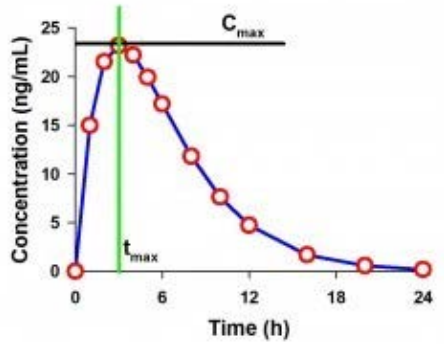
U.S. FOOD & DRUG ADMINISTRATION

Clinical Pharmacology:
Early Clinical Studies Described in The Investigator Brochure



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Disclaimer

- The opinions contained in this presentation are my own and do not necessarily represent the views of the FDA.

- You may think you are learning about the investigator brochure, but you are actually going to learn all about clinical pharmacology!

Objectives

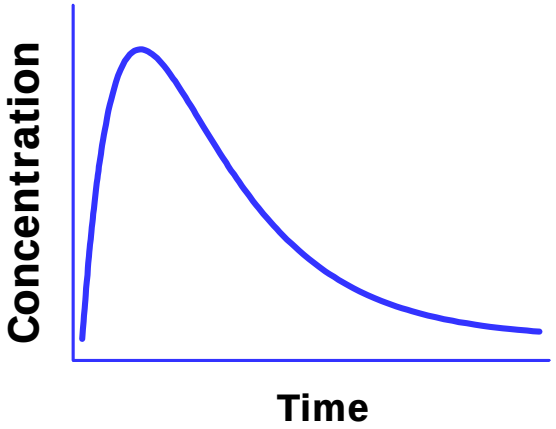
Overall objective: Understand clinical pharmacology information in investigator brochures (IB) and learn about early clinical trials.

- How will we get there?
  1. Define clinical pharmacology
  2. Find out what general clinical pharmacology information is in IBs and where it's located
  3. Get an overview of early clinical studies:
     - Timing
     - Goals
     - Key design elements
     - Information gained from these studies

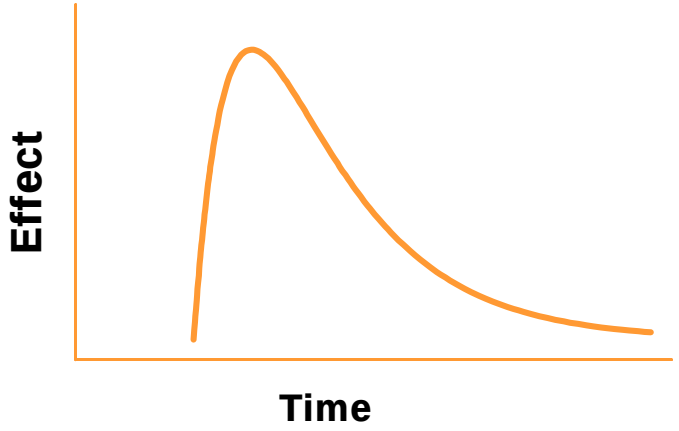
Clinical Pharmacology—What is it?

- 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)

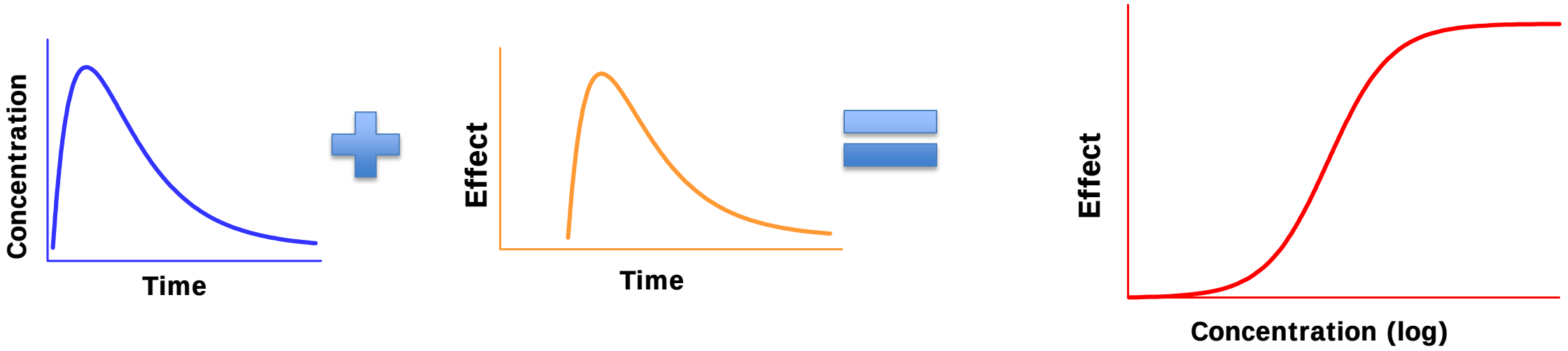


PD: what the drug does to the body



Clinical Pharmacology—What's so Important About it?

- What happens when we put it all together?
- We get a magical 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 Information in Investigator Brochures

What Does an Investigator Brochure (IB) Include?

- Presents both clinical and nonclinical data on the investigational drug
- Objective: to provide an understanding of key features of the drug, clinical protocols (i.e., dosing regimen, safety monitoring procedures)
- Ideally, information should be concise, simple, and objective
- Information is more and more dense as clinical development proceeds
- Primary readers? **YOU (clinical investigators)!!**

Investigator Brochure: *Where is Clinical Pharmacology Information?*

- The main section containing clinical pharmacology information is **Section 5**.

- Clinical pharmacology-*related* information can also hide out in other sections too!

Investigator Brochure: *Where is Clinical Pharmacology Information?*

Remember: any information that pertains to “dose” or the pharmacology of the investigational drug is clinical pharmacology information and is usually elucidated early in drug development (*in ideal situations*).

The Following Questions/Information Regarding a Drug's Pharmacological Properties aren't Always Contained in an IB, but are Important for Drug Development Nonetheless

Clinical Pharmacology Properties of a Drug

- **ABSORPTION:**
  - What is the bioavailability and PK variability?
  - Does it exhibit linear PK (e.g. dose-proportional increases in Cmax & AUC) or accumulate over time?
  - Is exposure significantly affected by concomitant food, pH-altering medications, grapefruit, alcohol, etc?
  - Is absorption affected by transporters?

Clinical Pharmacology Properties of a Drug

- **DISTRIBUTION:**
  - Does drug reach the target site(s) of action immediately and at effective/nontoxic concentration? Does it accumulate in non-target organs?
  - Does it bind to plasma proteins? Is the extent of protein binding concentration- or time-dependent?
    - only free or unbound drug is active
    - PK in terms of total drug concentrations often sufficient (e.g., in PK studies in renal and hepatic impairment)
  - CSF and others

Clinical Pharmacology Properties of a Drug

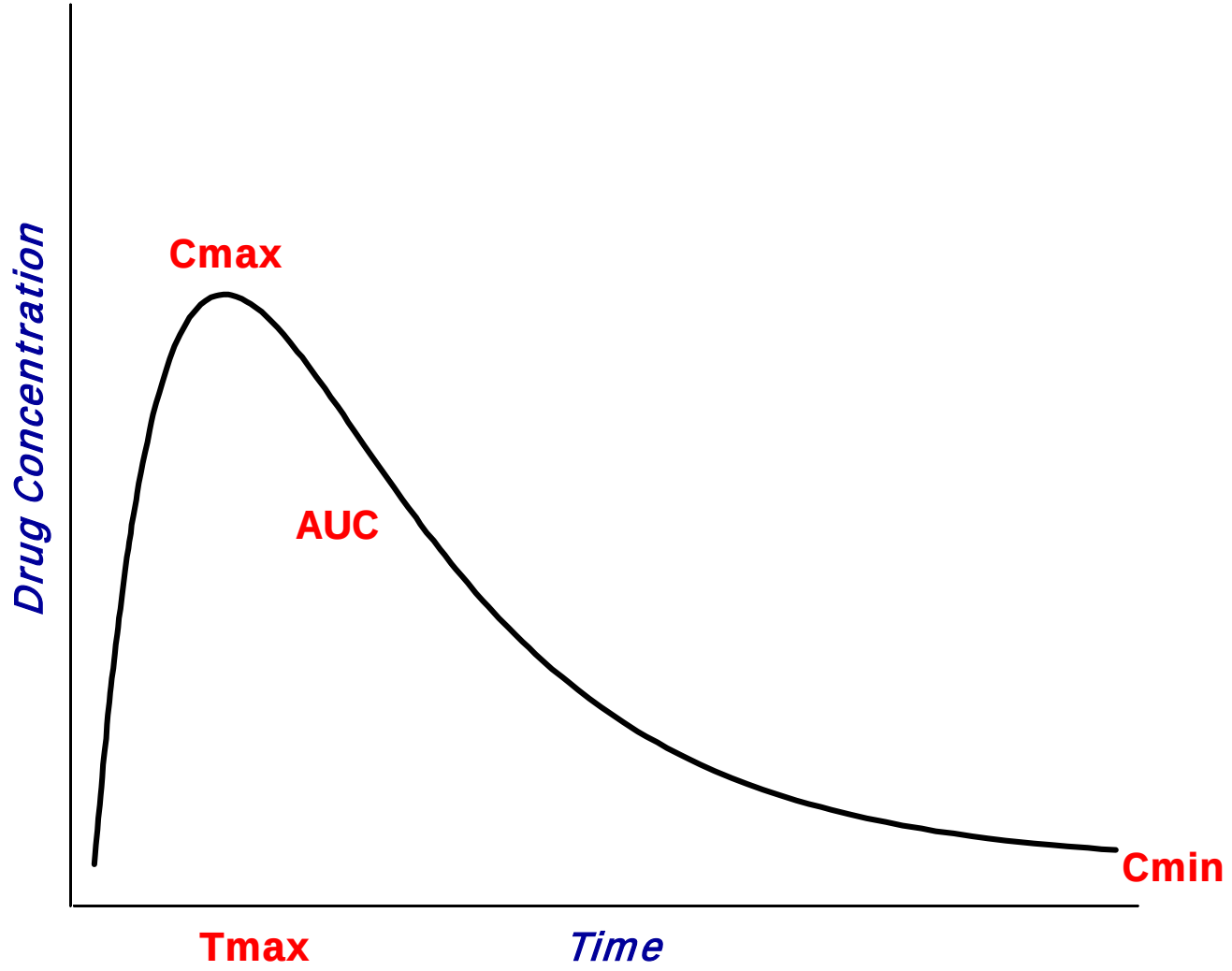
- **METABOLISM/EXCRETION:**
  - Is it metabolized by a CYP or other enzyme?
  - Is CL variable and dependent on ‘covariates’ such as age, race, gender, disease/comorbidities?
  - Is CL time-dependent (e.g., metabolic auto-induction, diurnal variation)?

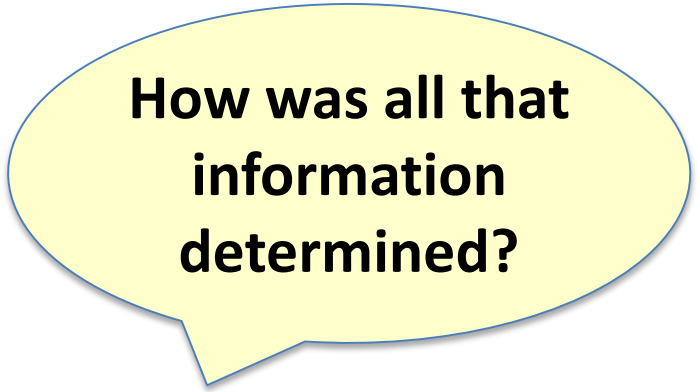
Clinical Pharmacology Properties of a Drug

- **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

Important Exposure Parameters of a Drug

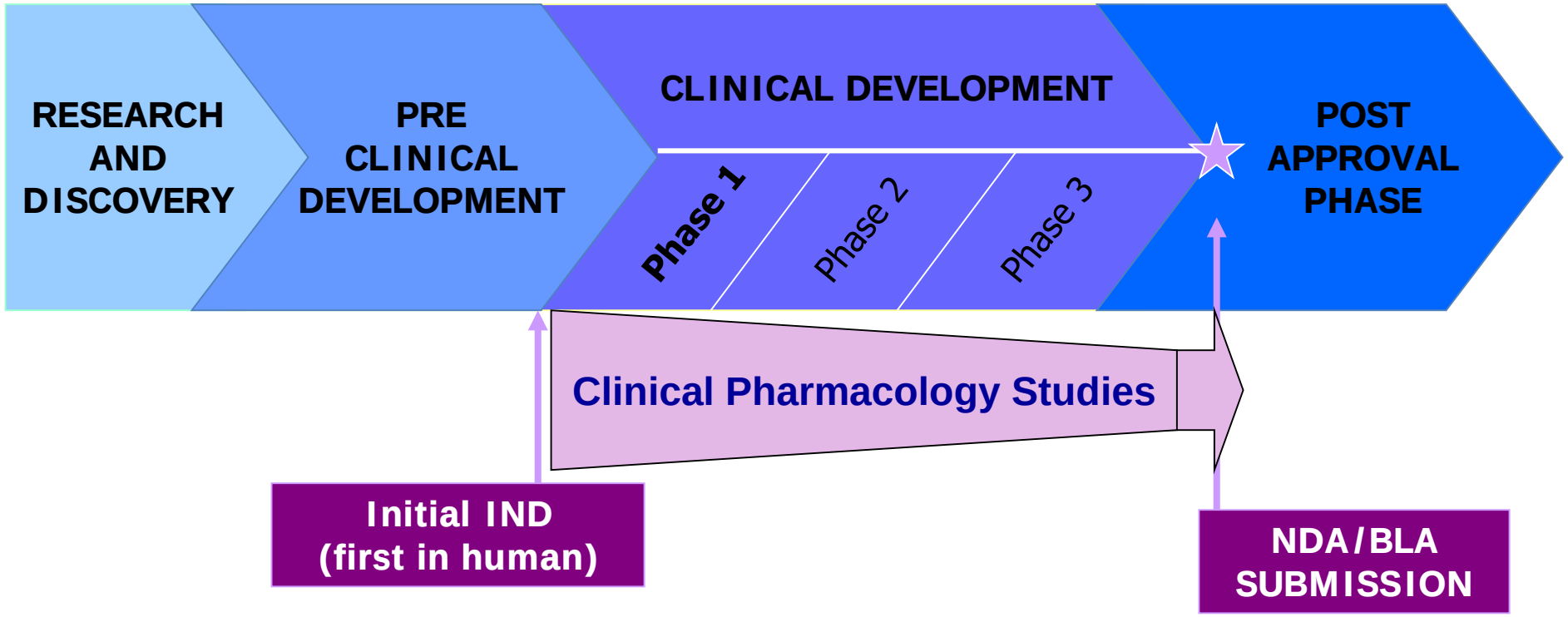
- Area under the Curve (AUC)
- Cmax
- Cmin
- T1/2
- Tmax





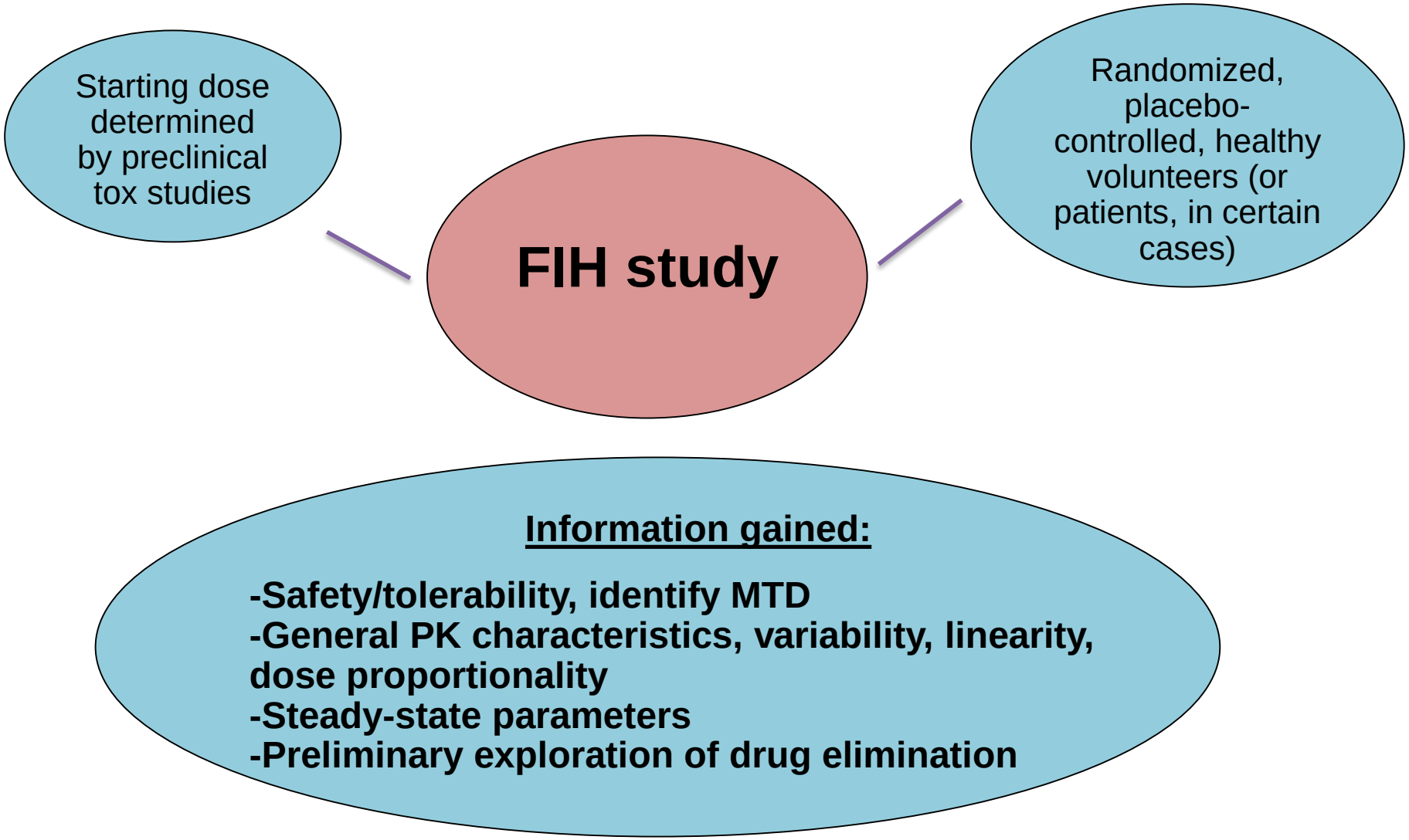
Early Clinical Studies

First, Timing—When are Clin Pharm 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

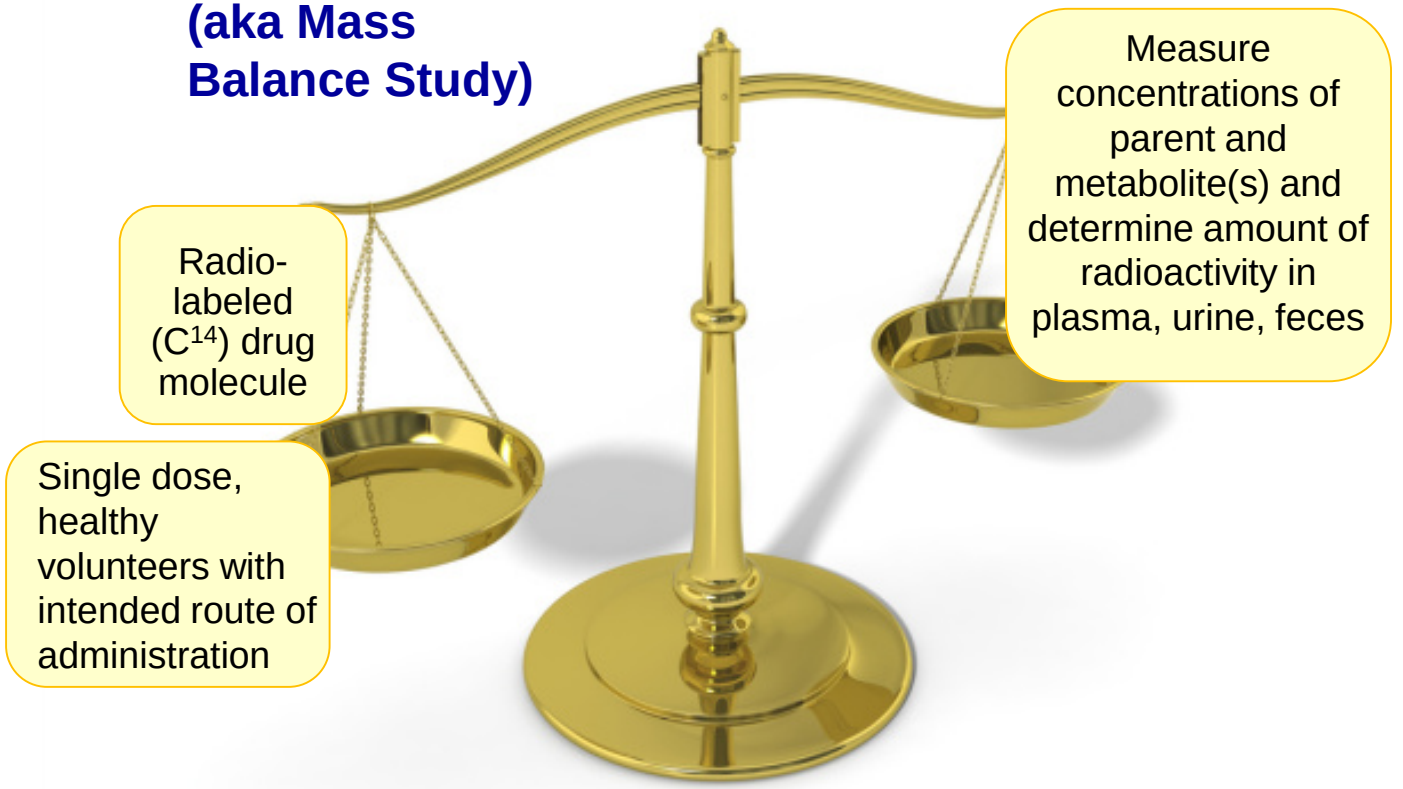
Starting at the Beginning: First-in-Human (FIH) Studies



ADME (Absorption, Distribution, Metabolism, Excretion) Study

(aka Mass Balance Study)

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



Information gained:

-Primary mechanism(s) of metabolism and excretion from the body

-Proportion of parent drug converted to metabolite(s)

Bioavailability (BA) Studies

- Objective: To evaluate the rate (Cmax, Tmax) and extent (AUC) of absorption of drug from a test formulation (vs. reference formulation)

- Typically 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:
-Comparison of amount of drug that reaches systemic circulation from each tested formulation

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 strength 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.

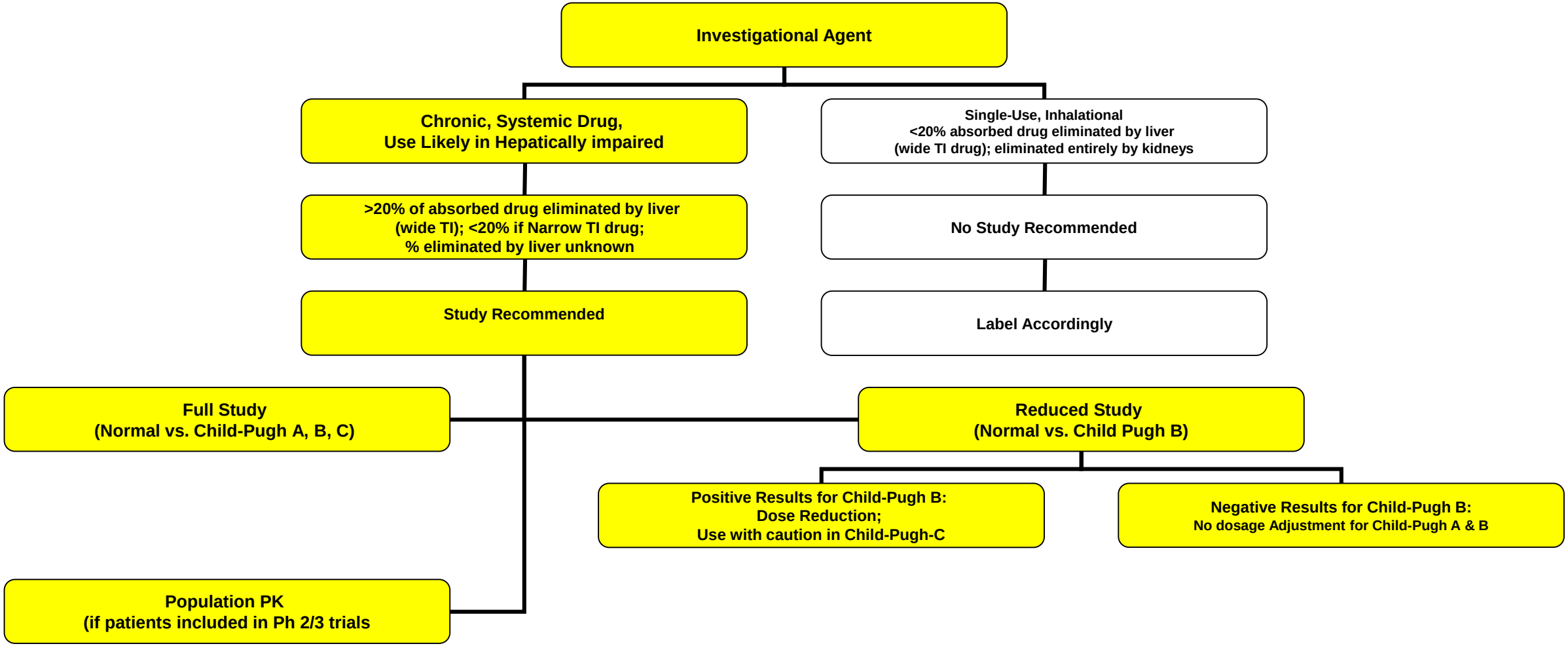
Information gained:

-How to administer drug in clinical trials

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

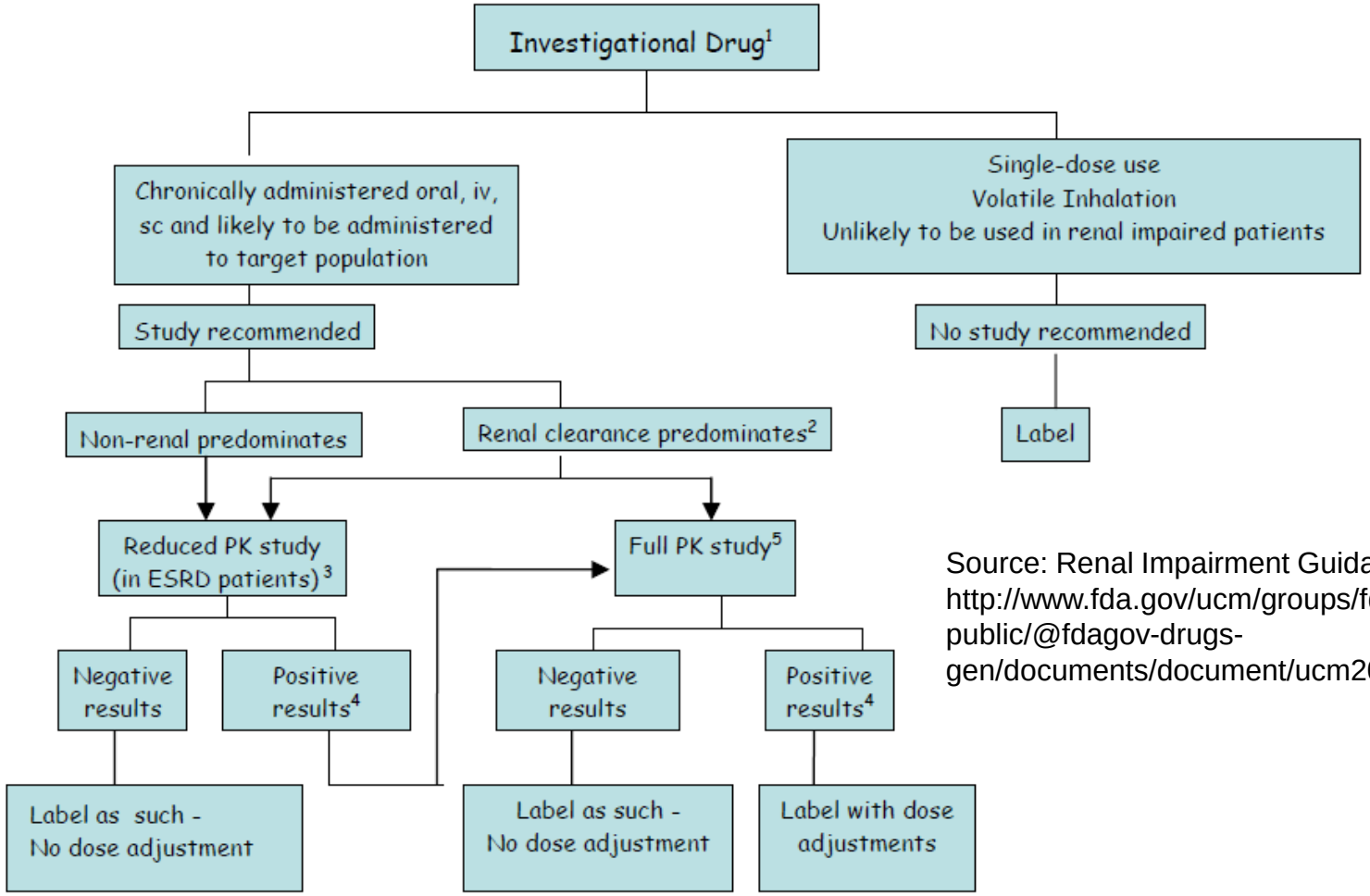
[1]Source: Food effect guidance (2002): http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-gen/documents/document/ucm126833.pdf

Hepatic Impairment Study Decision Tree



[1]Source: Hepatic Impairment guidance (2003): http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm072123.pdf

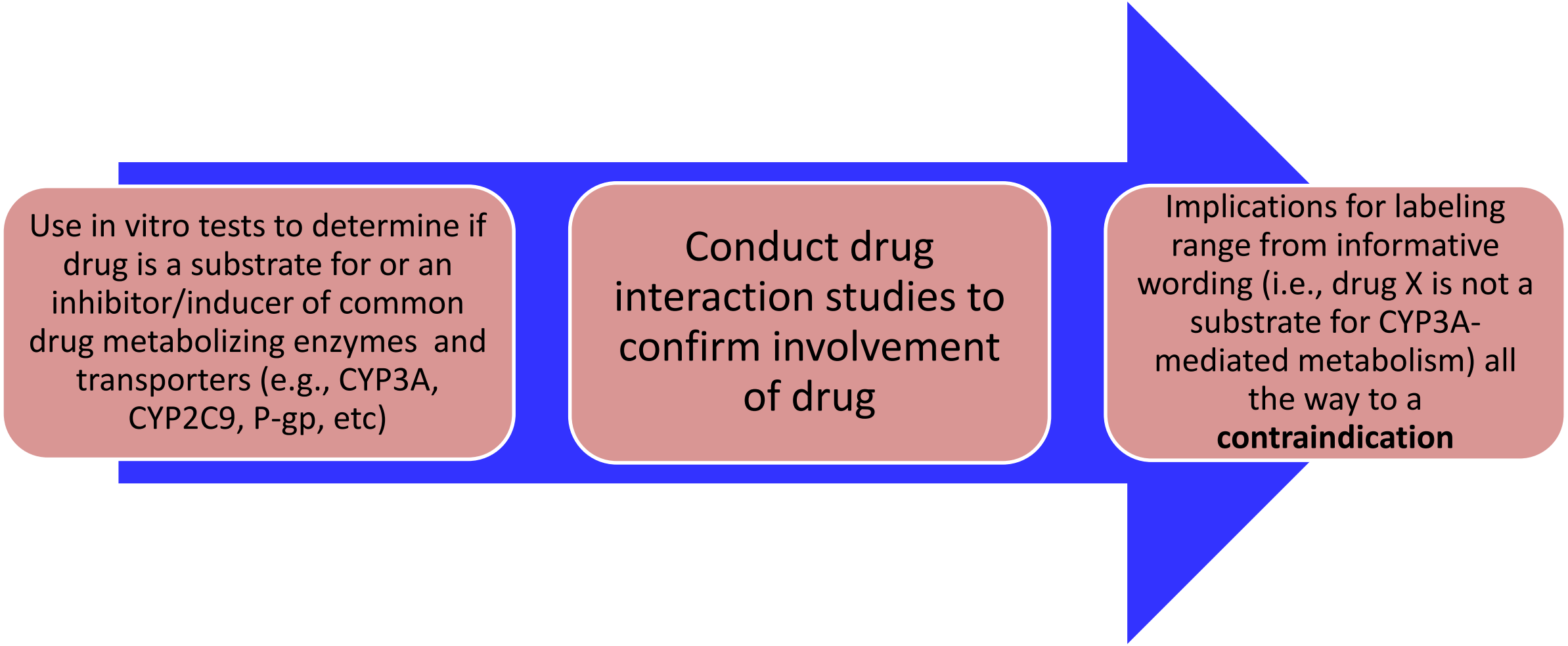
Renal Impairment Study Decision Tree



Source: Renal Impairment Guidance (2010): http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm204959.pdf

1. Metabolites (active/toxic) follow the same decision tree.
2. The sponsor has the option of conducting a reduced study in ESRD patients or a full study.
3. To be conducted in ESRD patients not yet on dialysis
4. The results are "positive" when the PK changes are clinically significant based on exposure-response of the drug
5. See section IV.B for the full PK study design, or additional studies can be conducted including a population PK evaluation

Drug Interaction Studies



Additional detailed information can be found in the Guidance for Industry: Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications (2017)

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.

To Summarize, Investigator Brochures Contain Critical and Valuable Clinical Pharmacology Information!

- The IB contains what's currently known about the pharmacokinetics (PK; exposure) and the pharmacodynamics (PD; biologic effect) of an investigational drug
- Should ideally be updated regularly
- Can provide useful information for the design of Phase 3 clinical trials

Challenge Question

True or False:

Most clinical pharmacology information in the IB is contained in a section titled: “Effects in Humans”

TRUE!

Challenge Question

Which of these are considered early phase studies?

a. ADME study

b. Bioavailability study

c. Food effect study

d. Efficacy study in patients

e. DDI study

f. Case study

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