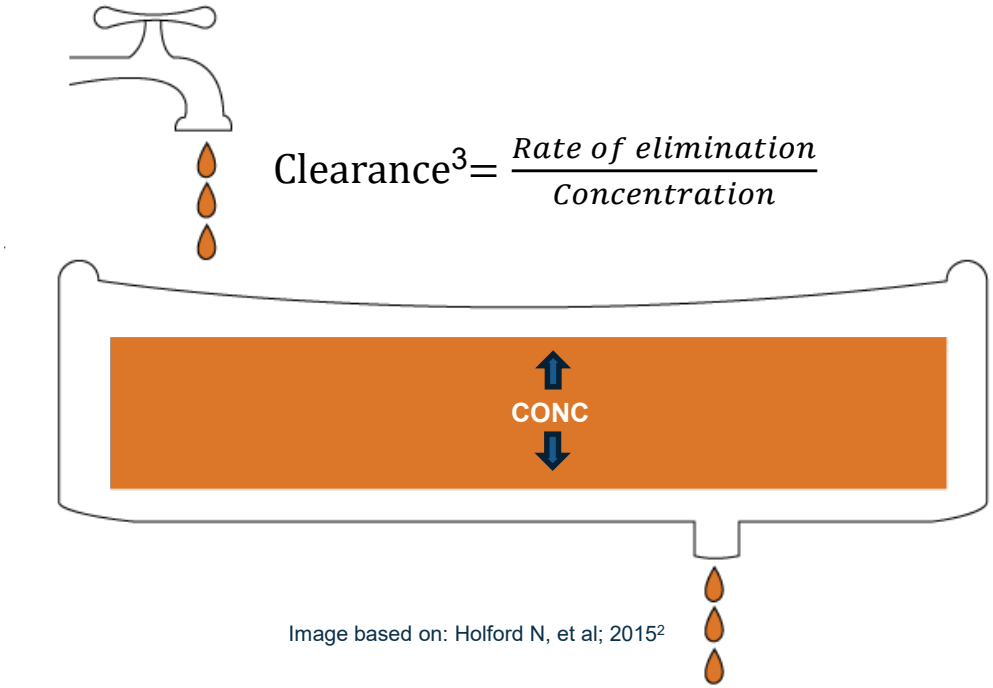


Image based on: Holford N, et al; 2015[2]

Conc, concentration.

1. Winter ME (ed). *Basic Clinical Pharmacokinetics*. 5th ed. Lippincott Williams & Wilkins; 2010.
2. Holford N, et al. *Translational and Clinical Pharmacology*. 2015;23(2):42-45.
3. Brunton LL, et al (eds). *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. McGraw-Hill; 2005.

Elimination

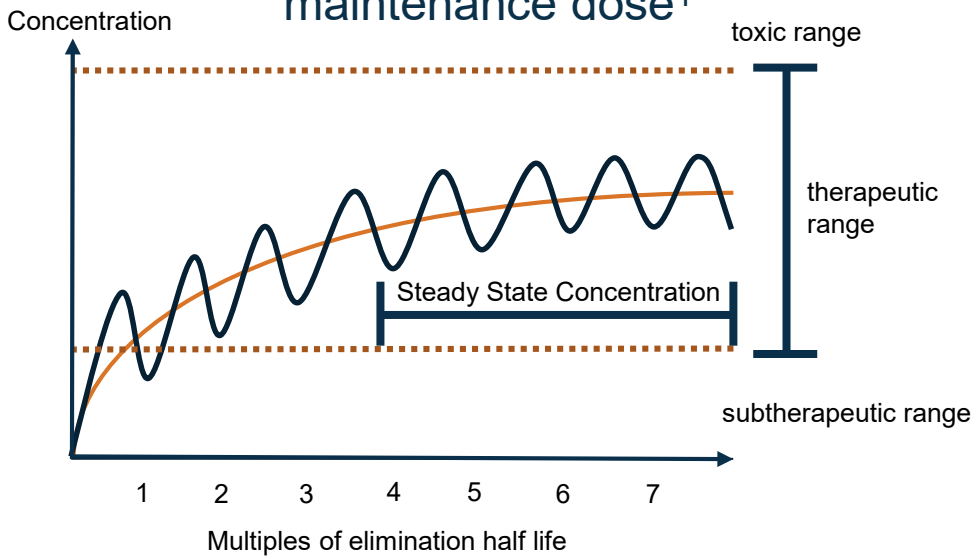
- Elimination is the irreversible loss of drug from the site of measurement (eg, blood, serum, plasma)[1]
- Elimination pathways[2]:
  - Renal clearance
  - Metabolic clearance
- Renal and metabolic clearance[2]:
  - Both processes are additive and assumed to be independent of one another
  - Both processes make up the total clearance

1. Jambhekar SS, et al (eds). *Basic pharmacokinetics*. 1st ed. Pharmaceutical Press; 2009.
2. Winter ME (ed). *Basic Clinical Pharmacokinetics*. 5th ed. Lippincott Williams & Wilkins; 2010.

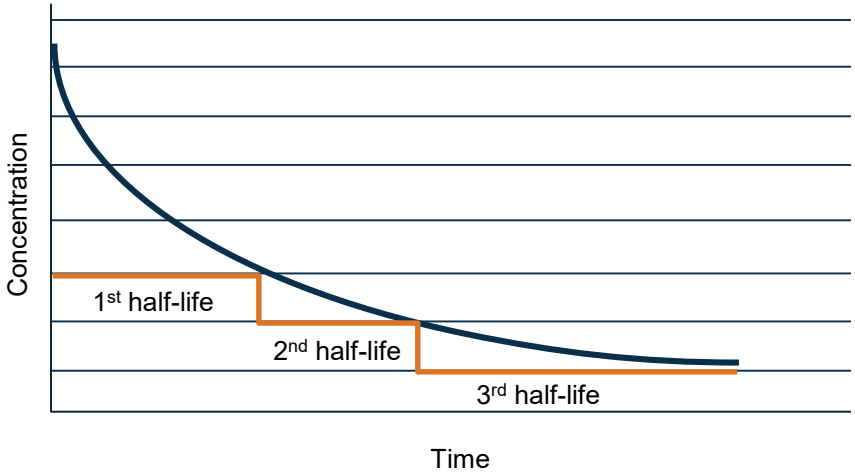
Clinical Application of Elimination Rate Constant and Half-Life

The elimination rate constant and half-life can be used to:

Estimate the time to reach steady state plasma concentration after initiation or change in the maintenance dose[1]



Estimate the time required to eliminate all or a portion of the drug from the body once it is discontinued[1]



Figures based on: Winter ME; 2010[1] and Brunton LL, et al; 2005[2]

1. Winter ME (ed). *Basic Clinical Pharmacokinetics*. 5th ed. Lippincott Williams & Wilkins; 2010.
2. Brunton LL, et al (eds). *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. McGraw-Hill; 2005.

Important Concepts to Understand[1]

- Elimination half-life is the time required for the total amount of drug in the body to decrease by 50%
- Elimination rate constant is the fraction of drug eliminated in a given time period
  - Depends on clearance and volume of distribution
  - Often expressed in terms of drug's half-life
- At steady state, the rate of drug administration and rate of drug elimination must be equal
  - In most clinical situations, steady state can be assumed after three to five half-lives

1. Winter ME (ed). *Basic Clinical Pharmacokinetics*. 5th ed. Lippincott Williams & Wilkins; 2010.

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