

Topic 11

University Medicine

What this course is, and how to use it

This is the eleventh course in University Medicine: **pharmacology** – what the body does to a drug (kinetics) and what a drug does to the body (dynamics). MED02 supplied the receptor chemistry, MED05 the physiology, MED08 the antimicrobial targets.

Scope limit, stated once: a study course, not a medical degree; every case is fictional, every number is an illustrative teaching value inside a labelled calculation, drug names are international nonproprietary names (INN), and nothing here is prescribing guidance or a regimen.

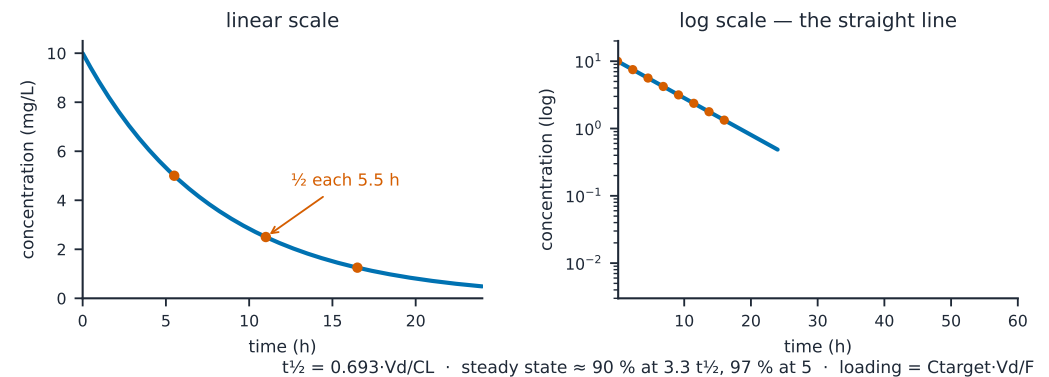
- Units 11.1–11.2 are the engine: pharmacokinetics and pharmacodynamics.
- Units 11.3–11.6 are systems: autonomic, cardiovascular/renal, antimicrobial/anticancer, CNS and analgesia.
- Unit 11.7 is safety: adverse reactions, interactions, error prevention.

The pharmacology habit: **mechanism predicts effect, arithmetic predicts exposure** – every curve below is read in both directions, and every half-life is something you recompute.

Pharmacokinetics

Why it matters. Kinetics turns a dose into a concentration – and concentration, not dose, is what the body sees. **Half-life**, clearance and volume are the three levers.

The idea, with a picture. **Volume of distribution** V_d (the apparent volume a drug "occupies"), **clearance** CL (volume cleared per time), linked by $t_{1/2} = 0.693 \cdot V_d / CL$ ✓; absorption with **bioavailability** F (fraction reaching circulation); **first-pass metabolism** cuts oral F ✓.



Half-life is the log-linear slope; steady state arrives after ~4–5 half-lives, loading doses skip the wait

The derivation (why 4–5 half-lives reach steady state). Repeated dosing adds drug each interval while clearance removes a fixed fraction: the gap closes exponentially toward **steady state** – after 3.3 half-lives ~90 % of steady state, after 5 half-lives ~97 % ✓. A **loading dose** fills the tank at once: $D_L = C_{target} \cdot V_d / F$ (illustrative calculation: target 10 mg/L, V_d 40 L, F 1.0 → 400 mg – a teaching value, not a prescription) ✓.

Worked example 1 – the three levers (illustrative values). V_d 40 L, CL 5 L/h: $t_{1/2} = 0.693 \times 40 / 5 = 5.5$ h ✓. Halve clearance (liver disease): $t_{1/2}$ doubles to 11.1 h – the same dose now accumulates; steady state is later and higher ✓.

Worked example 2 – clinical link: the first-pass toll. (Fictional teaching value) a drug with oral $F = 0.6$: of a labelled 100 mg oral dose, 60 mg reaches the circulation – the liver extracts 40 % on the first pass ✓. Portal failure or a bypass raises F and the same tablet behaves like a bigger one: kinetics, not pharmacology, changed the effect.

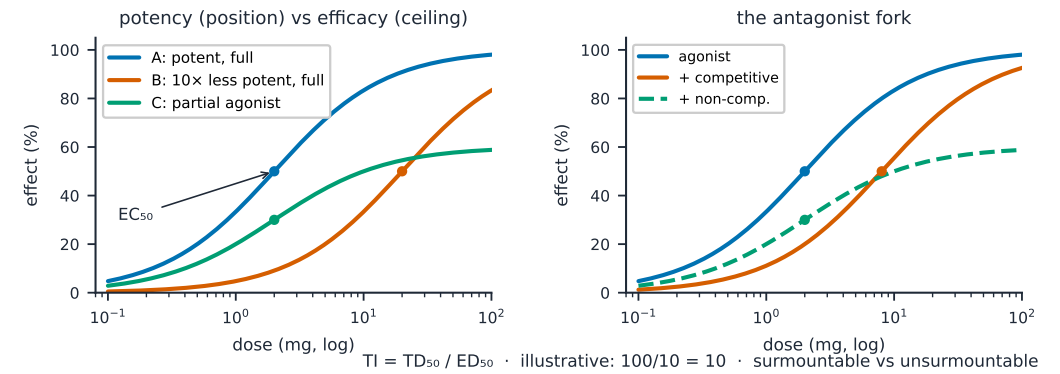
Common mistakes. Equating half-life with duration of effect (effect depends on concentration vs the drug's target range). Reading V_d as a real volume (it is a proportionality constant – about 3 L means the drug stays in plasma, 500 L means tissue binding). Forgetting maintenance dosing aims at $CL \cdot C_{ss}$.

Summary. $t_{1/2} = 0.693 V_d / CL$; steady state ≈ 90 % at $3.3 t_{1/2}$, 97 % at 5; loading $C_{target} V_d / F$; oral F = fraction past the first pass; clearance sets maintenance, volume sets the load.

Pharmacodynamics

Why it matters. Dynamics is the grammar of every drug chart: what a receptor does with a molecule – potency, efficacy, and the antagonists that undo both.

The idea, with a picture. The dose–response curve (log dose): position along the x-axis = **potency** (EC_{50}); ceiling = **efficacy** (E_{max}) ✓. Agonists reach E_{max} ; **partial agonists** reach a lower ceiling (and displace full agonists); competitive antagonists shift the curve **RIGHT** in parallel; non-competitive lower E_{max} ✓.



Potency is position, efficacy is ceiling – antagonists shift right or cut the ceiling

The derivation (why the therapeutic index is a ratio). Therapeutic index $TI = TD_{50}/ED_{50}$ – the toxic dose over the effective dose, each read from its own cumulative curve (illustrative: TD_{50} 100 mg, ED_{50} 10 mg → TI 10) ✓. A drug with TI 2 asks for care; TI 100 forgives. Narrow-TI drugs (the ones needing level monitoring) are those whose toxic and effective curves overlap.

Worked example 1 – reading a curve pair. (Fictional curves) drug A: EC_{50} 2 mg, E_{max} 100 %; drug B: EC_{50} 20 mg, E_{max} 100 % – B is 10× less potent but equally efficacious; drug C: EC_{50} 2 mg, E_{max} 60 % – a partial agonist, potent but capped ✓. Three claims, three curve features.

Worked example 2 – clinical link: the antagonist fork. (Fictional) a competitive antagonist co-administered: the curve shifts right – the agonist’s effect can be overcome by concentration (surmountable). A non-competitive antagonist cuts E_{max} – no concentration wins ✓. The overdose logic follows: one is a tug-of-war, the other removes the rope.

Common mistakes. Calling a potent drug a strong one (potency is dose-position; efficacy is the ceiling). Expecting a partial agonist to behave like a weak full agonist in combination (it **COMPETES** – lowering the mixture’s ceiling). Reading TI from a single curve (it needs two: effect and toxicity).

Summary. Potency = EC_{50} position; efficacy = E_{max} ; partial agonist = lower ceiling that displaces; competitive → parallel right shift (surmountable); non-competitive → lower ceiling; $TI = TD_{50}/ED_{50}$ (illustrative 100/10 = 10).

Autonomic pharmacology

Why it matters. The autonomic receptor map (MED09 §5) is the most-prescribed territory in medicine – every agonist and blocker is a prediction exercise, and the **toxidromes** are its emergencies.

The idea, with a picture. The code: $\alpha 1$ constricts vessels and dilates pupils; $\beta 1$ drives the heart; $\beta 2$ opens airways; M3 drives secretion, constricts the pupil and speeds the gut, while M2 slows the heart ✓. Agonists push the receptor; blockers remove its tone.

the map, read upside down, is the toxidrome — every finding is a receptor row								
$\alpha 1$	vasoconstriction · mydriasis	agonist ↑ pressure; blocker ↓ (postural drop)						
$\beta 1$	heart rate and contractility	agonist ↑ output; blocker ↓ rate						
$\beta 2$	bronchodilation · vasodilation	agonist opens airways						
M3	glands · gut motility · miosis	agonist = wet, cramps; blocker = dry						
M2	slows the heart	agonist = slow; blocker = fast						
<table><tr><th>CHOLINERGIC</th><th>ANTICHOLINERGIC</th><th>ADRENERGIC</th></tr><tr><td>wet and slow: salivation, miosis, bronchorrhoea, bradycardia, cramps</td><td>dry, blind, fast: dry mouth, fixed dilated pupils, tachycardia, retention</td><td>fast and tight: tachycardia, high pressure, mydriasis, sweating</td></tr></table>			CHOLINERGIC	ANTICHOLINERGIC	ADRENERGIC	wet and slow: salivation, miosis, bronchorrhoea, bradycardia, cramps	dry, blind, fast: dry mouth, fixed dilated pupils, tachycardia, retention	fast and tight: tachycardia, high pressure, mydriasis, sweating
CHOLINERGIC	ANTICHOLINERGIC	ADRENERGIC						
wet and slow: salivation, miosis, bronchorrhoea, bradycardia, cramps	dry, blind, fast: dry mouth, fixed dilated pupils, tachycardia, retention	fast and tight: tachycardia, high pressure, mydriasis, sweating						

One map, five receptor rows – every autonomic drug is an arrow into it

The derivation (why toxidromes are the map upside down). Cholinergic excess = everything M stands for: salivation, lacrimation, miosis, bronchorrhoea, bradycardia, gut cramps and diarrhoea ✓. Anticholinergic = M blocked: dry mouth, dilated fixed pupils, tachycardia, urinary retention, hot dry skin ✓. Adrenergic excess = $\alpha + \beta$ on: tachycardia, hypertension, mydriasis, sweating. The syndrome is the arithmetic of the map.

Worked example 1 – predict four drugs. (Fictional INN teaching set) a $\beta 1$ blocker lowers heart rate and contractility (cardio-selective logic); an $\alpha 1$ blocker lowers blood pressure and can cause postural drop; a $\beta 2$ agonist opens airways with little cardiac effect; an M blocker dries secretions and blurs vision ✓ – four predictions straight off the table.

Worked example 2 – clinical link: two overdoses, two maps. (Fictional) patient A: pinpoint pupils, sweating, cramps and diarrhoea – cholinergic; patient B: dry, dilated, fast – anticholinergic ✓. Each finding is one receptor row; the collection names the class before any test returns.

Common mistakes. Expecting β -blockade to lower blood pressure instantly (output falls first; the full antihypertensive effect takes weeks of remodelling). Forgetting muscarinic versus nicotinic (M effects dominate toxidromes; N is ganglia and the NMJ). Treating sweating as an adrenergic sign only (sweat glands are sympathetic but cholinergic, at muscarinic receptors – the MED09 exception, which is why the anticholinergic patient is hot and dry).

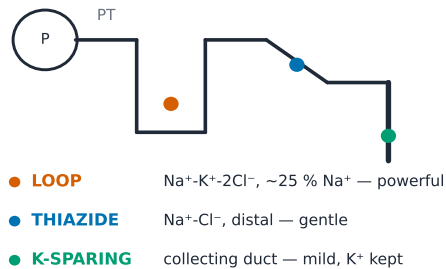
Summary. $\alpha 1$ constrict/dilate pupil · $\beta 1$ heart · $\beta 2$ airway · M3 secrete/constrict pupil/speed gut, M2 slow heart; agonist = push, blocker = silence; cholinergic = wet and slow; anticholinergic = dry, blind, fast; adrenergic = fast and tight; predictions come off the map, not memory.

Cardiovascular and renal drugs

Why it matters. Hypertension, heart failure and thrombosis are mechanism-rich: each drug class is a named pressure-regulating or clotting step turned down, and the nephron is the **diuretic** map.

The idea, with a picture. Antihypertensives by mechanism: diuretics (volume), **ACE inhibitors** ACE (block angiotensin II formation; the bradykinin cough), angiotensin receptor blockers, calcium-channel blockers (vasodilation), $\beta 1$ blockers (output and renin) ✓. Diuretics by nephron site: loop ($\text{Na}^+\text{-K}^+\text{-2Cl}^-$, thick ascending, ~25 % of Na^+), thiazide ($\text{Na}^+\text{-Cl}^-$, distal tubule), potassium-sparing (collecting duct) ✓.

three diuretic sites down the nephron — the fraction of Na^+ falls as you go



anticoagulants — mechanism sets the monitor

heparin: immediate, IV — aPTT

warfarin: blocks vitamin-K factor CARBOXYLATION — stored factors must decay first; INR, days to onset

direct oral anticoagulants: one factor (Xa or thrombin), predictable kinetics, mostly unmonitored

ACE inhibitor cough = bradykinin not degraded

Loop, thiazide and potassium-sparing act at three descending sites – the fraction reabsorbed shrinks as you go

The derivation (why anticoagulants monitor differently). Unfractionated heparin acts immediately and is monitored with the aPTT; **warfarin** blocks vitamin-K clotting-factor synthesis – existing factors must decay first, so onset lags days and the INR measures the effect, not the dose ✓; direct oral **anticoagulants** target one factor (Xa or thrombin) with predictable kinetics, mostly unmonitored. The monitoring test is a property of the mechanism.

Worked example 1 – site to electrolyte. (Fictional) loop diuretic at the thick ascending limb: powerful Na^+ loss, K^+ loss (downstream flow), and Ca^{2+} loss; a potassium-sparing agent at the collecting duct: mild, K^+ -retaining ✓. Each site's chemistry predicts its electrolyte fingerprint.

Worked example 2 – clinical link: the cough that isn't infection. (Fictional) on an ACE inhibitor, a dry persistent cough: bradykinin no longer degraded in that pathway ✓ – mechanism names the side effect, and the class switch (to an ARB) follows from the mechanism, not trial and error.

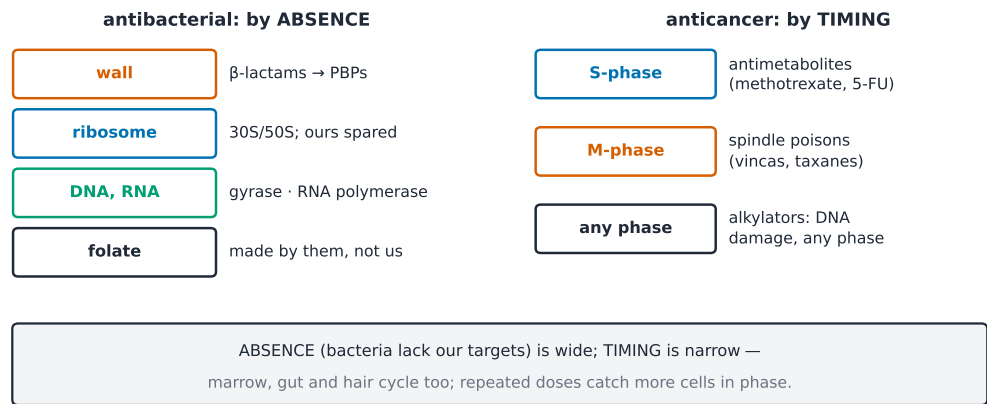
Common mistakes. Placing thiazides in the loop (they act distally – weaker, slower, Ca^{2+} -retaining). Expecting warfarin to act on factors already made (it blocks CARBOXYLATION of new ones). Confusing anticoagulants (clots) with antiplatelets (platelet plugs – different pipeline, different monitoring).

Summary. Volume/ACE/ARB/CCB/ $\beta 1$ = the antihypertensive mechanisms; loop 25 %, thiazide distal, K-sparing collecting duct; heparin→aPTT now; warfarin→INR after factor decay; DOACs one factor, predictable; mechanism names the side effect.

Antimicrobial and anticancer drugs

Why it matters. The two attack maps share one logic – **selective toxicity** against cells that differ from ours – and the plan defers to MED08 §6 for the antibacterial targets.

The idea, with a picture. Antibacterial targets (MED08): wall (β -lactams), ribosome, nucleic-acid enzymes, folate ✓. Anticancer: **cell-cycle-specific** agents hit cycling cells – S-phase (antimetabolites: methotrexate, fluorouracil), M-phase (vinca alkaloids, taxanes) – while alkylators damage DNA regardless of cycle ✓.



One target map across both fields: bacteria-specific targets left, cell-cycle phases right

The derivation (why selectivity differs between the fields). Antibacterial selectivity rides on structures human cells LACK (wall, different ribosome) – a wide margin. Anticancer selectivity rides on TIMING (cycling cells take the hit) – a narrow margin, because marrow, gut and hair cycle too ✓. The margin predicts the side-effect profile before any list is memorised.

Worked example 1 – the arithmetic of resistance (from MED08). β-lactamase cleaves the ring (enzyme); altered PBP2a is target reshaping; the 10⁻⁷–10⁻⁹ per-cell mutation supply explains why combinations outlast single agents ✓ – the pharmacology of failure is arithmetic.

Worked example 2 – clinical link: schedule is mechanism. (Fictional teaching schedule) an S-phase antimetabolite given as a short bolus misses cells not in S at that moment – the same total dose fractionated over time meets more cells in their vulnerable phase; an M-phase vinca depends on cells arriving at mitosis ✓. Cycle specificity dictates scheduling logic.

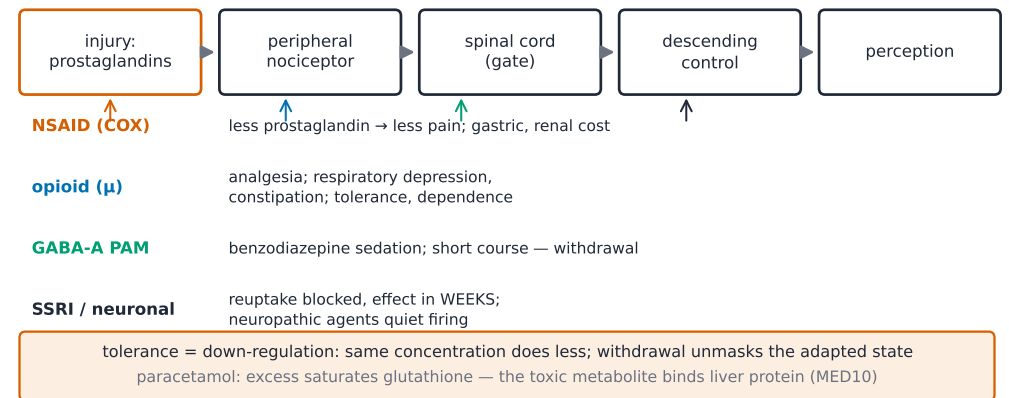
Common mistakes. Expecting anticancer “selectivity” to spare normal cycling tissue (marrow and mucosa cycle – the predictable toxicities). Treating resistance as a drug failure only (it is evolution in a dish: pressure selects). Calling antimetabolites non-specific (they are S-phase SPECIFIC).

Summary. Antibacterial: wall/ribosome/DNA/folate (MED08). Anticancer: S-phase antimetabolites, M-phase vinca/taxanes, alkylators cycle-independent; selectivity by ABSENCE (bacteria) vs TIMING (cancer); schedule follows the cycle.

CNS drugs and analgesia

Why it matters. CNS pharmacology is receptor physiology named: opioids, sedatives and antidepressants each sit at a known synapse – and **tolerance** and **dependence** are the learning the synapse does.

The idea, with a picture. Opioids act at μ receptors: analgesia with respiratory depression, constipation, miosis; tolerance and dependence develop ✓. NSAIDs block cyclo-oxygenase (COX-1 housekeeping/COX-2 inflammatory): less prostaglandin → less pain and inflammation, but gastric and renal cost ✓. Benzodiazepines are positive allosteric modulators at GABA-A; SSRIs block serotonin reuptake (weeks to full effect – receptor adaptation, not the synapse alone).



Peripheral COX, spinal modulation, descending opioid control – the pain pathway with its drug sites marked

The derivation (why tolerance is physiology, not weakness). Chronic receptor activation down-regulates and desensitises: the same concentration does less – larger doses restore effect (tolerance), and abrupt withdrawal unmasks the adapted state (dependence) ✓. This is why benzodiazepines are short-course and why opioids’ effective dose climbs; the WHO analgesic ladder (1986, revised 1996) is the classic framework naming pain severity to drug class.

Worked example 1 – three pains, three sites. (Fictional) prostaglandin-mediated inflammation – a NSAID at the peripheral COX site; severe post-operative pain – an opioid at μ receptors (with the respiratory price); neuropathic burning – neither class alone; agents acting on neuronal excitability ✓ – matching the site to the drug, not the severity alone.

Worked example 2 – clinical link: the paracetamol lesson. (Fictional teaching case) an overdose of paracetamol saturates the safe conjugation pathways and uses up glutathione, so the toxic metabolite (NAPQI) binds liver proteins – the MED10 necrosis rulebook applies ✓. Mechanism names both the antidote logic (acetylcysteine restores glutathione) and the organ at risk.

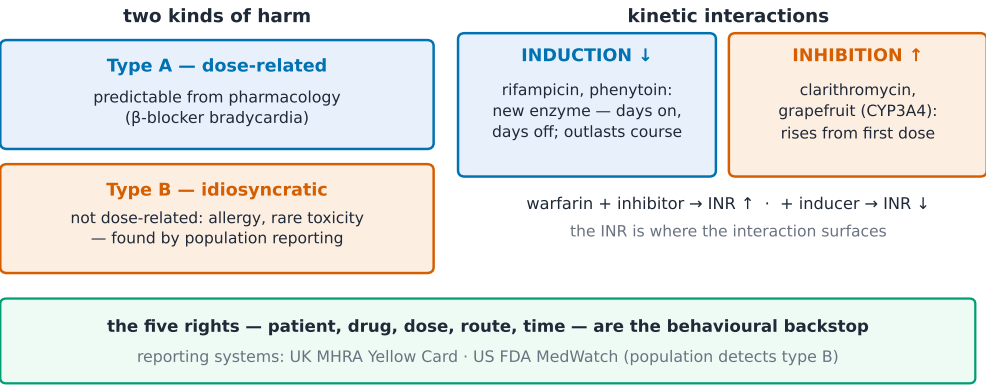
Common mistakes. Equating analgesic classes by strength (they act at different SITES – combinations are additive by mechanism). Expecting SSRIs to work in days (reuptake blockade is immediate; clinical effect needs weeks of adaptation). Forgetting constipation is the opioid effect that barely tolerises.

Summary. Opioid μ : analgesia + respiratory depression + constipation, tolerance/dependence; NSAID COX-1/2: periphery, gastric/renal cost; benzodiazepine GABA-A PAM; SSRI reuptake, weeks; tolerance = down-regulation; paracetamol = glutathione and liver.

Adverse reactions, interactions and safe-medication principles

Why it matters. Every drug chart is an experiment with **adverse drug reactions**, interactions and human error – the last unit is where the course’s mechanisms become safety habits.

The idea, with a picture. Type A reactions: DOSE-RELATED, predictable from pharmacology (β -blocker bradycardia); type B: idiosyncratic, not dose-related (allergy, rare toxicity) ✓. Interactions: **enzyme induction** (rifampicin, phenytoin → a co-medication’s levels fall) versus **enzyme inhibition** (clarithromycin, grapefruit at CYP3A4 → levels rise) ✓.



Induction lowers exposure, inhibition raises it – and the ADR types split by dose-relatedness

The derivation (why induction and inhibition move levels for days). Induction builds new enzyme – days to build, days to unwind; inhibition occupies existing

enzyme – begins with the first co-dose ✓. So a new inhibitor raises a substrate’s level within doses (warfarin effect climbs with it), while an inducer’s effect arrives late and outlasts its stop date. Timing is the mechanism made visible.

Worked example 1 – one interaction, three questions. (Fictional) warfarin + a new CYP inhibitor: INR rises (more warfarin effect); warfarin + rifampicin: INR falls (induction clears it); either change is detectable by the INR’s rhythm, which is why monitoring interval follows interaction risk ✓.

Worked example 2 – clinical link: the five rights and the report. (Fictional ward) a near-miss caught at the bedside: the five rights – right patient, drug, dose, route, time – are the behavioural backstop for every mechanism above; national reporting systems (the UK MHRA Yellow Card scheme; the US FDA MedWatch) exist because type B reactions are found only by population reporting ✓ – dated jurisdiction-bound statements, as the plan requires.

Common mistakes. Blaming type B reactions on dose (they are idiosyncratic – dose neither predicts nor prevents them). Forgetting the inducer’s tail (its effect on enzyme outlasts the course). Treating interactions as pharmacological trivia – most are kinetic, and the INR/aPTT/level is where they surface.

Summary. Type A = dose-related, type B = idiosyncratic; induction → levels fall (slow on, slow off), inhibition → levels rise (fast on); five rights as the behavioural backstop; Yellow Card (UK) / MedWatch (US) for population detection of type B.