Pharmacokinetics and Pharmacodynamics 101

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Disclosures

No financial disclosures to report

The views and opinions are solely my own

Background and Career

Education

- BS Biology, BS Laboratory Science
- Ph.D. Pharmaceutical Sciences (Pharmacokinetics)

Career

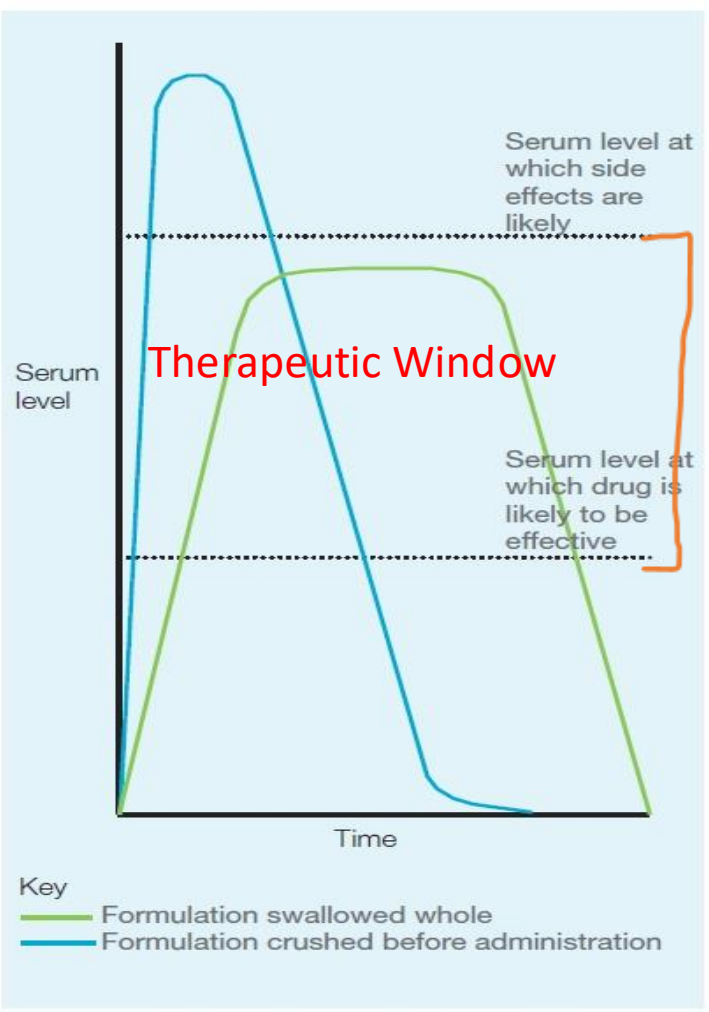
- Pharmacokinetic Reviewer, Division of Biopharmaceutics, CDER, Food and Drug Administration
- Mid 90's departed FDA, transitioned to Regulatory Affairs, Made several stops along the way small, medium, big-pharma and start-up companies
- Big Pharma Novartis 14 years
- Retired after 35+ years in Pharma

Agenda

- Pharmacokinetics
  - Concept
  - Key PK parameters
- PK Studies and Objectives Conducted for a New Oral Drug
- In vitro dissolution
- Pharmacodynamics

What is the importance of the drug concentration?

- Drug that is absorbed into the body must reach a concentration that delivers the desired drug effect
  - If concentration too high, super effective but unacceptable toxicity
  - If concentration too low, ineffective
  - If within the "therapeutic window", drug is effective with acceptable safety



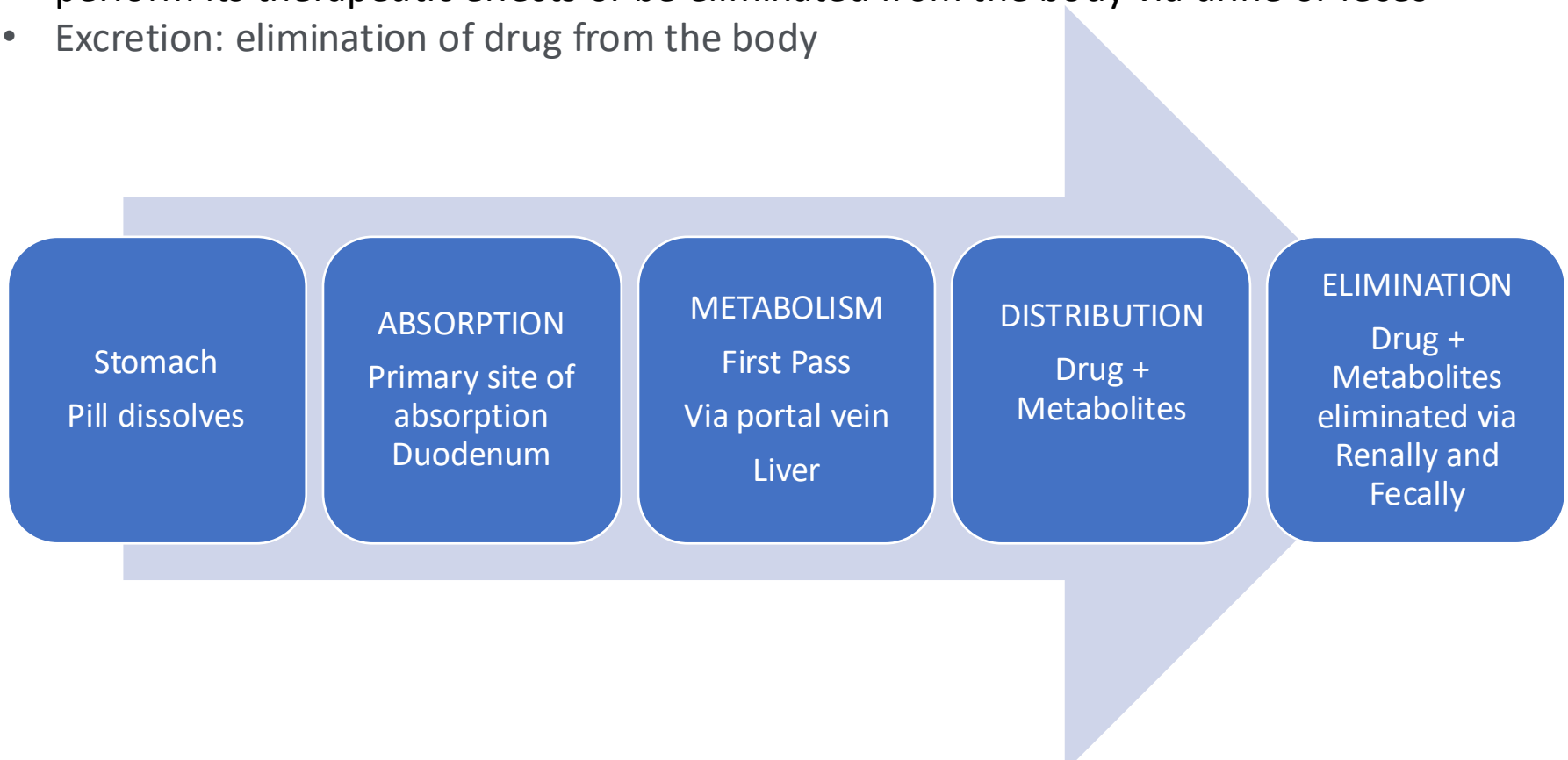
Theoretical release of active from a modified release formulation which is swallowed whole and crushed

Pharmacokinetic

- Every medication has 2 stories, what it is designed to do and what the body does to it. PK is the science of that second story
- Kinetic - rate of change over time (d/dT)
- Drug concentration determined by rates of drug formulation, drug dissolution, absorption, and elimination
- Pharmacokinetics branch of pharmacology that evaluates the rate of absorption, distribution, metabolism, and excretion (ADME) of drug over time by conducting Phase 1 studies
- Phase 2 dose ranging study in patients conducted with low, medium, and high doses to determine the therapeutic window of the drug

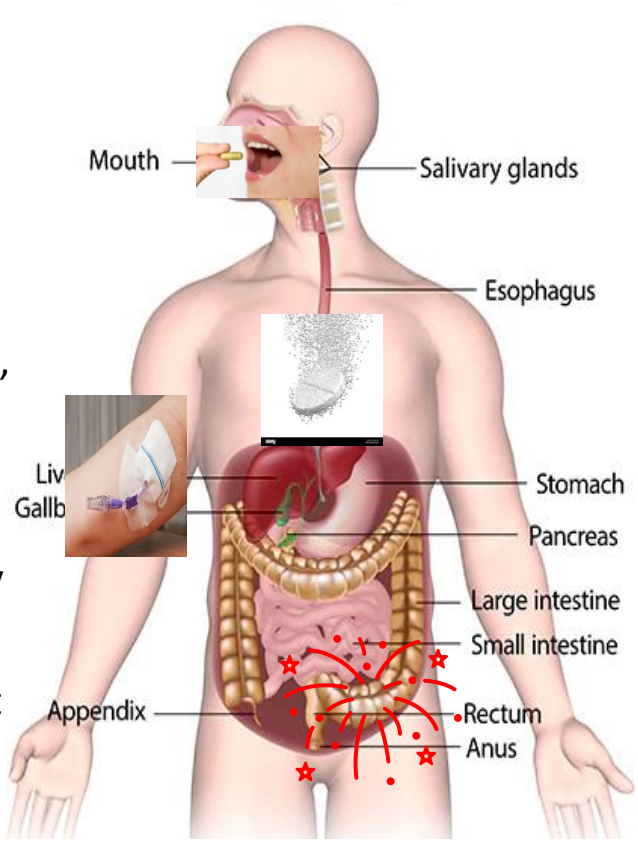
Fate of Drug After being Swallowed

- Absorption: drug absorbed after administration (stomach/intestine)
- Distribution: distribution of drug throughout the body
- Metabolism: biochemical process which chemically alters the drug so it can either perform its therapeutic effects or be eliminated from the body via urine or feces
- Excretion: elimination of drug from the body

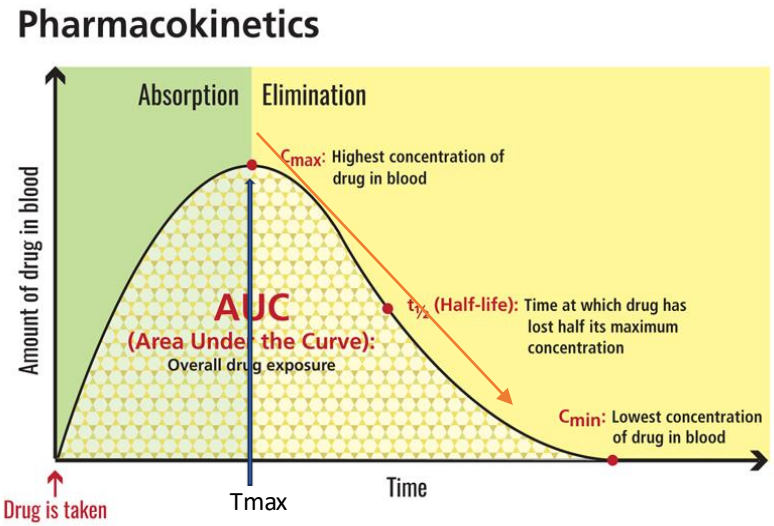


How is PK of a drug determined?

- Phase 1 Single Dose PK Drug Study
- Study objective
  - To determine the PK of a drug
- Study procedure
  1. Recruit, Screen, Informed Consent
  2. Study subjects: HV (N=24)
  3. After overnight fast, swallow pill (time 0)
  4. Withdraw serial blood samples at 0, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, and 24 hours
  5. Analyze serum by validated analytical technique used to separate, identify, and quantify components in a mixture eg High-Performance Liquid Chromatography
  6. Determine drug concentrations (ug/mL)
  7. Plot drug concentrations (ug/mL) against Time (Hr) at the time each samples were withdrawn



Conc vs Time Curve
PK Parameters Derived



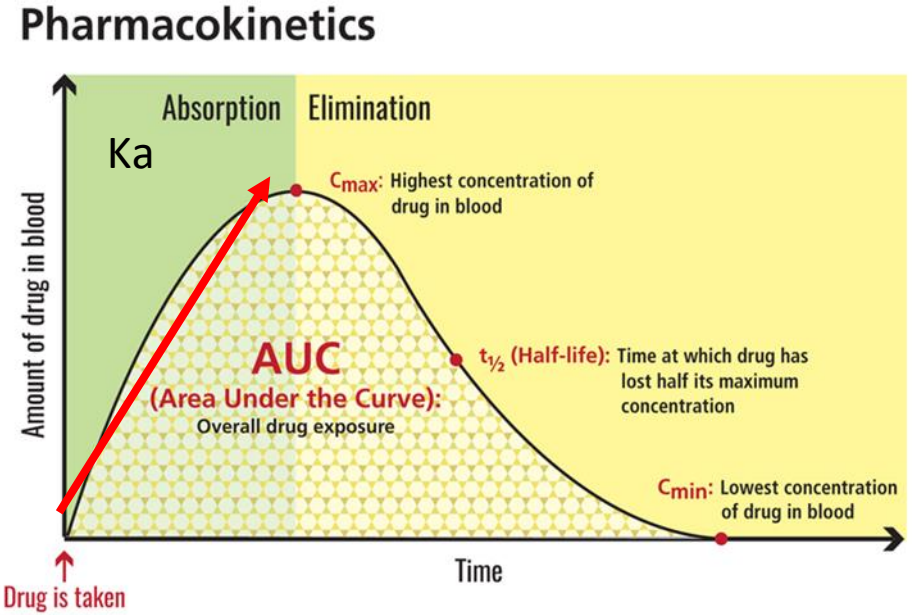
X axis = Time (h)
Y axis = Plasma Drug Concentration

- Area Under the Curve (AUC)
  - Unit: ug*h/L
  - Represents total drug exposure across time.
- Maximum Concentration (Cmax)
  - Unit: ug/mL
- Tmax
  - Unit: Hr
  - Time of maximum drug concentration

- Elimination rate (Ke)
  - Unit: ug/hr
  - Rate of drug elimination from body
- Elimination half-life ($T_{1/2}$)
  - Unit: Time
  - Time drug concentration decreases from 50% of Cmax
- Minimum Concentration (Cmin)
  - Unit: ug/mL
  - Lowest concentration of drug

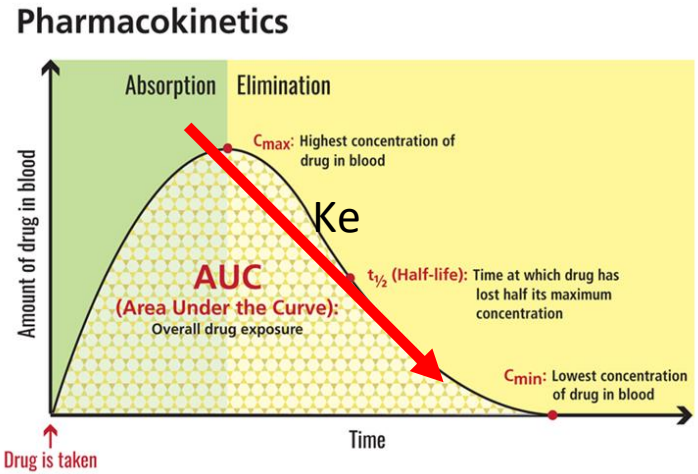
Drug Absorption

- Drug dissolves in stomach (pH 2)
- Dumped into duodenum which has extensive surface area for absorption
- Absorption rate = rate at which a drug enters the system
- Factors that affect absorption include dissolution, solubility, and permeability of the drug and gastric emptying (when the stomach dumps its contents into the duodenum)



Drug Elimination: Two Routes of Drug Elimination

- Hepatic Metabolism
  - Type of drug: Lipid soluble
  - Hepatic cytochrome P-450 metabolic enzymes eg CYP3A4, CYP2D6
  - Metabolites dumped into bile and eliminated fecally
  - First pass determines extent of metabolism of parent to metabolites
    - X% parent drug (active drug); X% metabolites (inactive drug)
    - Pro-Drugs are 100% metabolized to active drug
    - Significance is Potential for Drug-Drug Interaction of Comeds
      - Induce liver enzymes (decreases half-life)
      - inhibit liver enzymes (increases half-life)
- Renal Elimination
  - Type of drug: Water soluble
  - Eliminated via kidneys



Pharmacokinetic Parameters

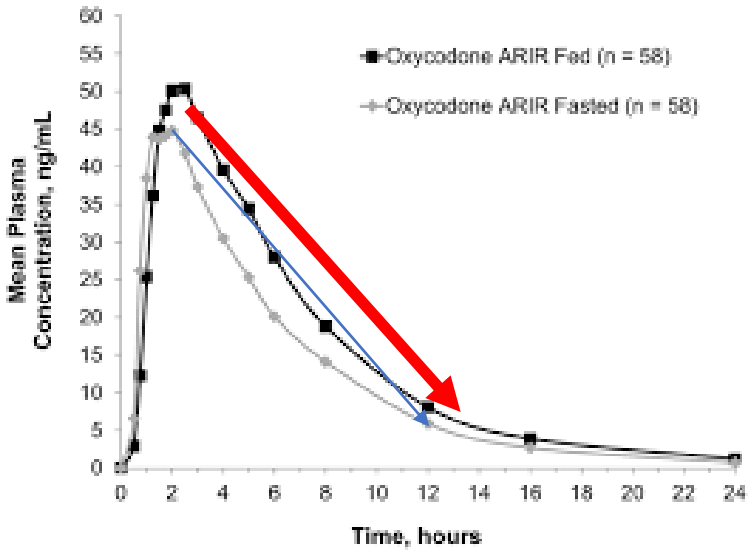
- AUC, Cmax, Cmin
- Half-life
- Steady-state
- Volume of distribution
- Clearance

Half-life ($T_{1/2}$)

- Determined from slope of line post Cmax
- Different drugs have different half-lives; however, they all follow this rule: after one half-life has passed, 50% of the initial drug amount is removed from the body

- $T_{1/2} = 0.693/K$
  - Ke = elimination rate

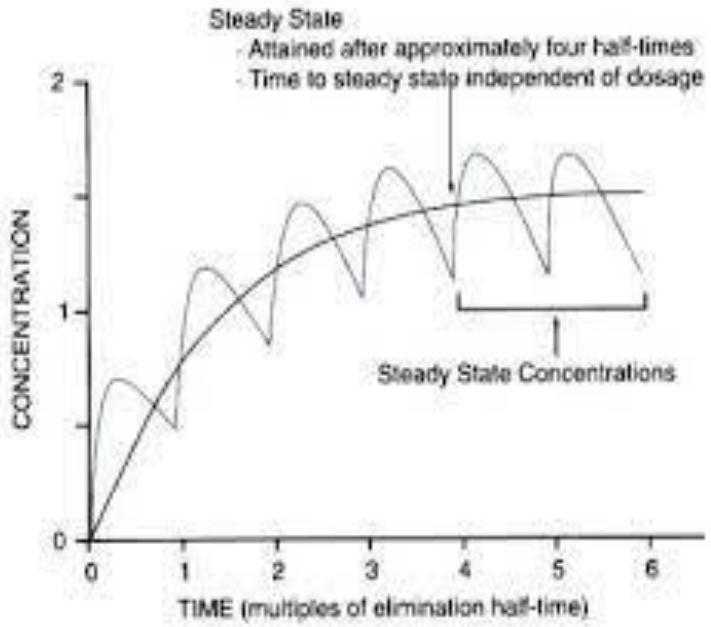
- $T½ = 0.693 \times Vd / CL$
  - Vd = volume of distribution
  - Cl = drug clearance



Time (h)	Conc (mg/L)
0	160
8	80
16	40
24	20
32	10
40	5
48	2.5
56	1.25
64	0.625

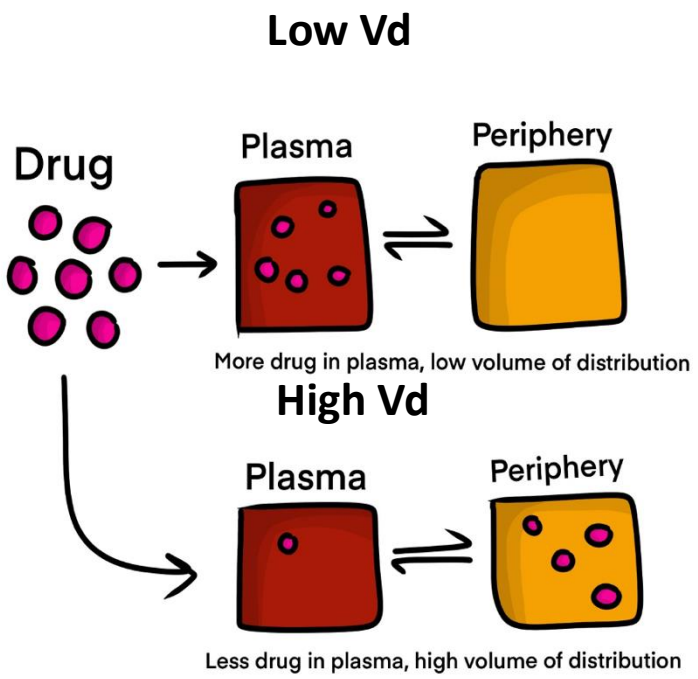
Steady-State

- Steady-state
  - Depends on $T_{1/2}$ of the drug
  - Reached after 5 half-lives of dosing when Rate of absorption = Rate of elimination
- Total elimination of drug from body
  - Reached 5 half-lives
- Example
  - Drug X
    - 6-hour half-life
    - Steady state reached with every 6 hr dosing x $T_{1/2}$ = 30 hrs
    - After drug administration is stopped, drug is totally eliminated 30 hrs after stopping the drug



Volume of Distribution (Vd)

- Represents drug's propensity to remain in
  - plasma (1st compartment) or
  - distribute to other tissue compartments (2nd compartment)
- Characteristic of Drugs with a low Vol of distribution
  - more hydrophilic remains in blood (1st compartment)
  - renally eliminated
  - short T½
- Characteristic of Drugs with a high Vol of distribution
  - more lipophilic able to diffuse more into surrounding tissues (2nd compartment)
  - can only be eliminated when in blood so drug can be slow to diffuse out of tissues and back into blood
  - Hepatically metabolized
  - Longer to elimination
  - longer T½



Clearance (Cl)

- Defined as the volume of body fluid eg blood, containing the drug from which the drug is removed in a specific period of time

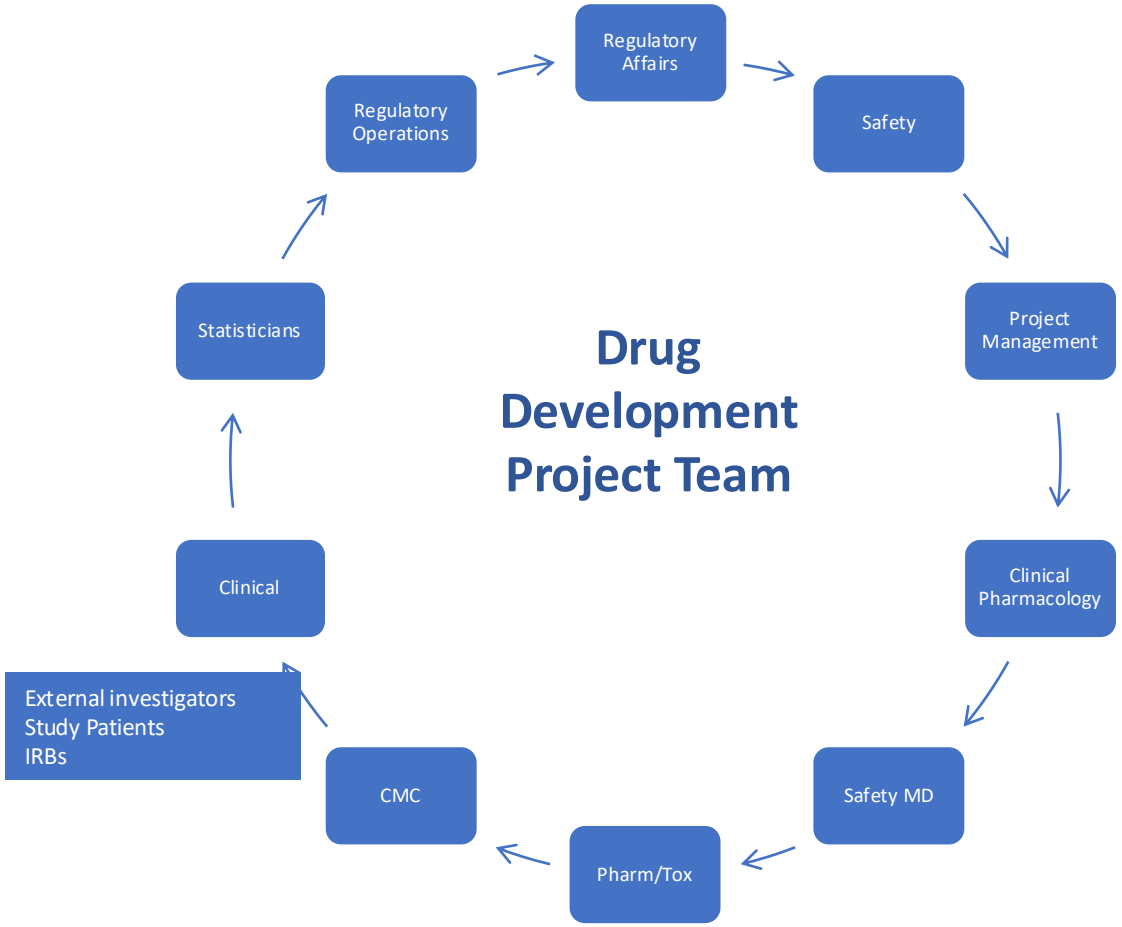
- Clearance (Cl) = $\frac{\text{Elimination Rate (Ke)}}{\text{Plasma drug concentration (C)}}$

- Total body clearance = sum of individual clearance by all eliminating organs, renal, liver, lung

- Cl_T -= $Cl_r + Cl_h + Cl_L$

Types of Phase 1 PK Studies and Objectives Conducted for a New Oral Drug

Sponsor's Drug Development Project Team



- Clinical Pharmacology
- Chemist/Manufacturing
- Statisticians/Data programmers
- Project managers
- Clinical (MDs)/Clinical Operations
- Toxicologists/Pharmacologists
- Regulatory Affairs + Reg Ops
  - Liaise with FDA
  - Prepare submissions
  - Leads teams in preparation of Briefing Books
  - Leads team in preparing for meetings with FDA

Healthy volunteers and patients are most crucial participants to clinical development

- Phase 1 Healthy volunteers
- Phase 2 Patient population
- Phase 3 Patient population

Clinical Study Protocol

Study Protocol **pre-specifies** (*a priori*) rationale, trial design, statistical analysis, inclusion and exclusion criteria, indicates the control (placebo and/or active control), **statistical methods and outcome required for declaring a positive study outcome**

Intended for trial investigators and staff to follow in conducting the study in terms of inclusion/exclusion, study assessments and timing

Required for all studies including Pre-Clinical, Phase 1, 2, 3 and 4 clinical trials

Submitted by sponsor to FDA prior to study initiation (means sponsor is locked into the study design and pre-specified outcome)

Types of Phase 1 PK Studies

1. Single ascending dose study in HV (Typically the first PK study conducted after the IND is opened)
   - Objectives
     - To determine maximum tolerated dose (MTD)
     - To determine PK parameters in humans
     - Dose proportionality (linear) and safety
   - Design
     - N=6 subjects (4 active + 2 placebo)
     - After overnight fast, First dose is lowest safe dose then increase doses to the MTD
2. Multiple dose study
   - Objective
     - To determine dose linearity, optimum frequency of dosing based on $T_{1/2}$ and safety
   - Design
     - N=12 (10 active + 2 placebo)
     - After overnight fast start dosing BID for 7 days
     - Blood samples on Day 1 at 0-24 hrs, Days 2-6 at Cmin, Day 7 at 0-24 hrs
3. Food effect study
   - Objective: To determine if dosing with high fat food affects drug absorption and safety
   - Design
     - Two-way cross over study
     - N=12 (10 active + 2 placebo), after overnight fast, randomize to fast or high fast meal
     - Blood samples on Day 1 at 0-24 hrs

Types of Phase 1 PK Studies (cont)

4. Absolute Bioavailability study
   - Objective: To determine percent of drug absorbed from oral dosage form compared to drug administered in solution
   - Design
     4. N=12 (10 active + 2 placebo)
     5. Single-dose, Two-way cross-over study
     6. After overnight fast start dose Group 1 oral and Group 2 IV/oral solution
     7. Blood samples on Day 1 at 0-24 hrs
5. Hepatic impaired study
   - Objective: To determine hepatic impairment effect on drug PK and safety
   - Design
     4. Normal (N=6), Mild (N=6), Moderate (N=6) and Severe (N=3)
     5. Single-dose
     6. Blood samples on Day 1 at 0-24 hrs
6. Hepatic Enzyme *In Vitro* study
   - Test drug against panel of hepatic enzymes in vitro
   - Objective: To identify primary hepatic enzyme involved in the metabolism of the drug

Types of Phase 1 PK Studies (cont)

7. Renal impaired study
    - Objective: To determine renal impairment effect on drug PK and safety
    - Design
        - Single-dose
        - Stage 2: Mild reduction in GFR (60-89 mL/min/1.73 m 2)
        - Stage 3: Moderate reduction in GFR (30-59 mL/min/1.73 m 2)
        - Stage 4: Severe reduction in GFR (15-29 mL/min/1.73 m 2)
    - Blood samples on Day 1 at 0-24 hrs

8. Population PK modelling
    - Objective: used to investigate sources of variability in patient exposure and factors ie covariates, that may impact drug clearance
    - Design: All Pk data collected from all sources used for modelling (Mix Effect Model)
    - Covariates: Subject characteristics Gender, Age, disease severity, impairments,

Pharmacometrics Syst Pharmacol. 2013 Apr; 2(4): e38.
Basic Concepts in Population Modeling, Simulation, and Model-Based Drug Development—Part 2: Introduction to Pharmacokinetic Modeling Methods
D R Mould1,* and R N Upton1,2

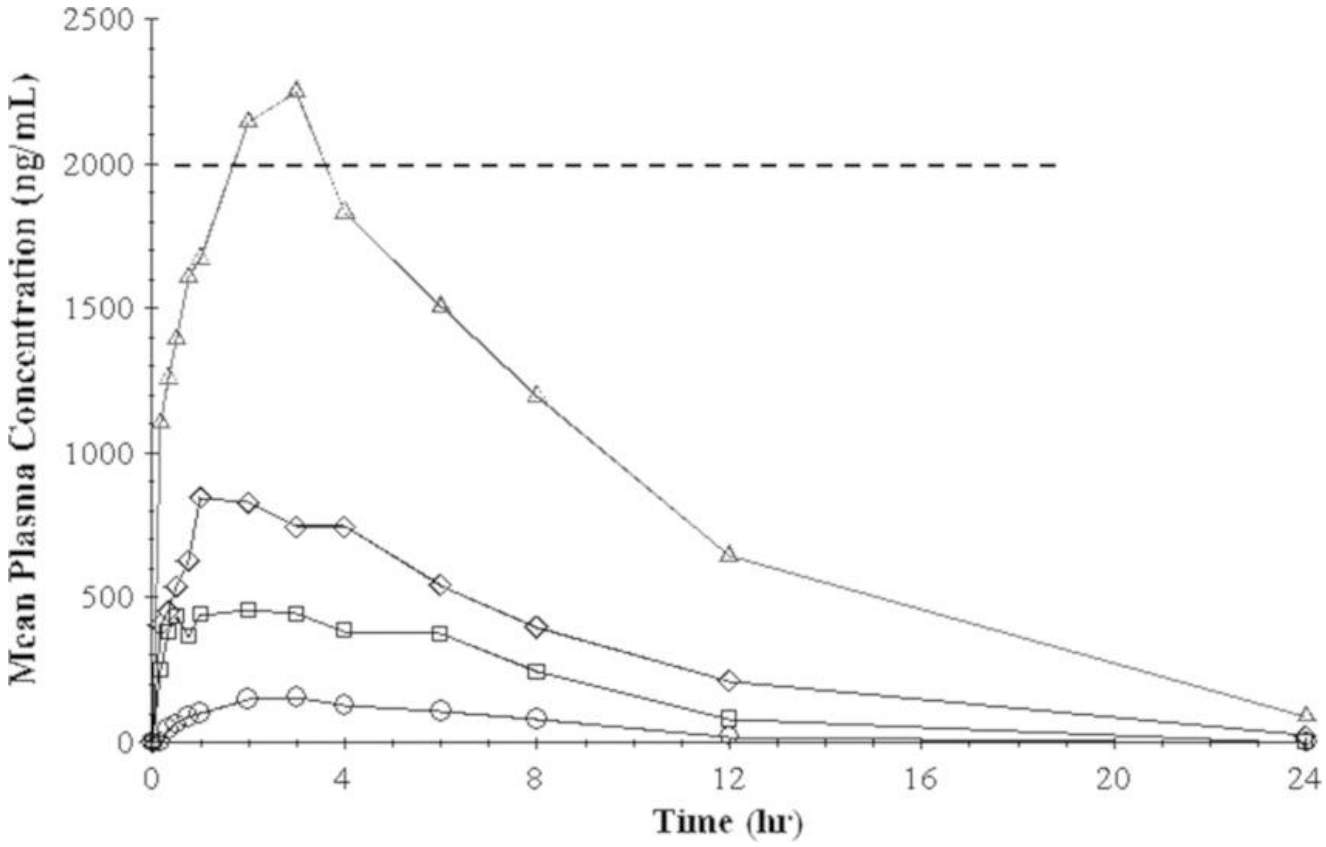
Phase 1 Single Ascending Dose PK Study

- IND submitted to FDA, 30-day review period, if FDA determines safety and CMC of the new drug is safe to proceed, then the first study to be conducted is Phase 1 Single Ascending Dose PK Drug Study
- Study objective
  - To establish safety, tolerability, and basic processing in the body.
- Study procedure
  1. A clinical site is contracted to conduct the study and is responsible to Recruit, Screen, and Informed Consent healthy volunteers
  2. Sequential groups (cohorts) of healthy volunteers given a single dose of an investigational drug + placebo, dose escalation, If no severe side effects are observed, subsequent groups receive progressively higher
  3. Withdraw serial blood samples at 0, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, and 24 hours
  4. Analyze serum by validated analytical technique
  5. Determine drug concentrations (ug/mL) and safety
  6. Plot drug concentrations (ug/mL) against Time (Hr) at the time each samples were withdrawn
  7. Evaluate PK and safety

Time versus Plasma Drug Concentration Curve

X axis = Time (h)

Y axis = Plasma Drug Concentration



5 mg
10 mg
20 mg
50 mg

Pharmacokineticists determines PK results

Table 1. PK parameters of 5, 10, and 20 mg and 50 mg dose

	Cmax +/- SD (ug/mL)	Tmax +/- SD (Hr)	AUC +/- SD mg*h/L	$T_{1/2}$ (Hr)	Safety
Placebo (N=2)	0	0	0	0	No Adverse Events
5 mg (N=4)	20 +/- 5	2	120 +/- 50	6	No Adverse Events
Placebo (N=2)	0	0	0	0	No Adverse Events
10 mg (N=4)	40 +/- 5	2	240 +/- 50	6	NAE
Placebo (N=2)	0	0	0	0	No Adverse Events
20 mg (N=4)	80 +/- 5	2	480 +/- 55	6	Headache
Placebo (N=2)	0	0	0	0	No Adverse Events
50 mg (N=4)	160 +/- 5	2	900 +/- 55	6	Headache, nausea and vomiting (4 out of 4)

Can determined from PK parameters that the drug is rapidly absorbed, dose proportional, eliminated by first-order kinetics and 50 mg appears to be the MTD

Drug-Drug Interaction (DDI) PK Studies

- Objective: To determine if PK of Drug A is impacted if administered with Drug B
- Source of DDI
  - induce metabolism
  - inhibit metabolism/renal excretion
- Two-arm, single-dose cross-over studies
  - Arm one: Drug A
  - Arm two: Drug A administered with Drug B
  - N=12 HV
- Serial blood samples withdrawn at 0, 0.5, 1, 2, 4, 8, 16, and 24 hours
- Analyze blood and plot
- Statistical analysis is 90% CI 80-125%
  - If outside CI, then dose adjustment may be warranted or contraindicated

Why is DDI Study Critical?

- Case Study (1990)
  - Young healthy female administered ketoconazole for toenail fungus by dermatologist and administered Seldane (terfenadine) by Allergist for Seasonal Allergic Reaction
  - After 3 days of dosing with both terfenadine and ketoconazole, patient died suddenly
  - Investigation determined
    - Terfenadine parent drug metabolized by CYP3A4 to active, carboxylated metabolite (fexofenadine)
    - CYP3A4 enzyme inhibited by ketoconazole
    - Terfenadine cardiotoxic
    - With 3 days of being administered with ketoconazole, metabolism inhibited, terfenadine concentration exceeded toxic concentration leading to sudden death by QTc prolongation
    - Significant and deadly drug-drug interaction

- This case was the impetus for
  - ICH M12 Drug Interaction Studies guidance
  - ICH E-14 ICH E14 Clinical evaluation of QT/QTc interval prolongation evaluation study guidance

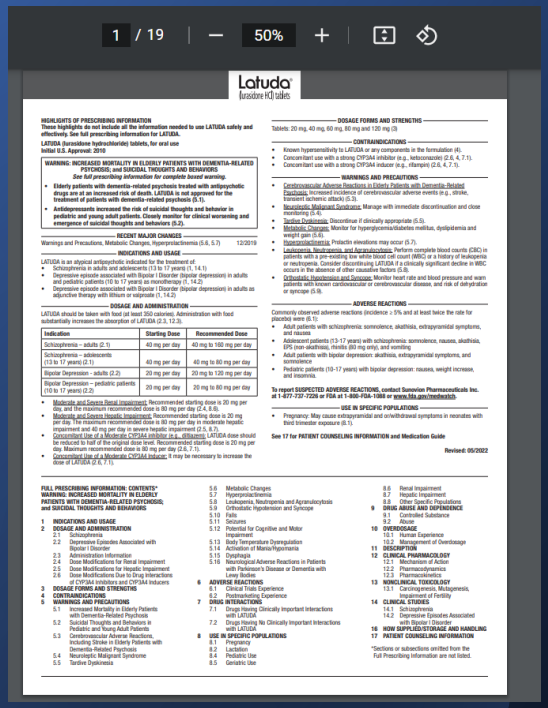
New Drug Application

- When all drug development activities are completed, analyzed, and study reports written, then Sponsor submits and NDA which contains ALL data and analysis conducted with investigational product
  - Patient level data
  - Phase 1, 2, and 3 clinical study reports
  - Drug substance and drug product CMC reports
  - Toxicology data and study reports
- Submitted electronically
- Approx 12-month standard review
- During review period, FDA Reviewers ask questions, request reanalysis, or ask for additional data
- At end of review period, focus turns to finalizing the Package Insert

FDA NDA Review Team

- Clinical Pharmacology / PK Reviewers
- Toxicology Reviewers

- Project Managers
- Medical Reviewers
- Biostatisticians
- Device Reviewers
- Interdisciplinary Review Teams for specialized consultations
- Chemistry, Manufacturing, and Controls (CMC) Experts
- Good X Practice (GXP) inspectors and auditors of manufacturing and research sites



Package Insert

- Upon completion of the review of the NDA and drug is deemed approvable, FDA finalizes Package Insert (PI)
  - Labeling document to ensure safe and effective prescribing by professionals
  - Provides “just the facts” intended to be informative, precise, and non-promotional
  - Summary of critical scientific information based on the submitted and reviewed data
  - Clinical Pharmacology and PK is summarized in Section 12
    - Section 12.1 Mechanism of Action
    - Section 12.2 Pharmacodynamics
    - Section 12.3 Pharmacokinetics
      - Food Effect
      - Drug Interactions
      - Pharmacokinetics in Patients with Impaired Renal Function
      - QTc Information

PK Study conducted to Bridge To-be-Marketed (TBM) to Clinical Service Form (CSF)

PK Study to Bridge Clinical Service Form (CSF) to To-be-Marketed Formulation (TBM)

- Two-arm, cross-over single dose study
- Compare CSF to TBM formulation
- N=24 HV
- Statistical analysis: Two-One Sided T-Test 90% Confidence Interval (80-125%)
- Sampling: Serial blood samples withdrawn at 0, 0.5, 1, 2, 4, 8, 16, and 24 hours

Table 1. PK parameters of Innovator Drug compared with Generic Formulation and 90% Confidence Interval (Two One-Sided T-test)

	CSF Drug	TBF	90% Confidence Interval	Equivalent
Cmax +/- SD (ug/mL)	20 +/- 5	24 +/- 5	90-115	✓
AUC +/- SD mg*h/L	180 +/- 5	176 +/- 5	89-110	✓
Tmax +/- SD (Hr)	40+/- 5	38 +/- 5		
T1/2 (Hr)	6 +/- 5	6 +/- 5		

Generic Drug Bioequivalence Study

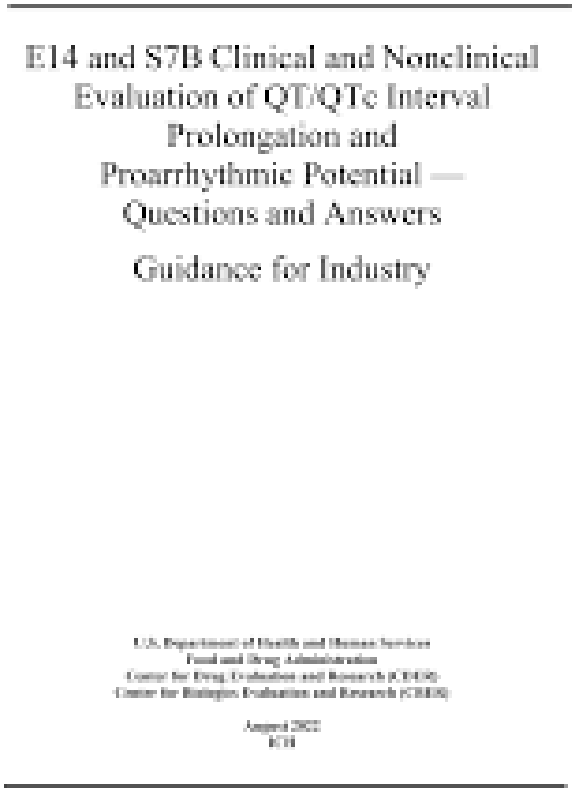
- Innovator drug goes off patent, generic drugs can come to market
- Clinical study: Two-arm, cross-over, single dose study comparing PK of generic drug to innovator drug N=24 HV
- Statistical analysis: Two-One Sided T-Test (90% Confidence Interval)
- Acceptance for bioequivalence within 80-125%
- Sampling: Serial blood samples withdrawn at 0, 0.5, 1, 2, 4, 8, 16, and 24 hours

Table 1. PK parameters of Generic compared with Innovator and 90% CI (Two One-Sided T-test)

	Innovator Drug	Generic Formulation	90% Confidence Interval
Cmax +/- SD (ug/mL)	20 +/- 5	24 +/- 5	90-115
AUC +/- SD mg*h/L	180 +/- 5	176 +/- 5	89-110
Tmax +/- SD (Hr)	40+/- 5	38 +/- 5	
T1/2 (Hr)	6 +/- 5	6 +/- 5	

ICH E14 PK Study Evaluation of QT/QTc prolongation

- Objective: To clinically assess a new drug's liability to prolong QT interval (adopted May 2005
- Design: Conducted in HV; blood sampling 0 – 24 hrs, Holter monitoring to match concentration with QT
- Arms: 4-arm study
  - Therapeutic dose, supratherapeutic dose, placebo, positive control to validate the study
- N: Robust enough to detect a 5 msec prolongation of QT interval
- Analysis: Concentration effect
- Significance: If negative, drug can proceed normally in development. However, if positive, all subsequent studies will need extra ECG monitoring and drug may be required to include specific instructions on its label, ranging from special dosing instructions to black box warnings.


E14 and S7B Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential — Questions and Answers

Guidance for Industry

https://www.appliedclinicaltrialsonline.com/view/abcs-thorough-qts

In Vitro Dissolution

In Vitro Dissolution

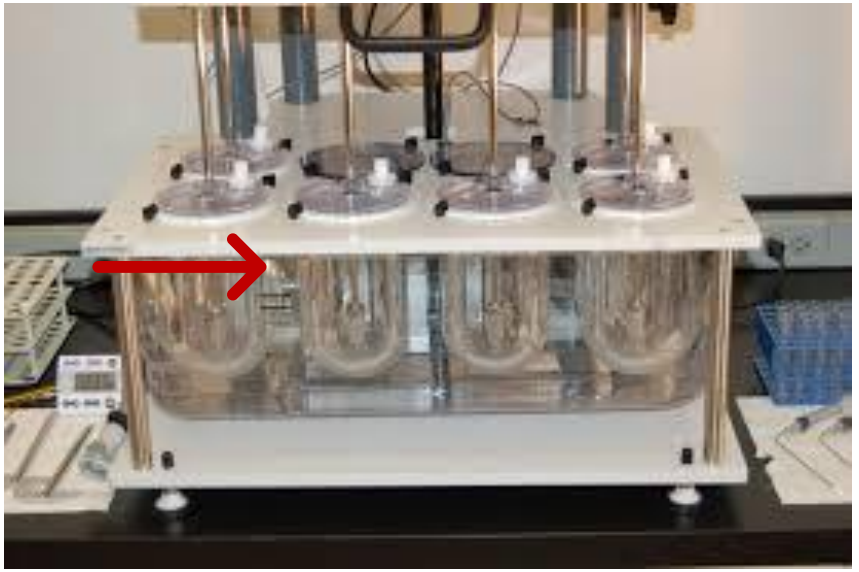
In vitro tests that measures rate and extent of dissolution and release of a drug substance from a drug product linked to the drug product's performance *in vivo*

Need for Dissolution testing

- Important QC release specification for a drug product
- Ensures Batch to batch drug uniformity
- Ensures quality and stability of the drug product

In Vitro Dissolution Procedure

- Seven types of dissolution apparatus defined in United States Pharmacopeia (USP)
  - basket type
  - paddle type
  - reciprocating cylinder
  - flow through cell
  - paddle over disc
  - rotating cylinder
  - reciprocating disc.



https://www.fda.gov/media/70936/download#:~:text=In%20vitro%20dissolution%20specifications%20are,problems%20with%20in%20vivo%20bioavailability.

In Vitro Dissolution Procedure

- Basket method testing
  - N = 8 tablets, one placed in bottom of each container
  - Basket method rotate at 50/100 rpm
  - Sampling at 15-minute intervals to generate dissolution profile
- For immediate release formulations
  - Sampling every 5- or 10-minute intervals
  - For highly soluble formulations (BCS classes 1 and 3),
  - Single-point dissolution test specification of NLT 85% (Q=80%) in 60 minutes or less is sufficient as a routine QC test for batch-to-batch uniformity.
- For slowly dissolving or poorly water-soluble drugs (BCS class 2),
  - Two-point dissolution specification, one at 15 minutes to include a dissolution range (a dissolution window) and the other at a later point (30, 45, or 60 minutes) to ensure 85% dissolution

- Dissolution data reviewed by Clinical Pharmacology reviewer confirms sponsor's proposed dissolution specification which is set as a release specification for that drug product

https://www.fda.gov/media/70936/download#:~:text=In%20vitro%20dissolution%20specifications%20are,problems%20with%20in%20vivo%20bioavailability.

Pharmacodynamics

Pharmacodynamics

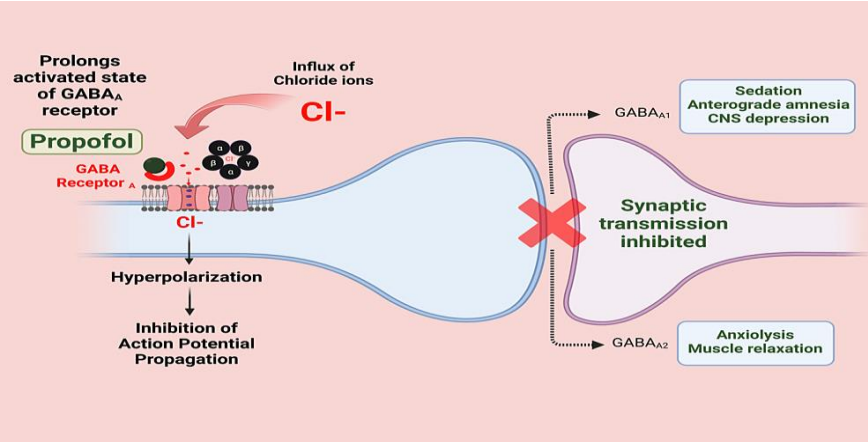
- Study of how a drug's concentration (C) relates to its effect (E)
- A drug has two key properties: its greatest possible effect (Emax) and concentration that produces half of that effect (C_{50})
- Body has many receptors, which are where drugs act
  - Nerve cells in brain and spinal cord carry opioid *Mu-1,* serotonin 5HTs, NMDA, D2, GABA receptors
  - Heart muscle carries alpha-1, beta-1, and M2-muscarinic receptors
  - T-cells carry IL-17A receptors (cytokines involved in inflammation and immune responses)
- Potency Ki (binding affinity)
  - Measures the absolute amount (dose) of a drug needed to produce an effect.
  - How strongly effect of a drug depends on how tightly it binds to its receptor
  - Drug concentration (nM) needed to fill half of the receptor

Lower Ki	Higher Ki
stronger binding small amount of drug needed to produce therapeutic effect	weaker binding more drug needed to produce therapeutic effect
Lower Ki = More potent	Higher Ki = Less potent

- https://www.ashp.org/-/media/store%20files/p2418-sample-chapter-1.pdf

Propofol Mechanism of Action

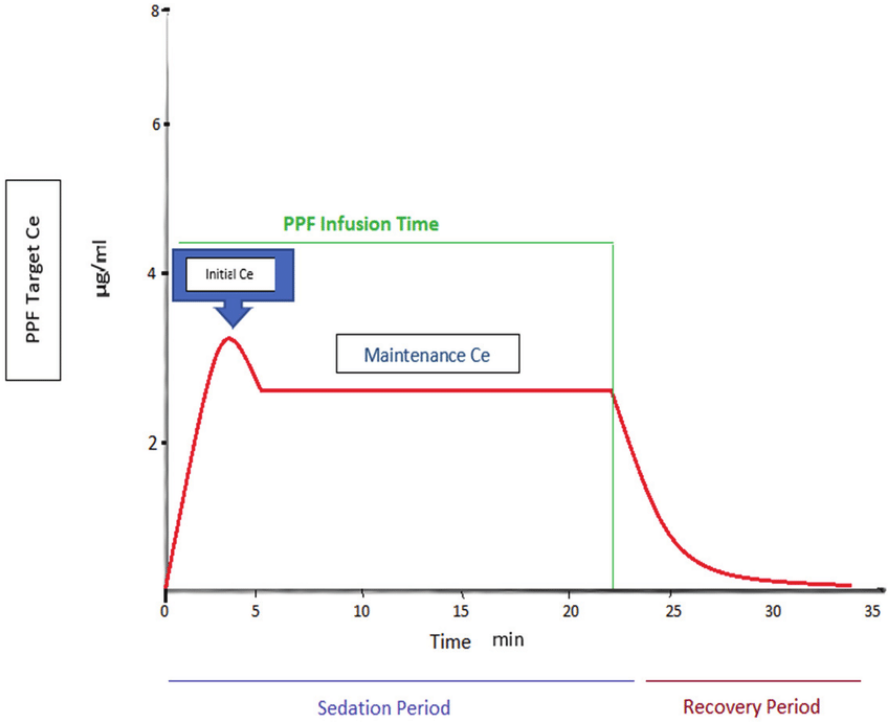
- Fast-acting intravenous medication used to induce and maintain general anesthesia, Due to its lipid emulsion formulation, Milky-white appearance often referred to as the "milk of amnesia.
- Therapeutic effect - sedation
- Transformative therapy that enabled day surgery by promoting faster recovery compared with general anesthesia.
- MOA- Potentiates GABA mediated inhibitory neurotransmission, resulting in suppression of central nervous system activity.



Paramsothy J et al; Propofol in ICU Settings: Understanding and Managing Anti-Arrhythmic, Pro-Arrhythmic Effects, and Propofol Infusion Syndrome; Cureus 15(6): e40456. doi:10.7759/cureus.40456

Propofol Pharmacokinetics

- Intravenous (IV) sedative-hypnotic agent
- Indication: fast acting, short acting sedation
- FDA Approved October 1989
- Drug characteristics
  - Very lipid soluble, Distributes from blood through Blood Brain Barrier to Brain RAPIDLY
- Administration:
  - Bolus for initiation
  - Infusion for maintenance
- Rate: 10 to 150 ug/kg/min
- Effective Concentration: 1.00 ug/mL
- Site of action: Brain
- Once injected
  - Rapid distribution from plasma to CNS
  - PD effect: Unconsciousness
  - Time to onset: 15-30 sec
- Elimination $T_{1/2}$: 4 min
  - Once infusion stops, rapid elimination
  - Recovery within 20 min

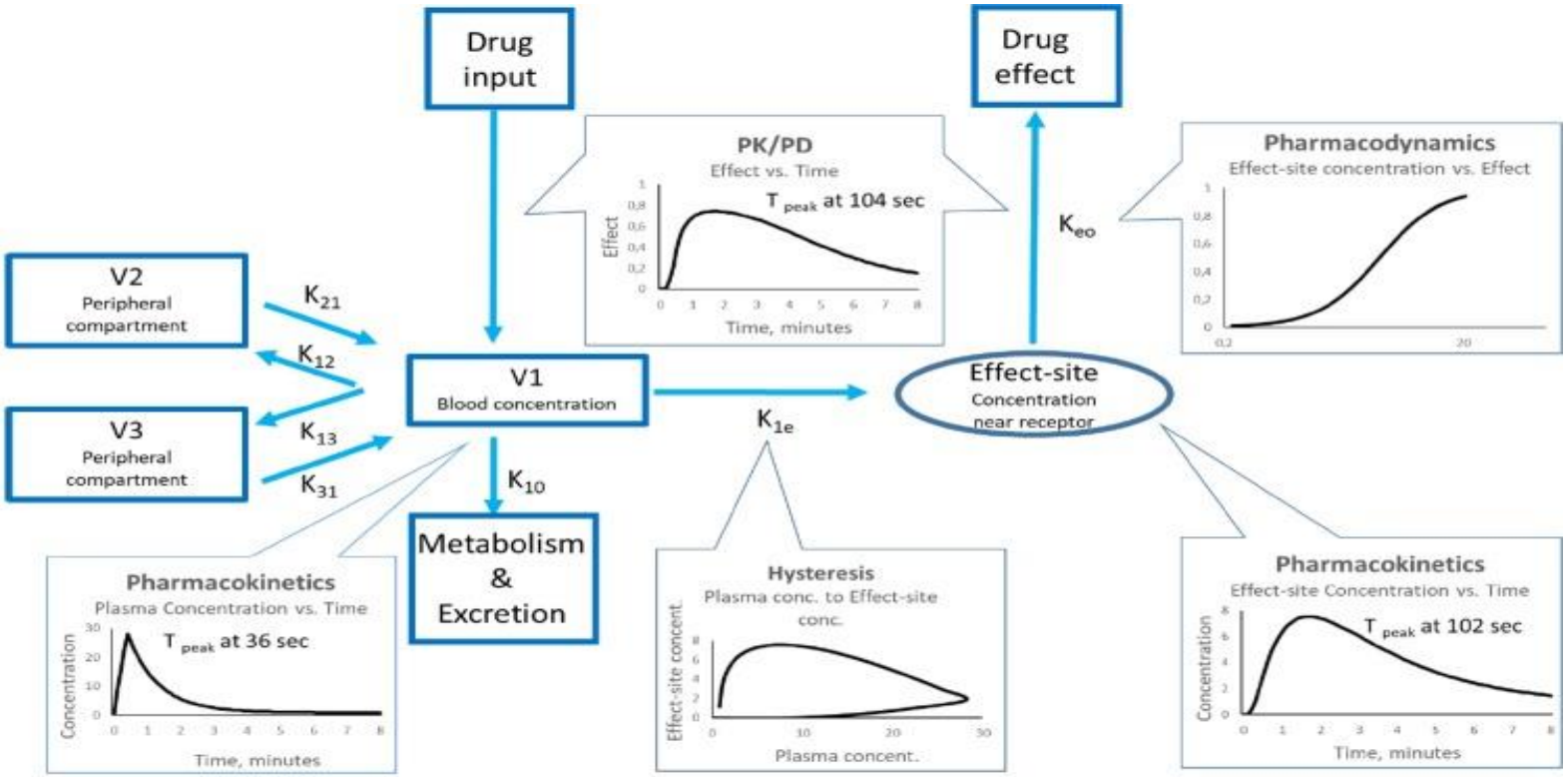


THANK YOU

QUESTIONS?

BACKUP SLIDES

Propofol Population PK Modelling



Intercompartmental transfer constants:

$$K_{21}/K_{12} = CL_2$$

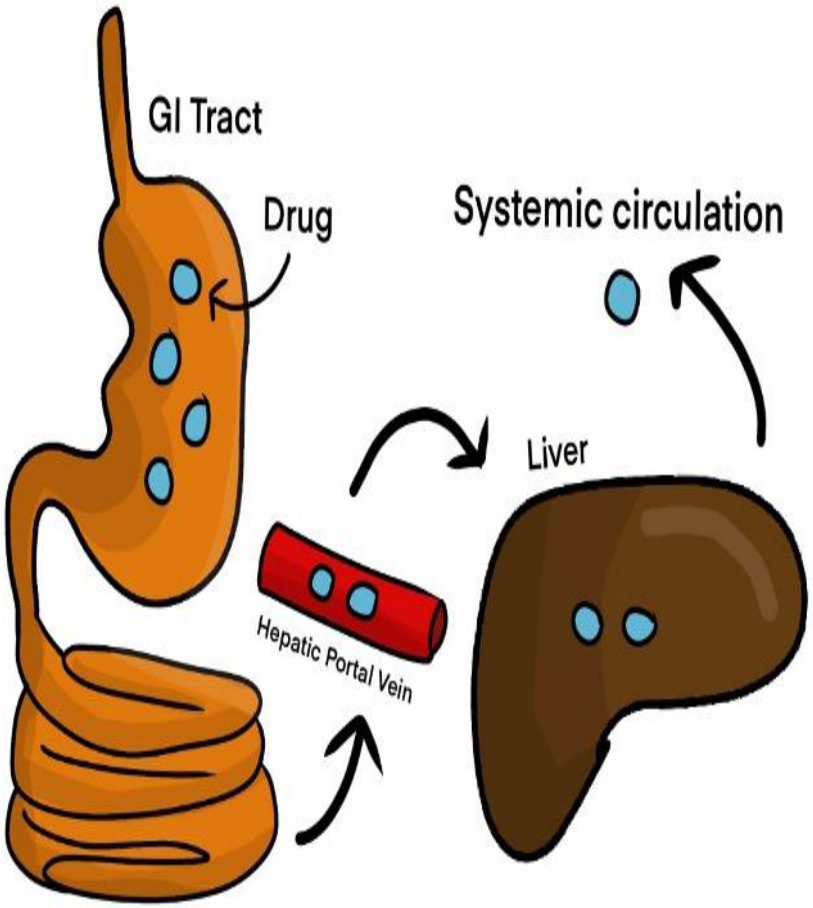
$$K_{31}/K_{13} = CL_3$$

Marko M, Clin Pharmacokinet. Clinical Pharmacokinetics and Pharmacodynamics of Propofol, 2018; 57(12): 1539–1558. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6267518/

Single Dose Drug Study to determine PK of a drug

- Procedure

1. Recruitment, Screening, Informed Consent
2. Study HV subjects swallow pill
3. Serial blood samples withdrawn at 0, 0.5, 1, 2, 4, 8, 16, and 24 hours
4. Serum analyzed by validated HPLC/MS
5. Drug concentrations (ug/mL) determined
6. Drug Concentrations (ug/mL) plotted against Time (Hr) the samples were withdrawn



Plasma Drug Concentration versus Time Curve