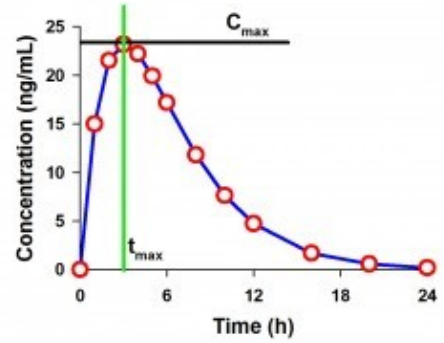
U.S. FOOD & DRUG ADMINISTRATION

Clinical Pharmacology:
Concepts to Support Drug Development



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FDA Clinical Investigator Training Course

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Disclaimer

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

Objectives

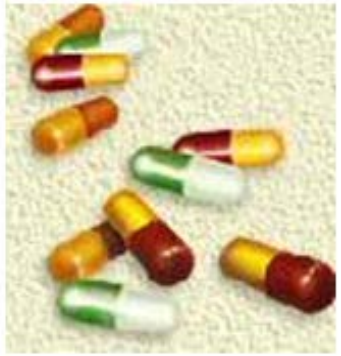
- Defining clinical pharmacology
- Clinical pharmacology studies:
  - Timing
  - Goals
  - Key design elements
  - Information gained from these studies
- Learn about typical clinical pharmacology properties that are characterized for a drug
- Labeling examples of the impact of clinical pharmacology studies

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?

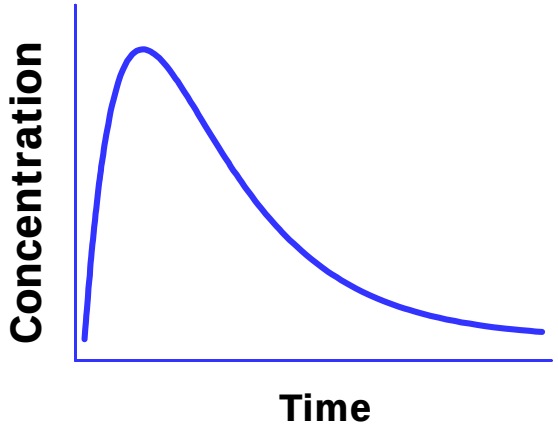


Right patient?

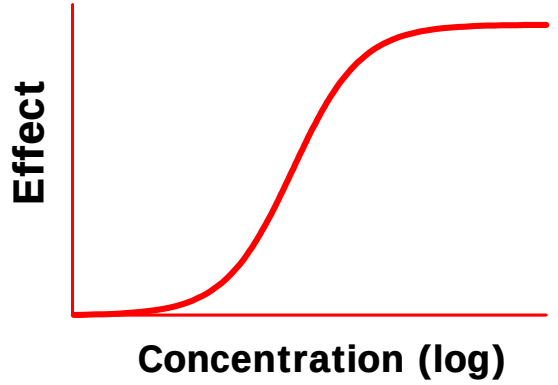
Clinical Pharmacology—What is it?

- 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)

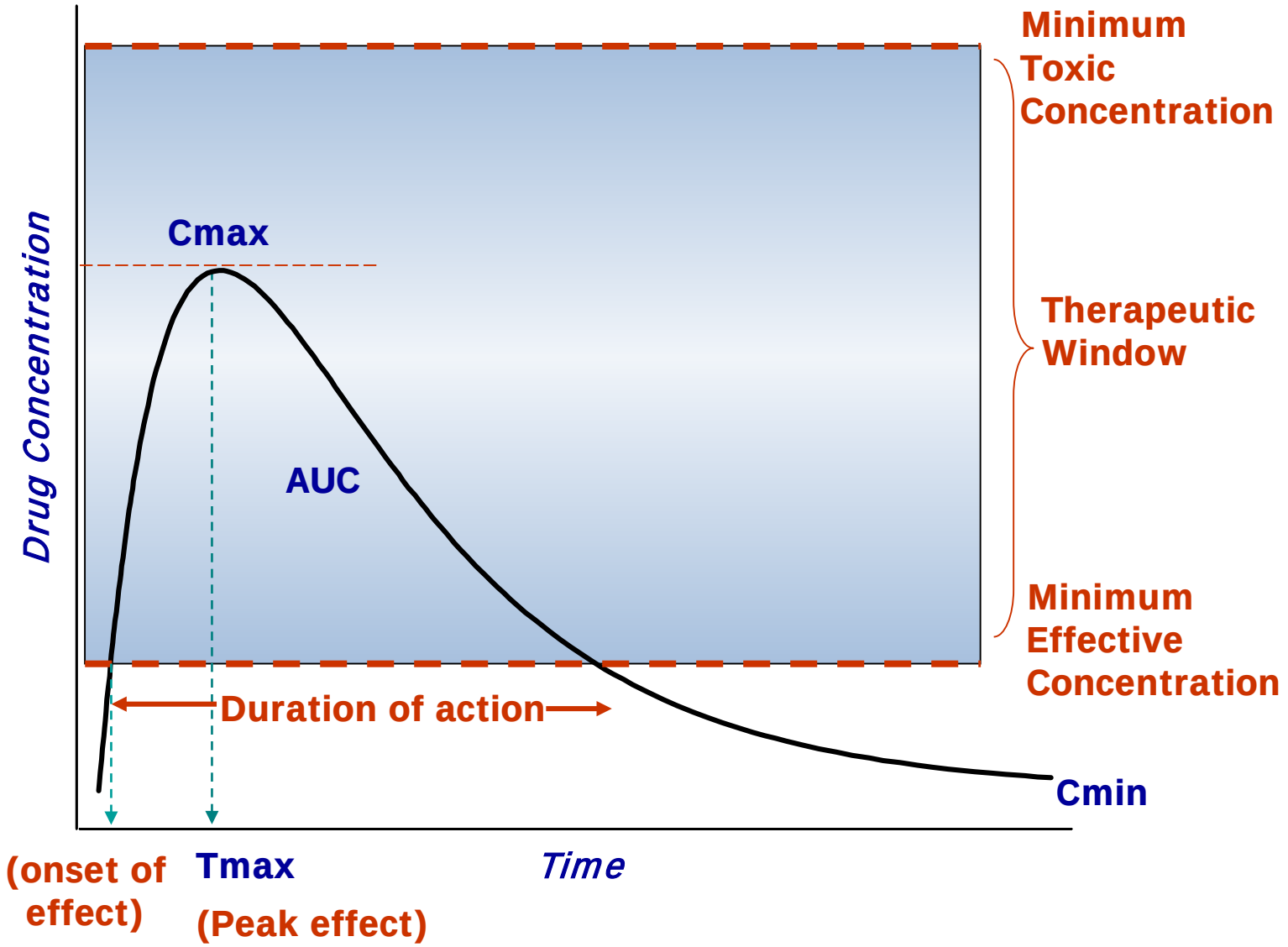


PD: what the drug does to the body



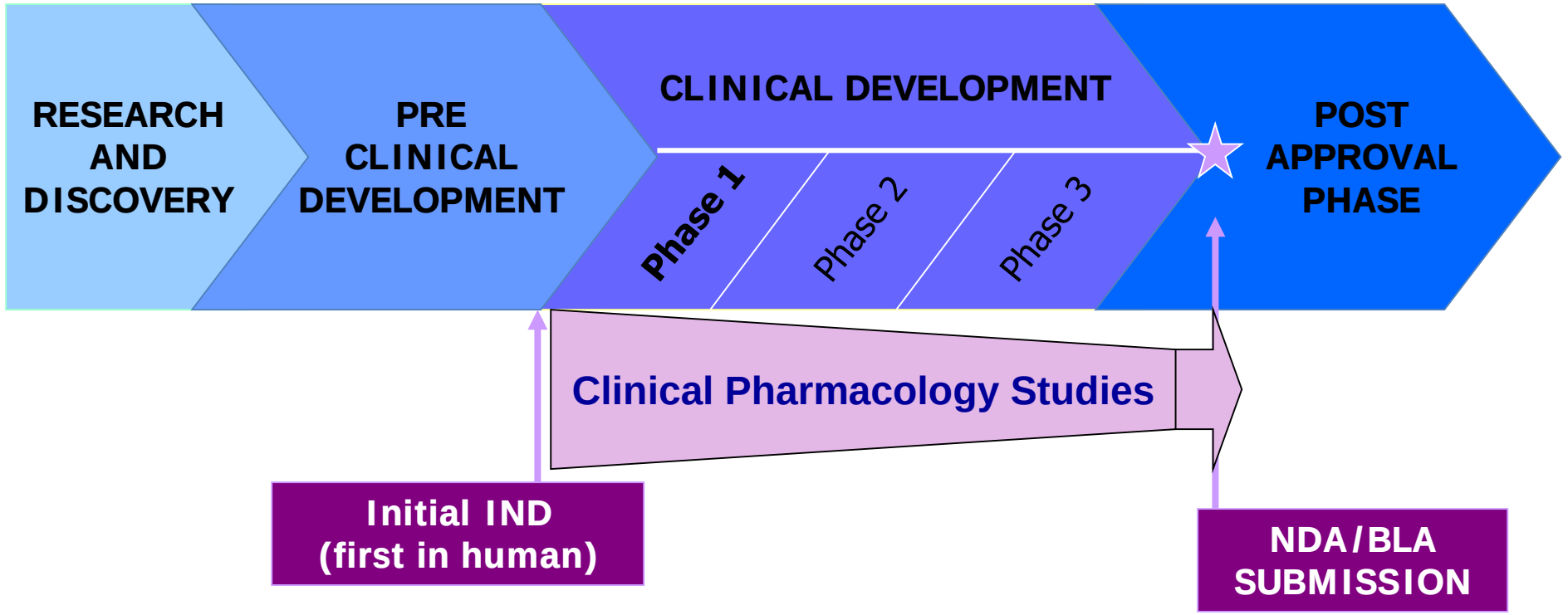
Commonly referred to as an exposure-response (ER) profile

PK and Drug Effect



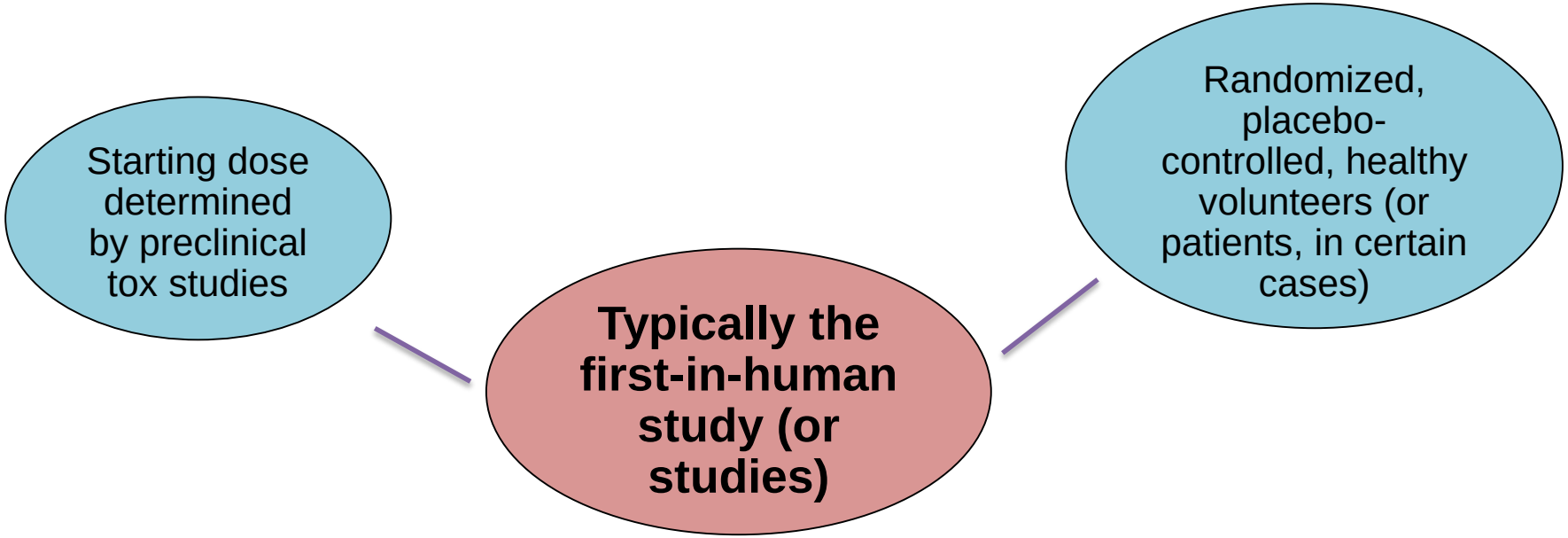
Clinical Pharmacology Studies

Timing



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

First-in-Human Study



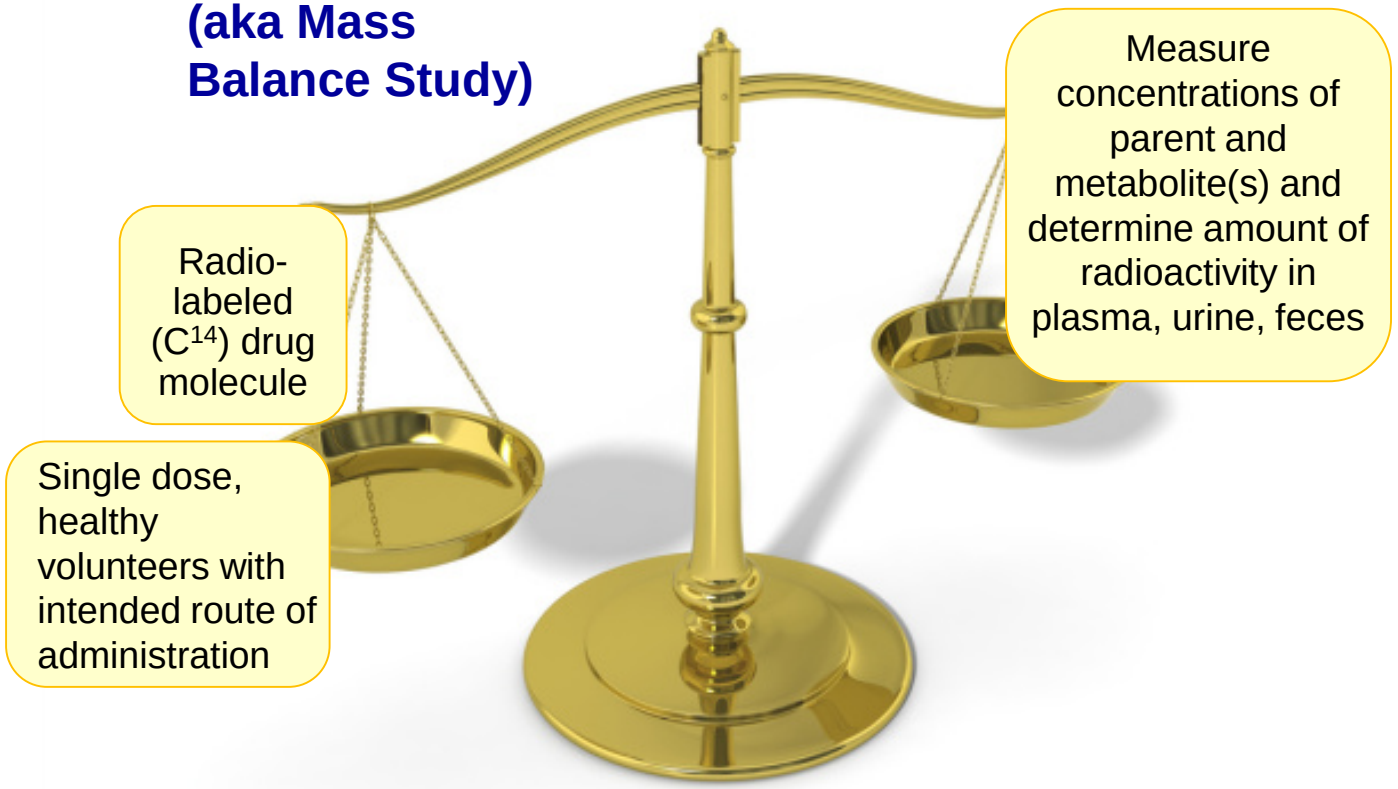
Information gained:

-Safety/tolerability, identify maximum tolerated dose
-General PK characteristics, variability, linearity, dose proportionality
-Steady-state parameters
-Preliminary exploration of drug elimination

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.

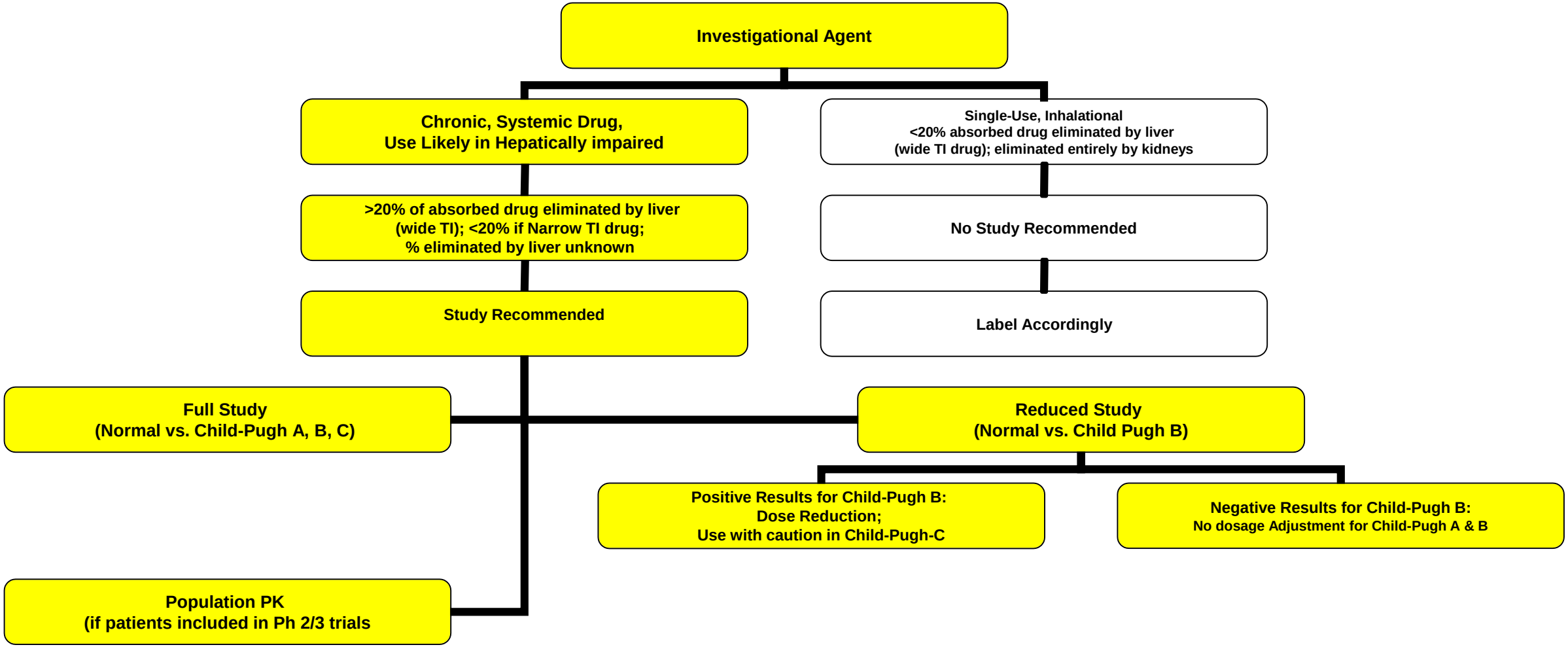
Information gained:

-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



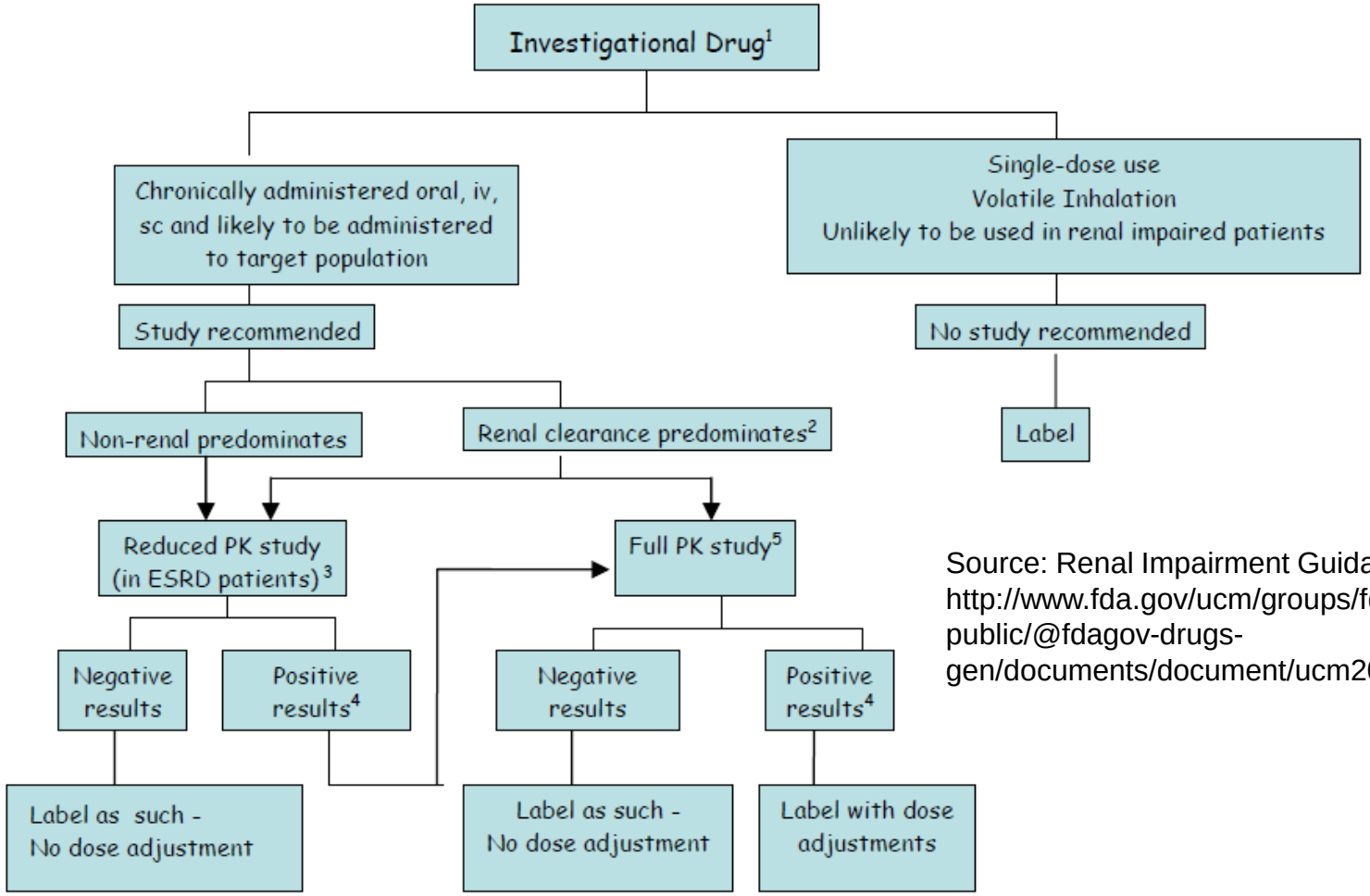
[1]Source: Hepatic Impairment guidance (2003): http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm072123.pdf

Hepatic Impairment Study

- **Study Designs:**
- Full study design: Single dose, parallel groups, males & females with varying degrees of hepatic impairment (≥6 per group)
  - Normal Hepatic Function (matched for age, sex, & BW to subjects with hepatic impairment)
  - Child-Pugh Class A (Mild)
  - Child-Pugh Class B (Moderate)
  - Child-Pugh Class C (Severe)
- Reduced study design: Normal vs. Child-Pugh B (Moderate) (≥8 per group)
- Pop-PK approach (pre-planned analysis):
  - Should include patients w/ varying degrees of hepatic impairment in phase 2 and 3 trials
  - Should include appropriate evaluation of severity of liver disease

Information gained:
-Effect of hepatic impairment on PK of parent drug and metabolites
-Dosage recommendations for various stages of hepatic impairment

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

Renal Impairment Study

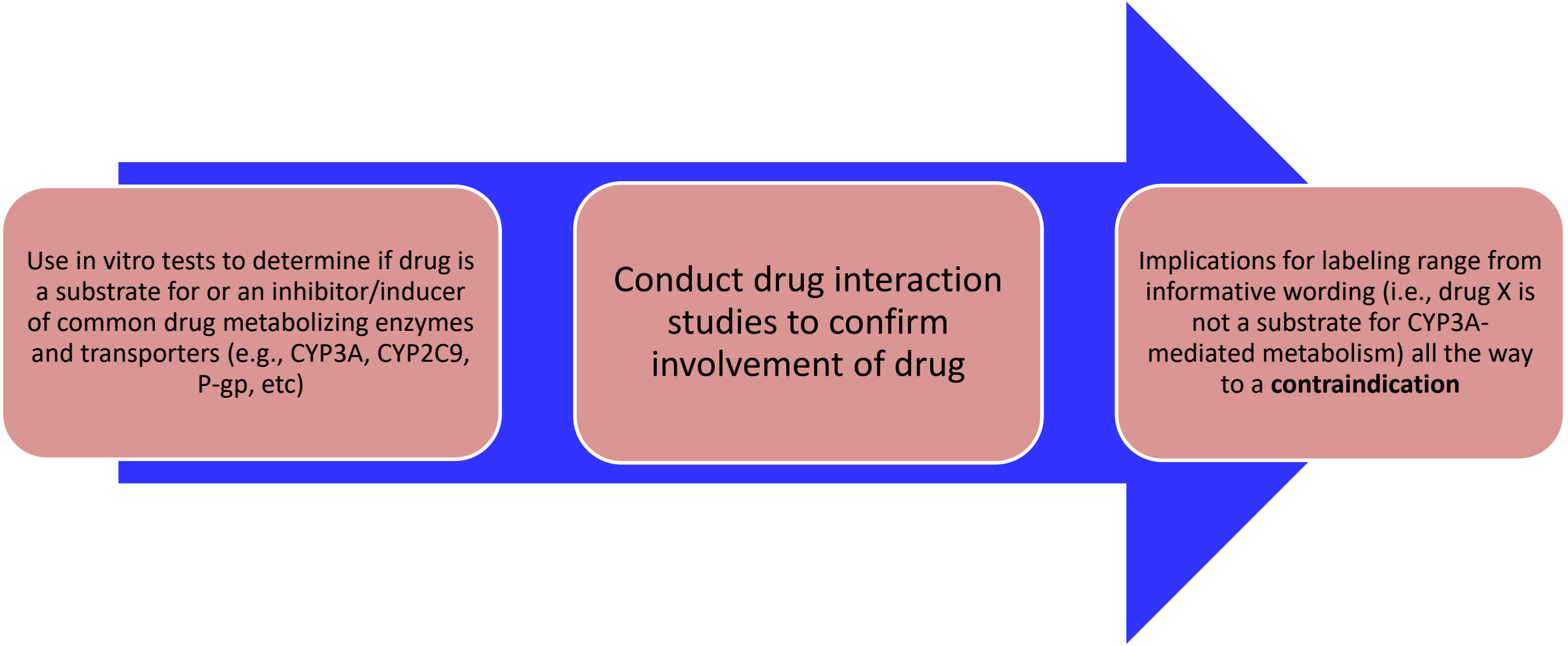
- **Study designs:**
- Full study design:
- Generally single dose, parallel groups, “healthy” males and females with varying degrees of renal function (≥6 per group, based on CrCl):
  - Normal (≥90 mL/min)
  - Mild (60-89 mL/min)
  - Moderate (30-59 mL/min)
  - Severe (15-29 mL/min)
  - ESRD (<15 mL/min) dialysis and non-dialysis
- Reduced study design:
- Same general design as full, except only study severes and normals
- Pop-PK approach
- Include appropriate number of subjects in each impairment group

Information gained:

-Effect of renal impairment on drug clearance; dosage recommendations for various stages of renal impairment

-Effect of hemodialysis (HD) on drug exposure; info on whether dialysis could be used as treatment for drug overdosage

Drug Interaction Studies



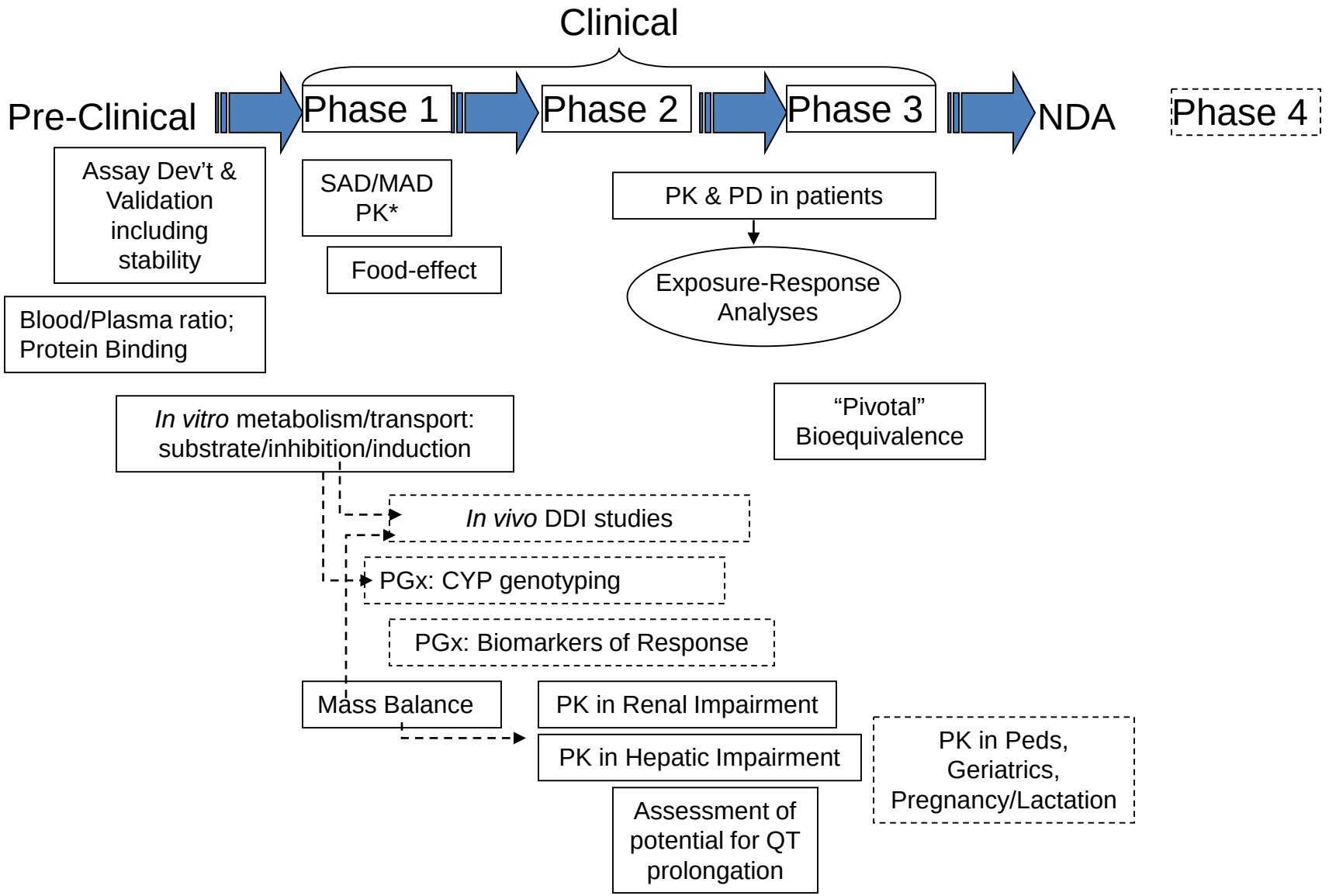
Additional detailed information can be found in the Guidance for Industry: Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications (2017)

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:
  - e.g., Drug causes ≥ 5-fold increase in midazolam AUC → "potent" inhibitor of CYP3A4
- Exposure-response information on the drug is important in assessing the clinical significance of the change in AUC of substrate by inhibitor/inducer.

Timing of Early and Clinical Pharmacology Studies



What do we need to know?

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?
    - Will impact the design of some studies
  - 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)?
    - May affect duration or timing of studies for PK profiling

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

Parent Drug and Active Metabolites:

- T_{max}
  -represents the most appropriate time(s) to perform safety assessments (e.g., vital signs, ECG, other immediate PD effects)
- t½
  - considered when determining dosage interval
  - related to time to steady state (t_{ss}) after dose initiation or dose adjustment; considered in evaluating need for a loading dose
  - influences the duration of monitoring after dosing and follow-up after withdrawal of therapy
  - determines adequate washout period between treatments (in crossover studies)
- Cmax, Cmin, AUC
  - important for dose selection (eg. PK/PD parameters predicting efficacy of anti-infective drugs)

Clinical Pharmacology Guidance Documents

- General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products (2014)
- Clinical Drug Interaction Studies (2017)
- In vitro Drug Interaction Studies (2017)
- Clinical Pharmacogenomics (2011)
- Clinical Lactation Studies (2005)
- Pharmacokinetics in Patients with Impaired Hepatic Function (2003)
- Pharmacokinetics in Patients with Impaired Renal Function (2010)
- Pharmacokinetics in Pregnancy (2004)
- Population Pharmacokinetics (1999)
- Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications (2003)

Site: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm

Biopharmaceutics Guidance Documents

- Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (2015)
- Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and 3 Drugs Guidance for Industry (2015)
- Bioanalytical Method Validation (2013)
- Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations (2014)
- Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application (2013)
- Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action (2003)
- Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations (1997)
- Food-Effect Bioavailability and Fed Bioequivalence Studies (2002)
- Statistical Approaches to Establishing Bioequivalence (2001)

Site: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064964.htm

The impact on labeling

Phase 1 Studies: Impact on Labeling

FULL PRESCRIBING INFORMATION:

Food Effect Example:
REYATAZ® (atazanavir) oral capsules

- Administration of a single dose of atazanavir (800 mg) with a light meal increased Cmax by 57% and AUC by 70%; a high-fat meal increased AUC by 35% with no change in Cmax. The %CVs of AUC and Cmax decreased by approximately one-half compared to the fasting state.

- Clinical trials were conducted under fed conditions.

Label directs administration with food.

Source: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021567s039,206352s004lbl.pdf

Renal Impairment Example:
DORIBAX® (doripenem) powder for IV use

- In an ADME study, ~93% of the dose was excreted in urine by 12 hours.
- Because doripenem is primarily eliminated by the kidneys, a full PK study in patients with renal impairment was conducted. The study demonstrated a significant difference in PK between patients with moderate and severe renal impairment compared to those with normal renal function. Also, 52% of the dose was recovered in the dialysate following dialysis.
- In Phase 2/3 trials, dosage was adjusted based on CrCL.

The label recommends dosage reduction for patients with moderate or severe renal impairment… and hemodialysis as a treatment for overdosage.

Source: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022106s015lbl.pdf

Hepatic Impairment Example:
ISENTRESS® (raltegravir) oral tablets

- A mass balance study showed that raltegravir is eliminated primarily by glucuronidation in the liver. Renal clearance is a minor pathway of elimination.
- In the hepatic impairment study (reduced study design), there were no clinically significant pharmacokinetic differences between subjects with moderate hepatic impairment and healthy subjects.
- PopPK analysis of Phase 2/3 trial data further indicates that the PK of raltegravir in Child Pugh B patients were not different from patients with normal hepatic function.

Labeling states: No dosage reduction for patients with moderate or mild hepatic impairment is recommended. The effect of severe hepatic impairment on the PK of the drug was not studied.

Source:
http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022145s035,203045s012,205786s003lbl.pdf

To Summarize, Clinical Pharmacology Studies…

- Are conducted to gain a fundamental understanding of the pharmacokinetics (PK; exposure) and the pharmacodynamics (PD; biologic effect) of the drug.
- Provide useful information for the design of Phase 3 clinical trials (e.g., using dose-response and exposure-response analyses).
- Inform patient care
  - identification of appropriate dosing regimen(s) in relevant patient subpopulations

Acknowledgements

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- Sarah Robertson, Pharm.D.