common reactions are oxidation, reduction & hydrolysis. Requires cytochrome P450 system (CYP450) of which isoform CYP3A4 carries out ~55% (different isoforms metabolise different drugs) and NADPH co-factor. Variability is affected by race, age, sex, species & physiological condition. Occurs in liver, less commonly in plasma, GI tract, kidney and lung, however some drugs can skip phase 1 of metabolism

- **CYP450 Pharmacogenetics** – Variation in CYP450 expression accounts for a great deal of inter-patient variability in drug response; constant throughout life
  - **Phase 2** – Phase 1 intermediates conjugated with polar molecule to form water soluble complex. Common conjugates are glucaronic acid (glucuronidation), sulphate ions (sulphation) and glutathione. Occurs in liver requiring specific cytosolic enzymes and UDPGA co-factor

- **Excretion** – Main route is the kidney, thus elimination is determined by glomerular filtration (only free fraction of drug is filtered), passive tubular reabsorption (dependant on pH) & active tubular secretion (occurs via organic anion/cation transporters)
  - **Weak Acid Drug** – Acid urine increases absorption, alkaline urine decreases absorption
  - **Weak Base Drug** – Acid urine decreases absorption, alkaline urine increases absorption

**Elimination Curves** – Slope of the elimination curve is the elimination rate constant (k), which is a ratio of clearance (c) to volume of distribution (Vd). T½ is proportional to volume of distribution or inversely proportional to clearance (GFR)

\[
T\frac{1}{2} = \frac{0.693 \times Vd}{\text{Clearance}}
\]

- **1st Order Kinetics** – Occurs in most drugs, rate of elimination is proportional to drug level as a constant fraction of drug is eliminated in unit time (half-life can be defined). Curved line on a linear scale, straight line on a log scale, dose increases give predictable therapeutic response
- **Zero Order Kinetics** – Rate of elimination is constant. Straight line on a linear scale, the therapeutic response can suddenly escalate, even with small dose changes, as elimination mechanisms saturated (e.g. alcohol); as a result are more likely to result in toxicity

**Loading Doses** – During repeated drug administration a new steady state is achieved in 5 half-lives, irrespective of dose, frequency or method of administration. If the half-life is long & a rapid effect is desired a loading dose can be given which quickly pushes concentration into steady state range.

Loading dose is not dependent on age or renal function (unless very severe), however maintenance doses need reducing in renal failure & as reduced clearance

\[
\text{Vd (volume of distribution)} = \frac{\text{Dose (amount of drug given)}}{\text{[Drug]}_{10} \text{ in plasma}}
\]

\[
\text{[Drug]}_{10} = \frac{\text{Amount of Drug/Volume of Compartment Entered (mg/L e.g.)}}{\text{Loading Dose (mg) = Vd x [Drug]_{target} or CpSS}}
\]

\[
\text{Steady State Concentration in Plasma (CpSS)} = \frac{\text{Dose Rate (mg/hr)}}{\text{Clearance (ml/hr)}}
\]

**Pharmacodynamic Process**

Pharmacodynamics describes what the drug does to the body, essentially how drugs work. Most work by interacting with endogenous proteins as agonists or antagonists, where some have unconventional means of action.

- Drugs may work at cell surface receptors, nuclear receptors, enzyme inhibitors, ion channel blockers, transport inhibitors or inhibitors of signal transduction proteins. Unconventional mechanisms of action include disrupting structural proteins, being enzymes, covalently linking to macromolecules, reacting chemically with small molecules and binding free molecules or atoms.

**Dose Response Curve** – Michaelis-Menten curves show that drug response is proportional to drug concentration

**Therapeutic Window** – Range between the lowest dose that can have a positive effect and highest dose before negative effects outweigh positive effects; examples of drugs with low therapeutic windows include warfarin, digoxin & aminoglycosides

- **MTC** – Minimum toxic concentration