

ANSWER KEY WITH EXPLANATIONS

FOR CHAPTER 2

Skill Drill Answers

SD 2.1: Route-Absorption Matching

1. **B** — Intravenous administration has 100% bioavailability by definition since drug enters systemic circulation directly.
2. **A** — Oral administration subjects drugs to first-pass metabolism in gut wall and liver.
3. **D** — Sublingual administration allows drug to enter systemic circulation via oral mucosa veins, bypassing hepatic first-pass metabolism.
4. **E** — Transdermal patches provide sustained, controlled delivery over hours to days.
5. **F** — Inhalation provides rapid absorption due to the large alveolar surface area ($\sim 100 \text{ m}^2$) and thin epithelium.
6. **C** — Intramuscular absorption depends on blood flow to the injection site.
7. **A** — Oral is the most common and convenient route for outpatient self-administration.
8. **D** — Nitroglycerin is given sublingually for rapid onset and to avoid extensive first-pass metabolism.
9. **F** — Volatile anesthetics are administered by inhalation to reach the CNS rapidly.
10. **A** — Oral absorption is affected by gastric emptying, intestinal motility, and food interactions.

SD 2.2: True/False with Correction

1. **F** — V_d is a theoretical (apparent) volume, not an actual physiological volume. A drug with V_d of 500 L clearly exceeds total body volume ($\sim 42 \text{ L}$).
2. **T** — Steady state is reached in 4-5 half-lives. For an 8-hour half-life: $4 \times 8 = 32$ -40 hours.
3. **F** — Loading dose is determined by V_d (not clearance). $LD = (V_d \times \text{Target concentration}) / F$.
4. **F** — First-pass metabolism occurs in both the intestinal wall (enterocyte metabolism) and liver.

5. **T** — Only unbound (free) drug can cross membranes, bind receptors, and undergo metabolism/elimination.
 6. **F** — High extraction drugs have clearance that depends primarily on hepatic blood flow, not protein binding.
-

SD 2.3: Fill in the Blank

1. **bioavailability (F)**
 2. **volume of distribution (Vd)**
 3. **half-life ($t_{1/2}$)**
 4. **clearance (CL)**
 5. **Steady**
 6. **first-pass (or presystemic)**
 7. **oxidation**
 8. **conjugation**
-

SD 2.4: Parameter Calculation

1. **Half-life calculation:** $t_{1/2} = (0.693 \times Vd) / CL = (0.693 \times 50 \text{ L}) / 5 \text{ L/hr} = 34.65 / 5 = \mathbf{6.93 \text{ hours}}$
(approximately 7 hours)
 2. **Loading dose calculation:** $LD = (Vd \times C_p) / F = (40 \text{ L} \times 10 \text{ mg/L}) / 0.8 = 400 / 0.8 = \mathbf{500 \text{ mg}}$
 3. **Time to steady state:** $\text{Time} = 4-5 \times t_{1/2} = 4-5 \times 12 \text{ hours} = \mathbf{48-60 \text{ hours (2-2.5 days)}}$
 4. **Bioavailability calculation:** $F = (AUC_{\text{oral}} / AUC_{\text{IV}}) \times (Dose_{\text{IV}} / Dose_{\text{oral}}) F = (200 / 250) \times (50 / 100) = 0.8 \times 0.5 = \mathbf{0.4 \text{ (or 40%)}}$
-

SD 2.5: Category Sorting

1. **I** — Oxidation is a Phase I reaction
2. **II** — Glucuronidation is a Phase II conjugation reaction
3. **I** — CYP450 enzymes catalyze Phase I reactions
4. **II** — Sulfation is a Phase II conjugation reaction
5. **II** — Phase II reactions increase water solubility for excretion (Phase I also may)
6. **I** — Hydrolysis is a Phase I reaction

7. **II** — Acetylation is a Phase II conjugation reaction
 8. **I** — Prodrug activation typically occurs via Phase I oxidation
 9. **II** — Conjugation defines Phase II reactions
 10. **I** — Reduction is a Phase I reaction
-

SD 2.6: Rapid Recall

1. **4-5** half-lives
 2. **100%**
 3. **Albumin**
 4. **Alpha-1-acid glycoprotein (AAG)**
 5. **Absorption, Distribution, Metabolism, Elimination**
 6. **CYP450 (cytochrome P450)**
 7. **plasma (or bloodstream)**
 8. **Volume of distribution (Vd)**
-

SD 2.7: Complete the Equation

1. $t_{1/2} = (0.693 \times \mathbf{Vd}) / \mathbf{CL}$
 2. Loading dose = $(\mathbf{Vd} \times \text{Target concentration}) / F$
 3. $F = (\text{AUC}_{\text{oral}} / \text{AUC}_{\text{IV}}) \times (\mathbf{Dose_{IV}} / \text{Dose}_{\text{oral}})$
 4. Maintenance dose rate = $\mathbf{CL} \times \text{Target concentration}$
 5. $\mathbf{Vd} = \text{Amount of drug in body} / \mathbf{\text{Plasma concentration}}$
 6. $\mathbf{CL_{total}} = \mathbf{CL_{renal}} + \mathbf{CL_{hepatic}} + \mathbf{CL_{other}}$
 7. Time to steady state = $\mathbf{4-5} \times t_{1/2}$
 8. $\text{CrCl (male)} = [(140 - \text{age}) \times \text{weight}] / (72 \times \mathbf{SCr})$
-

SD 2.8: Half-Life Determination

1. After 12 hours = 3 half-lives: $100 \rightarrow 50 \rightarrow 25 \rightarrow \mathbf{12.5 \text{ mg/L}}$
2. Essentially eliminated in 4-5 half-lives: $4-5 \times 6 \text{ hours} = \mathbf{24-30 \text{ hours}}$

3. Steady state in 4-5 half-lives: $4-5 \times 24 \text{ hours} = 96-120 \text{ hours} = \text{Day 4-5 of therapy}$
 4. $80 \rightarrow 40 \rightarrow 20 \rightarrow 10 \text{ mg/L}$ requires 3 half-lives. $9 \text{ hours} / 3 = \text{3-hour half-life}$
-

SD 2.9: Abbreviation Matching

1. **F** — V_d = Volume of distribution
 2. **G** — CL = Clearance
 3. **E** — F = Bioavailability
 4. **A** — AUC = Area under the curve
 5. **B** — C_{max} = Maximum concentration
 6. **C** — C_{min} = Minimum concentration
 7. **D** — T_{max} = Time to maximum concentration
 8. **H** — C_{ss} = Steady-state concentration
-

SD 2.10: Compartment Model Identification

1. **ONE** — Instantaneous distribution is a one-compartment assumption
 2. **TWO** — Biphasic decline indicates two-compartment kinetics
 3. **ONE** — Single exponential = one-compartment
 4. **TWO** — Initial distribution phase followed by elimination = two-compartment
 5. **ONE** — Single homogeneous unit = one-compartment
 6. **TWO** — Central and peripheral compartments = two-compartment model
 7. **TWO** — Aminoglycosides show two-compartment kinetics
 8. **ONE** — Small, water-soluble drugs typically fit one-compartment models
-

SD 2.11: Error Identification

1. **Error:** Formula uses CL instead of V_d **Correction:** Loading dose = $(V_d \times \text{Target concentration}) / F$
2. **Error:** Large V_d drugs are NOT easily removed by hemodialysis **Correction:** Drugs with large V_d distribute extensively into tissues and are poorly dialyzable

3. **Error:** High extraction drugs depend on blood flow, not protein binding **Correction:** Clearance of high-extraction drugs depends primarily on hepatic blood flow
 4. **Error:** Time to steady state depends only on half-life, not dose **Correction:** Higher doses achieve higher steady-state concentrations but do not reach steady state faster
-

SD 2.12: Dosing Interval Selection

1. **B** — Dosing interval equal to half-life produces approximately 2-fold fluctuation between peak and trough
2. **B** — For concentration-dependent killing, maximizing peak (high dose, extended interval) is more effective than frequent lower doses
3. **B** — Steady state in 4-5 half-lives: $4-5 \times 1 \text{ hour} = 4-5 \text{ hours}$
4. **C** — 90% of steady state is reached at ~ 3.3 half-lives: $3.3 \times 48 = 158.4 \text{ hours} \approx 160 \text{ hours}$

Case Study Answers

Case 2.1: Renal Impairment Dosing Adjustment

Question 1. $\text{CrCl} = [(140 - 72) \times 70] / (72 \times 2.4)$ $\text{CrCl} = [68 \times 70] / 172.8$ $\text{CrCl} = 4760 / 172.8$ $\text{CrCl} \approx 27.5 \text{ mL/min}$

Question 2. This patient's CrCl ($\sim 28 \text{ mL/min}$) is approximately 25% of normal (100-120 mL/min), indicating severe renal impairment (CKD stage 4). Since gentamicin is eliminated almost entirely by glomerular filtration, its clearance will be reduced proportionally, leading to **prolonged half-life and accumulation without dose adjustment**. This increases risk of nephrotoxicity and ototoxicity.

Question 3. If renal function is $\sim 25\%$ of normal, half-life increases approximately 4-fold. Normal half-life: 2.5 hours Estimated half-life: $2.5 \times 4 = 10 \text{ hours}$

Question 4. Two approaches: **(1) Reduce the dose** while maintaining the interval, or **(2) Extend the interval** while maintaining the dose. For once-daily aminoglycoside dosing, **extending the interval** is generally preferred because it maintains the high peak concentrations needed for concentration-dependent bacterial killing while allowing adequate time for drug elimination between doses.

Case 2.2: Drug-Drug Interaction via CYP450

Question 1. Fluconazole inhibits CYP2C9, the primary enzyme metabolizing the S-enantiomer of warfarin (the more potent enantiomer). **Inhibition reduces warfarin clearance, causing accumulation**

and increased plasma concentrations. Higher warfarin levels produce excessive anticoagulation, elevating INR and causing bleeding.

Question 2. Low hepatic extraction means warfarin clearance depends on intrinsic hepatic clearance (enzyme activity) rather than hepatic blood flow. **CYP450 inhibition has a significant effect on low-extraction drugs** because their clearance is directly dependent on enzyme activity. If fluconazole were inhibiting metabolism of a high-extraction drug, the effect would be minimal because blood flow (not enzyme activity) limits clearance.

Question 3. If clearance is reduced by 50%:

- **Half-life doubles** (since $t_{1/2} = 0.693 \times V_d / CL$; if CL decreases by half, $t_{1/2}$ doubles)
- **Steady-state concentration doubles** (since $C_{ss} \propto \text{Dose}/CL$; if CL decreases by half, C_{ss} doubles)

Question 4. When initiating a CYP2C9 inhibitor with warfarin:

- **Reduce warfarin dose empirically** (often by 25-50%) when starting the inhibitor
- **Monitor INR more frequently** during initiation and after discontinuation
- Adjust warfarin dose based on INR response
- Consider alternative antifungal agents without CYP2C9 inhibition if possible

Diagram/Table Exercise Answers

DT 2.1: Plasma Concentration-Time Curve

1. C_{max} (initial concentration) = **50 mg/L**
2. Concentration at 6 hours = **25 mg/L** (one half-life)
3. Concentration at 12 hours = **12.5 mg/L** (two half-lives)
4. Half-life = **6 hours** (concentration decreases by half every 6 hours)
5. $V_d = 500 \text{ mg} / 50 \text{ mg/L} = \textbf{10 L}$
6. $CL = (0.693 \times 10 \text{ L}) / 6 \text{ hr} = \textbf{1.16 L/hr}$

DT 2.2: First-Pass Metabolism Pathway

1. Primary site of drug absorption: **Small intestine**
2. Blood vessel carrying absorbed drug to the liver: **Portal vein (hepatic portal vein)**
3. Site of presystemic hepatic metabolism: **Liver (hepatocytes)**

4. Blood vessel carrying drug from liver to systemic circulation: **Hepatic vein**
5. Drugs with high first-pass metabolism (any three): **Morphine, propranolol, nitroglycerin, lidocaine, verapamil, alprenolol**
6. Routes bypassing first-pass metabolism (any two): **Sublingual, intravenous, transdermal, inhalation, rectal (lower rectum)**

DT 2.3: CYP450 Enzyme Table

CYP Enzyme	Major Substrates	Inhibitors	Inducers
CYP3A4	Cyclosporine, tacrolimus, statins (atorvastatin, simvastatin), nifedipine	Ketoconazole, itraconazole, erythromycin, clarithromycin, grapefruit juice	Rifampin, phenytoin, carbamazepine, St. John's Wort
CYP2D6	Codeine, tramadol, metoprolol, fluoxetine, tamoxifen, dextromethorphan	Fluoxetine, paroxetine, quinidine, bupropion	Not significantly inducible
CYP2C9	Warfarin, phenytoin, NSAIDs, losartan, glipizide	Fluconazole, amiodarone, metronidazole	Rifampin, carbamazepine
CYP2C19	Omeprazole, clopidogrel, diazepam, phenytoin	Omeprazole, fluconazole, fluvoxamine	Rifampin, carbamazepine
CYP1A2	Theophylline, caffeine, clozapine, warfarin (R)	Fluvoxamine, ciprofloxacin, cimetidine	Smoking, chargrilled meat, rifampin

DT 2.4: Compartment Model Diagrams

1. Drug distributes **instantaneously (or rapidly/uniformly)**
2. **Single** exponential decline
3. Example drugs: **Aminoglycosides (in some analyses), lithium, small water-soluble drugs**
4. Central compartment: **Blood (plasma) and highly perfused organs**
5. Peripheral compartment: **Tissues with slower equilibration (fat, muscle, bone)**
6. Initial rapid decline: **Alpha (α) phase (distribution phase)**
7. Later slower decline: **Beta (β) phase (elimination phase)**
8. Example drugs: **Aminoglycosides, vancomycin, digoxin, lipophilic drugs**

Multiple-Choice Question Answers

Question 1. Answer: B — 10 mg/L

$V_d = \text{Dose} / \text{Concentration}$, therefore $\text{Concentration} = \text{Dose} / V_d = 100 \text{ mg} / 10 \text{ L} = 10 \text{ mg/L}$

Question 2. Answer: D — Intravenous

IV administration delivers drug directly to systemic circulation, defining bioavailability as 100%.

Question 3. Answer: B — Oral

Orally administered drugs pass through the portal circulation and liver before reaching systemic circulation, subject to first-pass metabolism.

Question 4. Answer: C — 24-30 hours

Steady state = 4-5 half-lives = $4-5 \times 6 \text{ hours} = 24-30 \text{ hours}$.

Question 5. Answer: C — Volume of distribution

Loading dose = $(V_d \times \text{Target concentration}) / F$. V_d determines how much drug is needed to fill the distribution volume.

Question 6. Answer: B — 7 hours

$t_{1/2} = (0.693 \times V_d) / CL = (0.693 \times 70) / 7 = 48.51 / 7 = 6.93 \approx 7 \text{ hours}$

Question 7. Answer: B — Free drug concentration increases transiently

Displacement from protein binding transiently increases free drug, but this free drug is then rapidly distributed and eliminated, returning to a new equilibrium. Total concentration may decrease while free concentration remains similar.

Question 8. Answer: B — Phase I — Oxidation

Phase I includes oxidation, reduction, and hydrolysis. Glucuronidation is Phase II.

Question 9. Answer: C — 4-5 days

Time to new steady state depends only on half-life ($4-5 \times 24 \text{ hours} = 96-120 \text{ hours} = 4-5 \text{ days}$), regardless of dose change.

Question 10. Answer: B — Extensive first-pass metabolism

Morphine undergoes extensive hepatic first-pass metabolism (glucuronidation), reducing oral bioavailability to ~25%.

Question 11. Answer: B — They distribute extensively into tissues

Large V_d indicates drug leaves plasma and distributes into tissues. These drugs are NOT efficiently dialyzed.

Question 12. Answer: B — Changes in hepatic blood flow

High extraction drugs ($E = 0.9$) have clearance that depends primarily on hepatic blood flow, not enzyme activity or protein binding.

Question 13. Answer: D — 5-fold longer

If 80% of the drug is renally eliminated and renal function is 20% of normal, renal clearance is reduced to 20% of normal. Total clearance = 20% (renal at reduced function) + 20% (non-renal, unchanged) = approximately 20-36% of normal. Half-life increases proportionally, approximately 4-5 fold.

Question 14. Answer: B — 2 hours

$100 \rightarrow 50 \rightarrow 25 \rightarrow 12.5 \text{ mg/L} = 3 \text{ half-lives in 6 hours}$. Half-life = $6/3 = 2 \text{ hours}$.

Question 15. Answer: B — 45 mg

Maintenance dose = $(CL \times C_p \times \tau) / F = (3 \text{ L/hr} \times 15 \text{ mg/L} \times 8 \text{ hr}) / 0.8 = 360 / 0.8 = 450 \text{ mg/day}$, or $450/3 \text{ intervals} = 150 \text{ mg per 8-hour interval}$

Let me recalculate:

- Target $C_{ss} = 15 \text{ mg/L}$
- $CL = 3 \text{ L/hr}$

- $\tau = 8 \text{ hr}$
- $F = 0.8$

Maintenance dose rate = $CL \times C_{ss} = 3 \times 15 = 45 \text{ mg/hr}$ Per interval: $45 \text{ mg/hr} \times 8 \text{ hr} = 360 \text{ mg per interval}$
Adjusted for bioavailability: $360 / 0.8 = \mathbf{450 \text{ mg}}$

Question 16. Answer: D — Increased clearance, decreased INR

Rifampin induces CYP2C9, increasing warfarin metabolism and clearance. Increased clearance reduces warfarin concentrations, decreasing anticoagulant effect and lowering INR. Patients may require significantly higher warfarin doses during rifampin therapy.