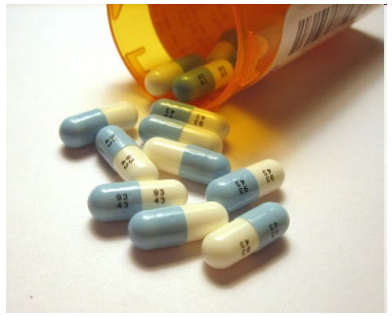
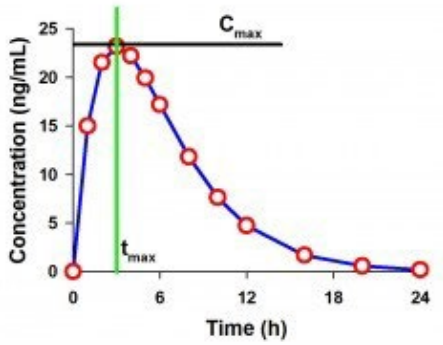
U.S. FOOD & DRUG ADMINISTRATION

Clinical Pharmacology:
Early Drug Development





Shirley K. Seo, Ph.D.
Division Director
Division of Cardiometabolic and Endocrine Pharmacology
Office of Clinical Pharmacology/OTS/CDER/FDA
12/11/24

Objectives

Overall objective: Understand clinical pharmacology and learn about its role in early drug development

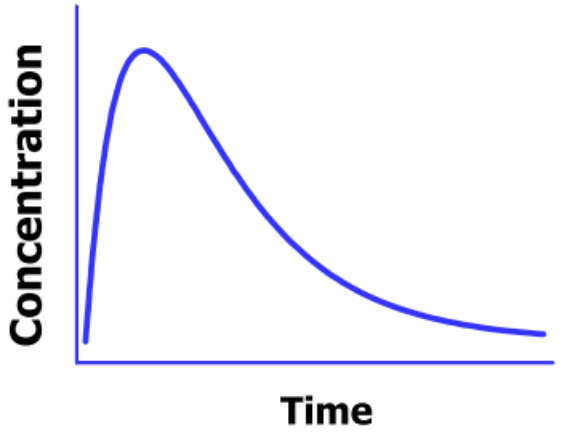
- How will we get there?
  1. Define clinical pharmacology
  2. Get an overview of early clinical studies:
     - Timing
     - Goals
     - Key design elements and information gained from these studies
     - PBPK
     - Model-informed drug development

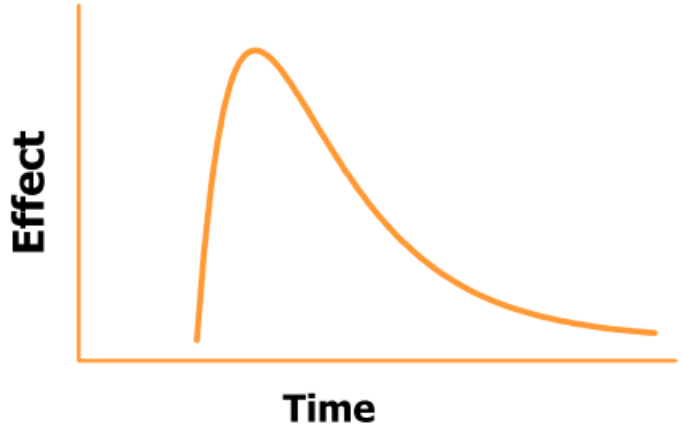
Clinical Pharmacology—What is it?

- Study of the Pharmacokinetics (PK) and Pharmacodynamics (PD) of a drug in humans

PK: what the body does to the drug
(Absorption, Distribution, Metabolism, Excretion)

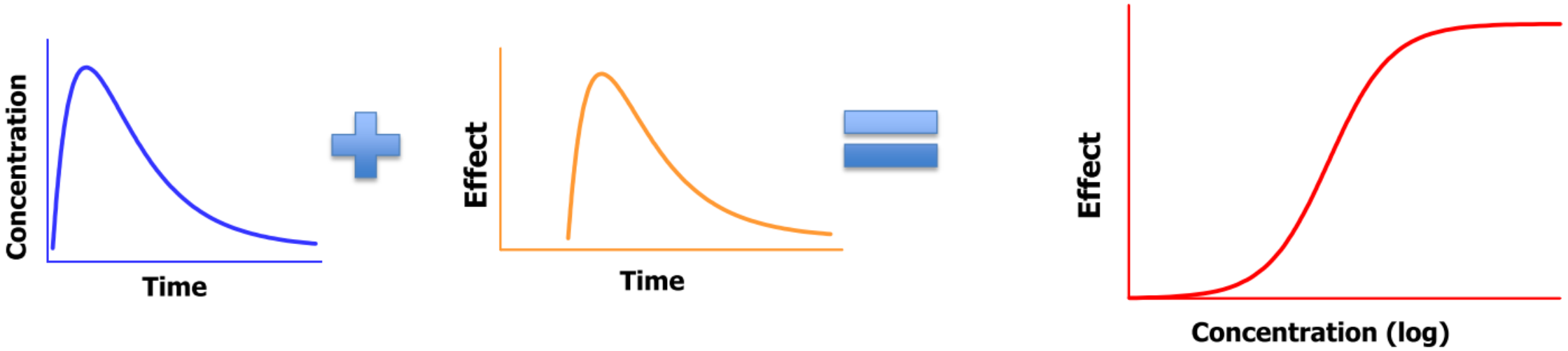
PD: what the drug does to the body





Clinical Pharmacology Tools

- What happens when we put it all together?
- We get a relationship called **PK/PD** or **exposure-response**

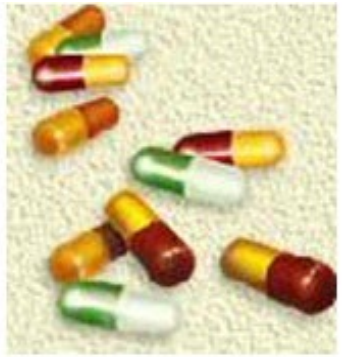


How do Clinical Pharmacologists Contribute to the Drug Development Process?

We "own the dose"

- Help determine the dosing regimen of a drug
  - How much to give?
  - How often to give it?
- Help determine if the dose of a drug needs to be adjusted due to various intrinsic/extrinsic factors

Right drug?
Right dose?
Right time?



Right patient?

Clinical Pharmacology Properties of a Drug (ADME)

ABSORPTION:

- Process of a drug reaching systemic circulation
- Can be impacted by several factors:
  - Food
  - pH-altering medications
  - Alcohol
  - Transporters or drug metabolizing enzymes in the gut
- Important information typically communicated in the USPI (*Absorption*, Section 12.3):
  - Bioavailability
  - Time to reach maximum concentration (Tmax)
  - Effect of food

Clinical Pharmacology Properties of a Drug (ADME)

DISTRIBUTION:

- Process of drug being distributed to different areas of the body
- Volume of distribution (Vd) is a numerical descriptor (given in units of L) of a drug's propensity to either remain in blood or distribute to various organs throughout the body
- Factors to consider:
  - Does drug bind to plasma proteins? Is the extent of protein binding concentration- or time-dependent?
    - Only free or unbound drug is active
    - Measurement of unbound drug is sometimes recommended when interpreting data
  - Is information on distribution to CSF relevant for this drug?
- Important information typically communicated in the USPI (*Distribution*, Section 12.3):
  - % protein bound
  - Vd

Clinical Pharmacology Properties of a Drug (ADME)

METABOLISM & EXCRETION:

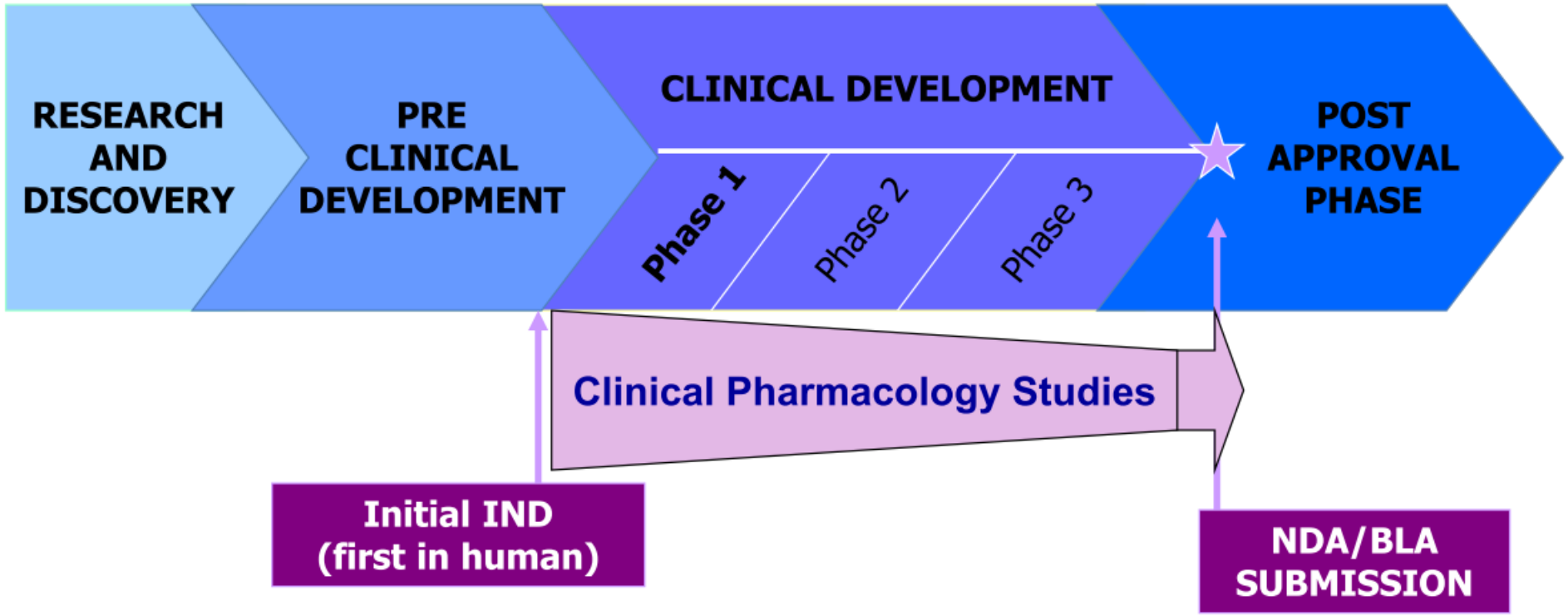
- Metabolism is the process by which lipophilic molecules are converted into more hydrophilic ones so they can be excreted by the body
- Excretion is the irreversible loss of drug from the body
- Factors to consider:
  - How is a drug metabolized and cleared from the body? Usually hepatic metabolism and/or renally excreted
  - What fraction of the drug is metabolized and are the metabolites active/toxic?
- Important information typically communicated in the USPI (*Metabolism, Excretion*, Section 12.3):
  - Half-life (T1/2)
  - Major route of elimination
  - % excreted in urine or feces

Clinical Pharmacology Properties of a Drug

- **OTHERS:**
  - A Narrow Therapeutic Index Drug?
    - If yes, slight changes in drug exposure may significantly impact efficacy/safety
    - May require therapeutic drug monitoring in clinical trials and clinical practice to minimize toxicities and lack of efficacy
  - A significant inhibitor or inducer of CYP enzymes or transporters?
    - If yes, further drug interaction evaluation may be needed

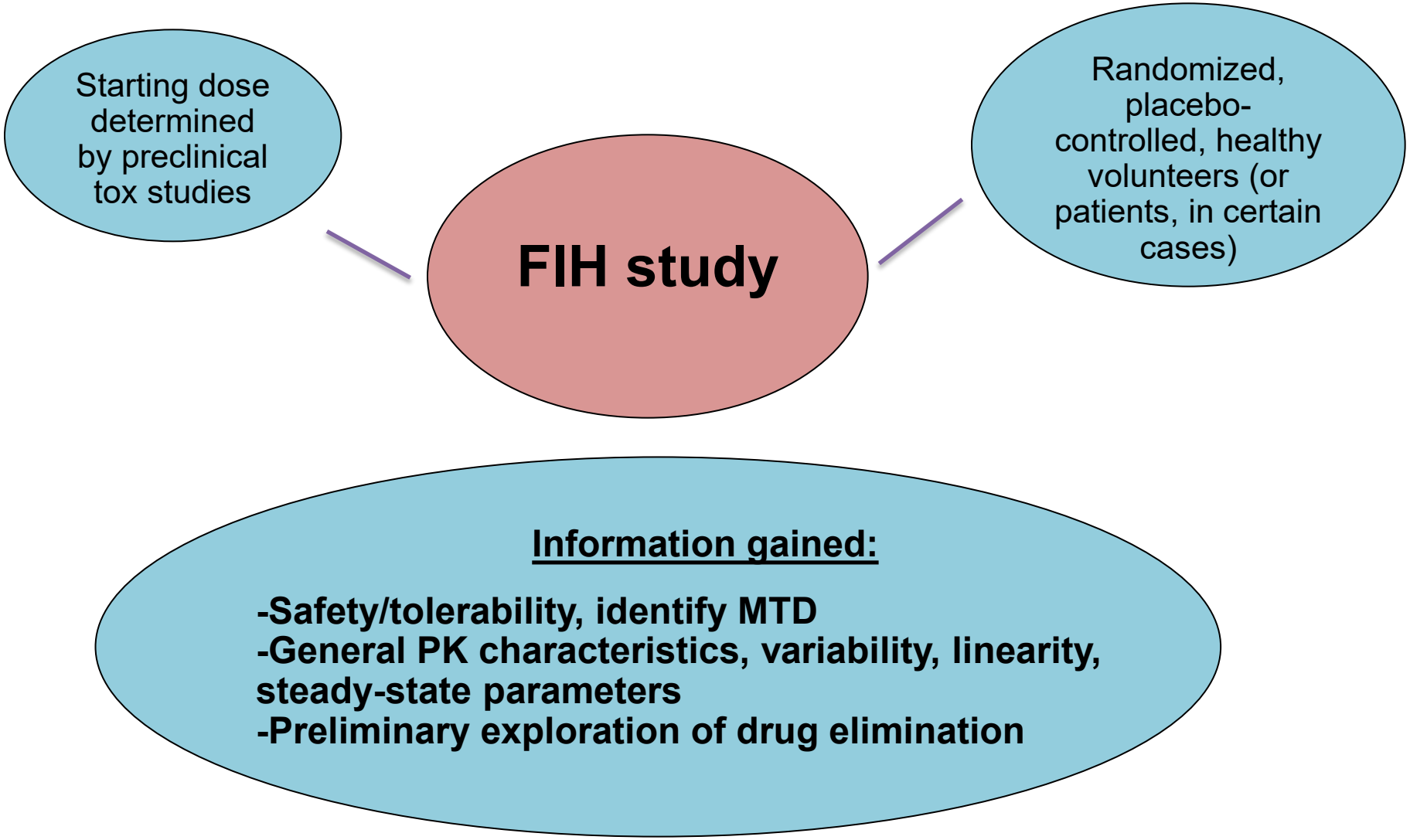
Early Clinical Studies

First, Timing—When are Clinical Pharmacology Studies Conducted?



Early phase studies are designed mainly to investigate the safety/tolerability (if possible, identify MTD) and pharmacokinetics of an investigational drug in humans

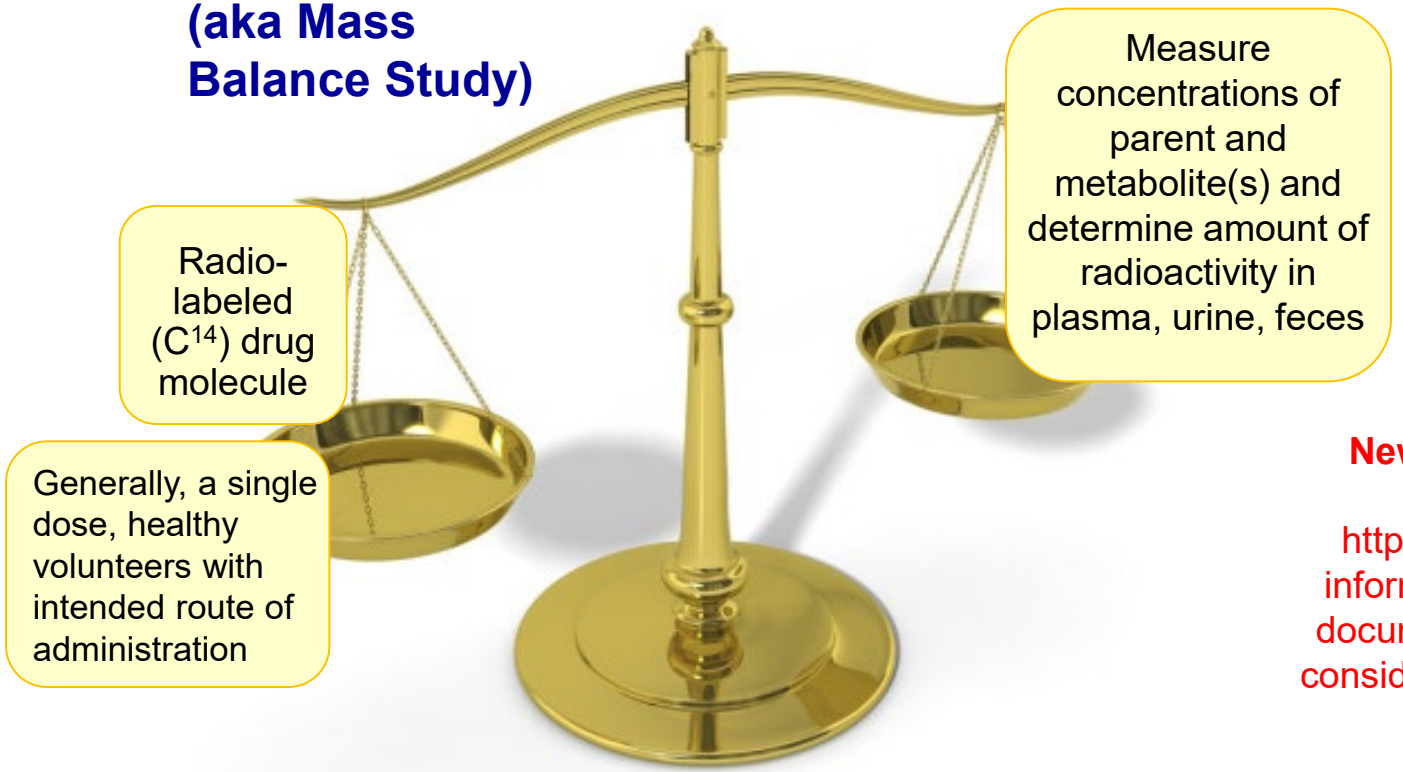
Starting at the Beginning: First-in-Human (FIH) Studies



ADME (Absorption, Distribution, Metabolism, Excretion) Study

Objective: To understand the full clearance mechanisms of the drug and its metabolites in humans

(aka Mass Balance Study)



Radio-labeled (C^{14}) drug molecule

Generally, a single dose, healthy volunteers with intended route of administration

Measure concentrations of parent and metabolite(s) and determine amount of radioactivity in plasma, urine, feces

New FDA guidance on mass balance studies
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-pharmacology-considerations-human-radiolabeled-mass-balance-studies

Information gained:

-Determine the overall pathways of metabolism and excretion of an investigational drug
-Identify circulating metabolites
-Determine the abundance of metabolites relative to the parent or total drug-related exposure

Bioavailability (BA) Studies

- Objective: To evaluate the rate (Cmax, Tmax) and extent (AUC) of absorption of drug from a test formulation and becomes available at the site of action

- Typically a crossover, single dose study in healthy subjects; measure extent and rate of absorption of parent drug and major active metabolites (if any)
  - Can assess relative (one formulation vs. another) or absolute (vs. IV formulation) bioavailability

Information gained:
-Amount of drug that reaches systemic circulation from a tested formulation

Source: Bioavailability Studies Submitted in NDAs or INDs — General Considerations Guidance for Industry (2022)

Food Effect Study

Objective: To evaluate the effect of food on rate and extent of drug absorption from a given formulation

- Single dose study in healthy subjects using highest therapeutic dose of drug product[1].
- Fed state should be FDA high-fat high-calorie meal (other meals can also be studied)
- PK assessments similar to BA study
- No food effect if 90% CI of fed/fasted Cmax and AUC ratios within 80-125%.
- The clinical significance of any observed food effect would be determined based on drug's exposure-response profile.

Information gained:

-How to administer drug in clinical trials

-Labeling instructions on how to administer drug with respect to food

[1]Source: Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations--Guidance for Industry (2022)

Hepatic Impairment Study

When should one be performed?

- Chronic and systemically available drug
- Hepatic metabolism and/or excretion accounts for a substantial portion (>20% of the absorbed drug) of the elimination of a parent drug or active metabolite
- It's a narrow therapeutic index drug (irrespective of proportion that is metabolized)
- Metabolism route is unknown

[1]Source: Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling—Guidance for Industry (2003)

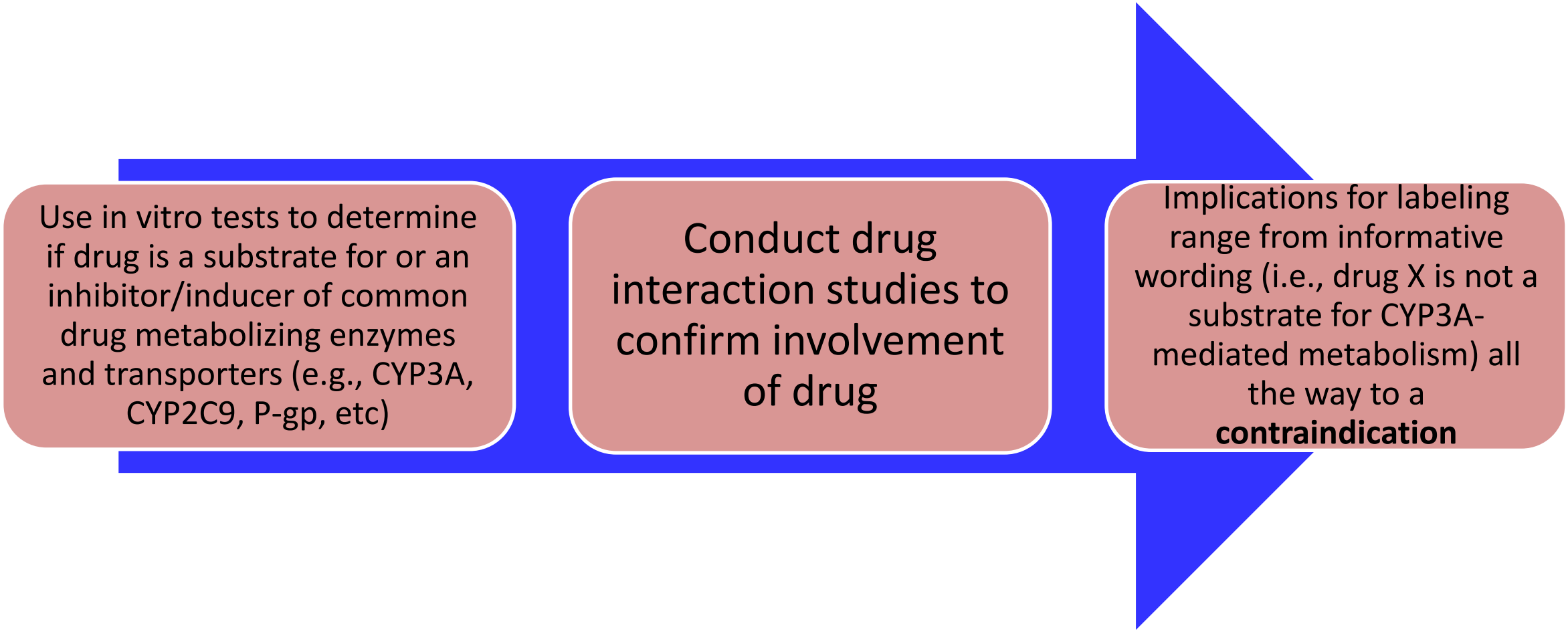
Renal Impairment Study

When should one be performed?

- When the drug is likely to be used in renally impaired patients and when impaired renal function is likely to alter the PK of the drug or its active metabolites because they are substantially eliminated by the renal route
- Therapeutic proteins and peptides with a molecular weight less than 69 kDa
- Drugs likely to be used in patients with end-stage renal disease (ESRD) undergoing dialysis should be evaluated both while the patient is on dialysis and off dialysis to determine the contribution of the dialytic method to the elimination of the drug and its potentially active metabolites

Source: Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing (2020)

Drug Interaction Studies



Additional detailed information can be found in the In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry and Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry (2020)

Drug Interaction Studies

Some key points to consider:

- Several factors should be taken into account to maximize the possibility of detecting an interaction (and also be clinically relevant):
  - Dose of inhibitor/inducer
  - Route(s) of administration
  - Timing of co-administration
  - Number of doses
- Degree of effect (inhibition/induction) is typically classified by change in the substrate AUC
- Exposure-response information on the drug is important in assessing the clinical significance of the change in AUC of substrate by inhibitor/inducer.

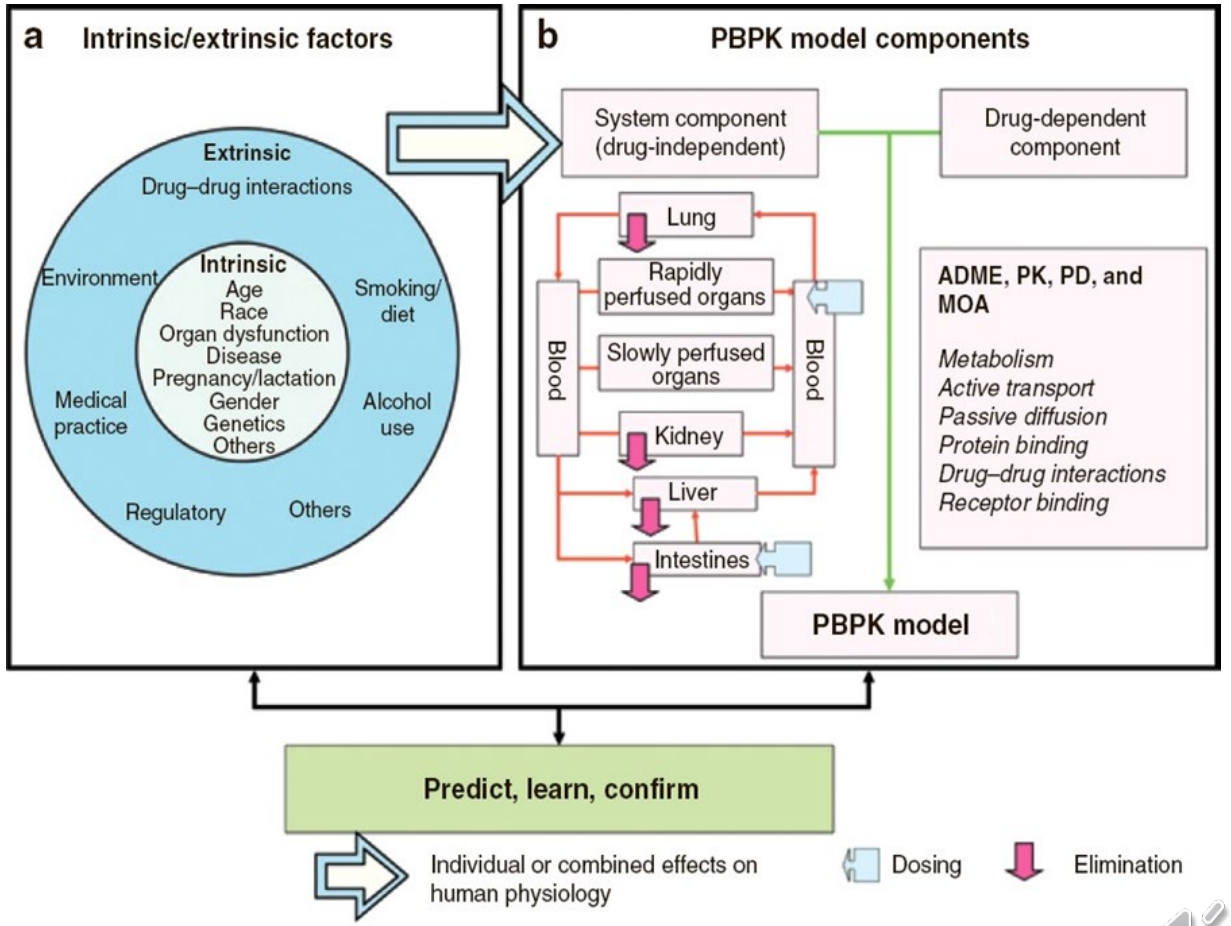
Physiologically Based Pharmacokinetics (PBPK)

What is it?

-PBPK is a mechanistic modeling approach that utilizes preclinical, in vitro, and/or in vivo data to predict the behavior of drugs in humans

What is it used for?

-It is useful for exploring the effects of various intrinsic and extrinsic factors such as age, ethnicity, disease status, or drug interactions on human PK



Early Dose Selection & Model-Informed Drug Development (MIDD)

- "Model-informed drug development (MIDD) is an approach that involves developing and applying exposure-based biological and statistical models derived from preclinical and clinical data sources to inform drug development or regulatory decision-making."
- Well-timed and well-designed dose-finding studies are critical for avoiding dose selection pitfalls later in development
- The FDA initiated the MIDD paired meeting program that allows sponsors to meet with the review team, led by clinical pharmacology. Some major focal points are:
  - Dose selection or estimation (e.g., for dose/dosing regimen selection or refinement)
  - Clinical trial simulation (e.g., based on drug-trial-disease models to inform the duration of a trial, select appropriate response measures, predict outcomes, etc.)
  - Predictive or mechanistic safety evaluation (e.g., use of systems pharmacology/mechanistic models for predicting safety or identifying critical biomarkers of interest)

Acknowledgements

- Kellie Reynolds, Pharm.D.
- Leonard Sacks, M.D.