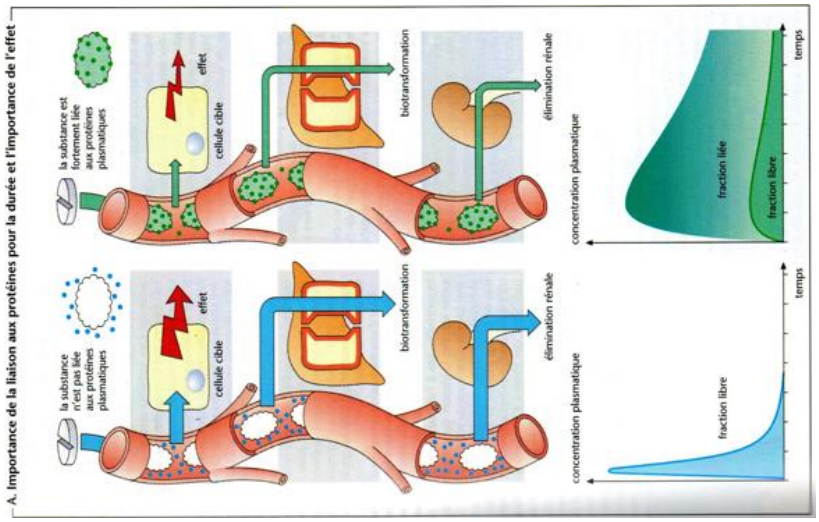
Pharmacokinetics (PK): Distribution

1. Distribution: The Transportation Network

Once in the blood, the drug doesn't just stay there; it should pass to tissues.

- Protein Binding: Many drugs bind to Albumin.
    - *Bound drug* = Inactive (cannot leave the blood).
    - *Free drug* = Active (can cross into tissues).



Drug	% Bound to Plasma Proteins	Biological Nature	Clinical Impact
Warfarin (Anticoagulant)	**99%**	Weak Acid	Highly sensitive to displacement.
Ibuprofen (NSAID)	**98%**	Weak Acid	Stays in the blood for a long time.
Diazepam (Anxiolytic)	**98%**	Weak Base/Neutral	High lipid solubility + high binding.
Phenytoin (Anti-epileptic)	**90%**	Weak Acid	Narrow therapeutic window.
Theophylline (Asthma)	**40%**	Weak Base	Moderate distribution.
Digoxin (Heart failure)	**25%**	Neutral	Low binding, high tissue distribution.
Gentamicin (Antibiotic)	**<10%**	Weak Base	Highly hydrophilic; moves very fast.
Metformin (Diabetes)	**0%**	Weak Base	Not bound; travels entirely free.

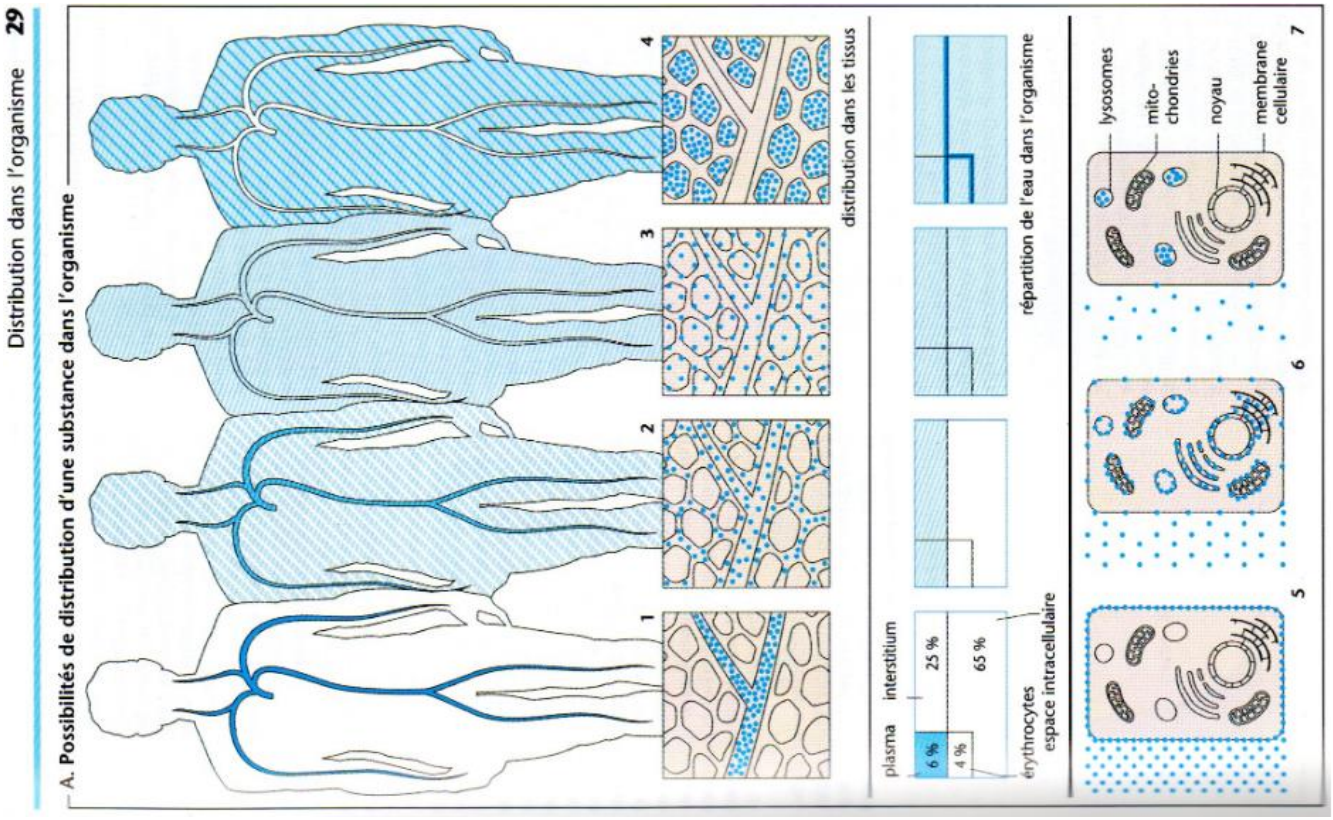
- **Volume of Distribution (Vd):** A theoretical volume that describes how much drug has left the blood to enter the tissues.

Vd = Total amount of drug in body/Plasma drug concentration

The Apparent Volume of Distribution (Vd) is one of the most confusing concepts because it isn't a "real" physiological volume. It is a proportionality constant that relates the amount of drug in the body to the concentration we measure in the blood.

In simple terms: Vd tells you if the drug is "staying in the blood" or "hiding in the tissues."

Drug	Vd (Approx. L/70kg)	Where is the drug "hiding"?	Why?
Heparin	**4 L**	**Plasma only**	Very large molecule; cannot leak out of vessels.
Warfarin	**10 L**	**Plasma / Albumin**	Highly bound to plasma proteins (the "taxi").
Aspirin	**11 L**	**Extracellular fluid**	Small but polar; leaves blood but stays near it.
Theophylline	**35 L**	**Total Body Water**	Distributed evenly throughout all body fluids.
Ethanol	**42 L**	**Total Body Water**	Small, neutral, and mixes perfectly with water.
Digoxin	**500 L**	**Tissue binding (Heart/Muscle)**	Loves binding to Na+/K+ pumps in muscle cells.
Chloroquine	**15,000 L**	**Deep Tissue (Fat/Organs)**	Extremely lipophilic; hides in lysosomes/fat.



2. Application Example: Determining the Fate of "Drug Z"

The Scenario:

A researcher administers a single intravenous (IV) bolus dose of 350 mg of an experimental antibiotic (Drug Z) to a healthy volunteer weighing 70 kg. After the drug has finished distributing (but before significant elimination has occurred), a blood sample is taken. The initial plasma concentration (C_0) is measured at 10 mg/L.

Biological Interpretation

Calculated Vd	Biological Interpretation	Membrane Status
3-4 L	Trapped in blood.	Cannot cross endothelium.
14L	In "the juice" between cells.	Crosses capillaries, but not cell membranes.
35L	Inside the cells.	Crosses cell membranes easily.
42L	Perfectly uniform distribution.	Treats the whole body like one big bucket of water.
100L	Sequestration/Accumulation.	"Addicted" to tissue binding (fat/proteins).

A Quick "Think-Pair-Share"

If Drug Z has a Vd of 35L, and we find out it's very effective at treating a cytoplasmic parasite (like malaria in its early stage), does this Vd make sense?

3. The distribution of biologics: Why Vd is Small

For biologics (especially Monoclonal Antibodies or mAbs), the **Volume of Distribution (Vd)** is consistently tiny.

- **The Numbers:** While a small molecule can have a Vd of **500 L**, a biologic typically has a Vd of only **3-8 L**.
- **The Biology:** Because they are so large (e.g., IgG is150 kDa), they are physically restricted to the plasma and the fluid immediately surrounding the cells (interstitial fluid). They simply cannot "diffuse" through a cell membrane to reach the intracellular space (35-42 L).

3.1. Mechanism: Convection, Not Diffusion

While small molecule drugs move (mainly) via **diffusion** (gradient-driven). Biologics are too big for that. Instead, they move via **convection**:

- They are carried along by the "bulk flow" of fluid as it leaks out of the capillaries and is sucked back up by the lymph.
- It’s like a leaf being carried by a river rather than a scent spreading through a room.

3.2. The "Target-Mediated Drug Disposition" (TMDD)

Because biologics are engineered to be highly specific, they often "stick" to their targets with extreme affinity.

- **The Trap:** If a patient has a lot of the target receptor (e.g., a massive tumor with thousands of receptors), the biologic will bind to those receptors and stay there.
- **The Distribution Paradox:** This means the distribution isn't just about fluid; it's about where the "magnets" (targets) are located. If the target is in the liver, the biologic will concentrate there, not because it's lipophilic, but because it's "locked" onto its target.