Clinical Pharmacology 1: Phase 1 Studies and Early Drug Development

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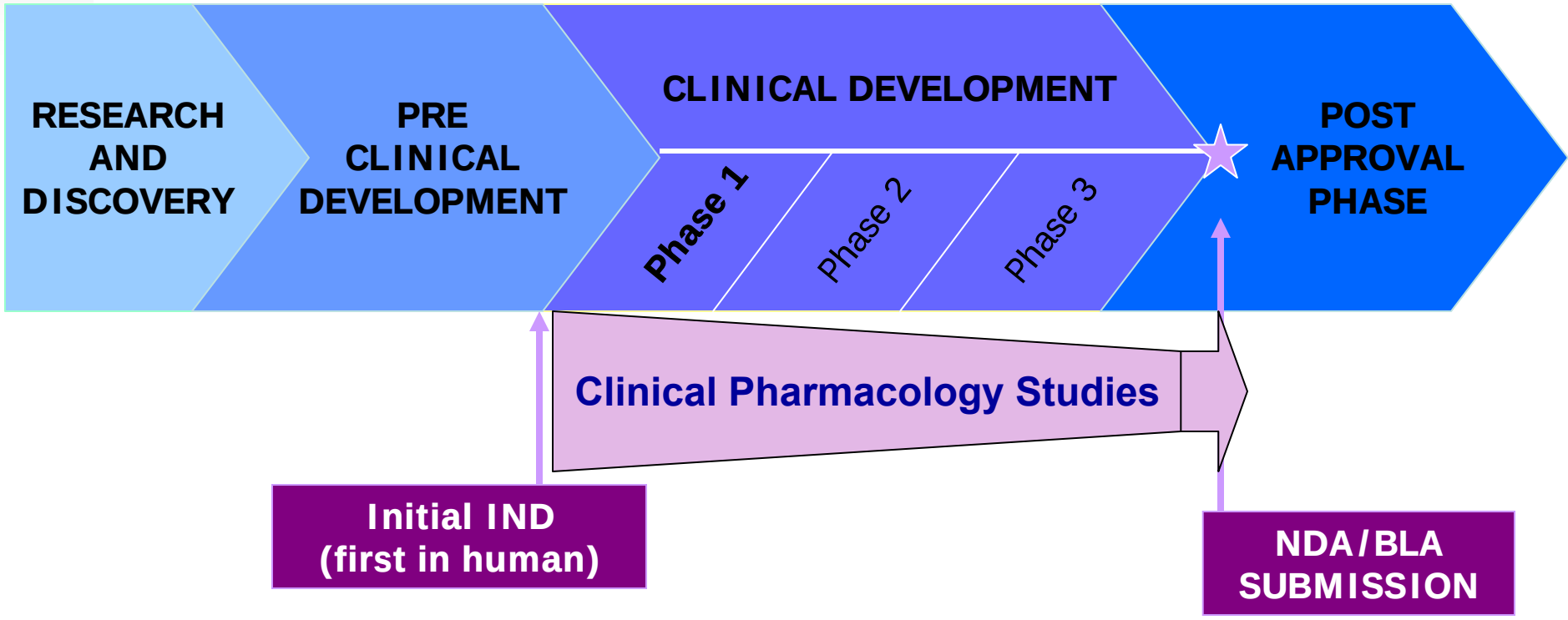
U.S. Department of Health and Human Services
Food and Drug Administration

Objectives

- Outline the Phase 1 studies conducted to characterize the Clinical Pharmacology of a drug; describe important design elements of and the information gained from these studies.
- List the Clinical Pharmacology characteristics of an Ideal Drug
- Describe how the Clinical Pharmacology information from Phase 1 can help design Phase 2/3 trials
- Discuss the timing of Clinical Pharmacology studies during drug development, and provide examples of how the information generated could impact the overall clinical development plan and product labeling.

Phase 1 of Drug Development



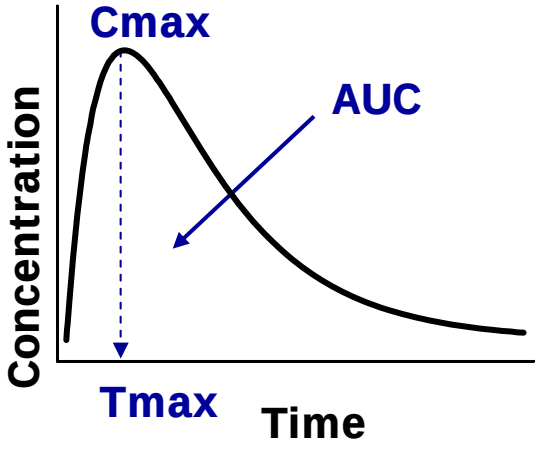
Phase 1

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

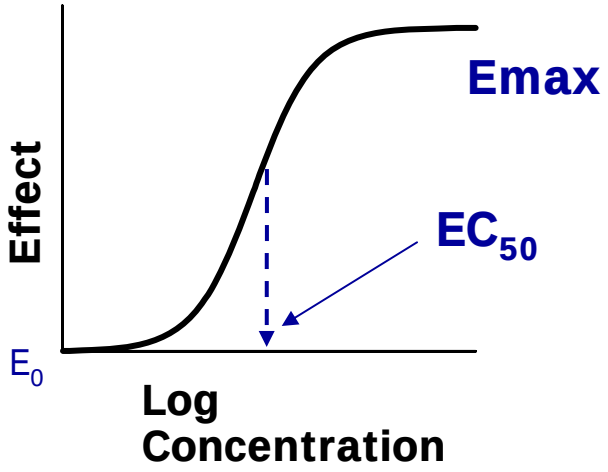
Clinical Pharmacology

- Study of the Pharmacokinetics (PK) and Pharmacodynamics (PD) of the drug in humans
  - PK: what the body does to the drug (Absorption, Distribution, Metabolism, Excretion)
  - PD: what the drug does to the body
- PK and PD profiles of the drug are influenced by physicochemical properties of the drug, product/formulation, administration route, patient's intrinsic and extrinsic factors (e.g., organ dysfunction, diseases, concomitant medications, food)

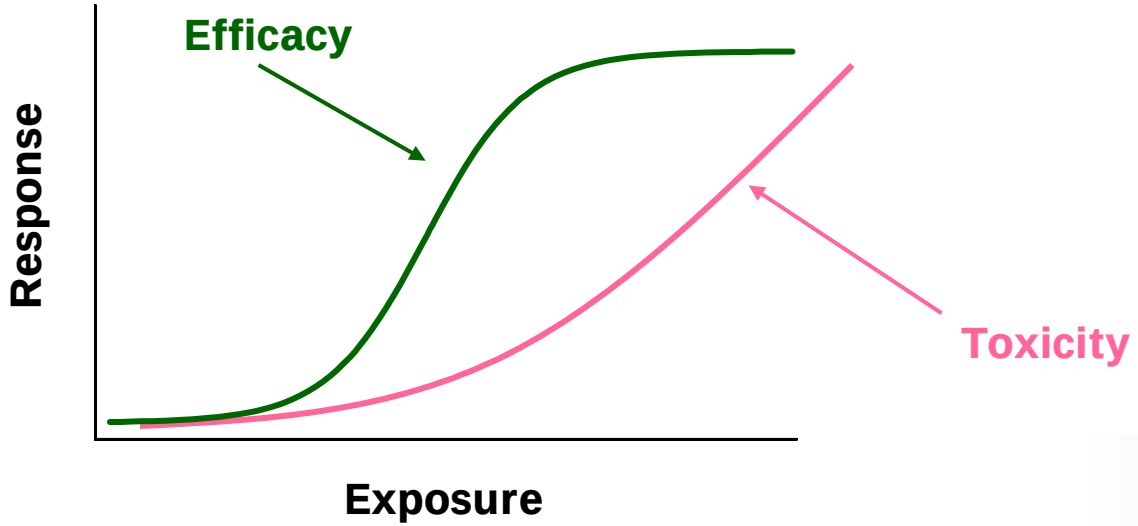
PK


Cmax
AUC
Concentration
Tmax
Time

PD


Emax
Effect
EC50
E0
Log
Concentration

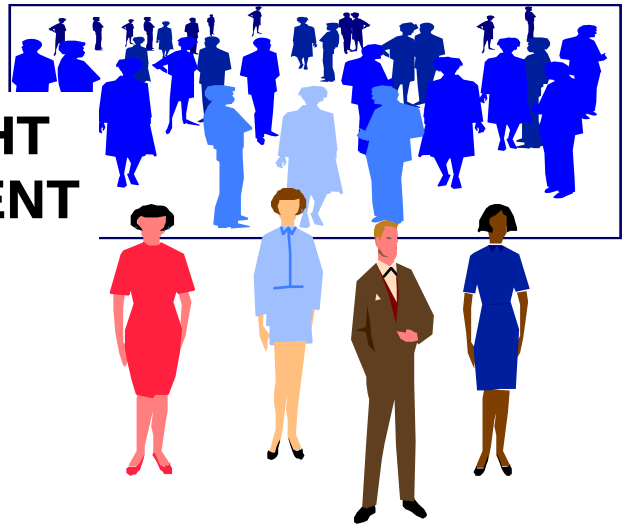
E/R


Efficacy
Response
Toxicity
Exposure

The Ultimate Goal:

RIGHT DRUG

RIGHT PATIENT

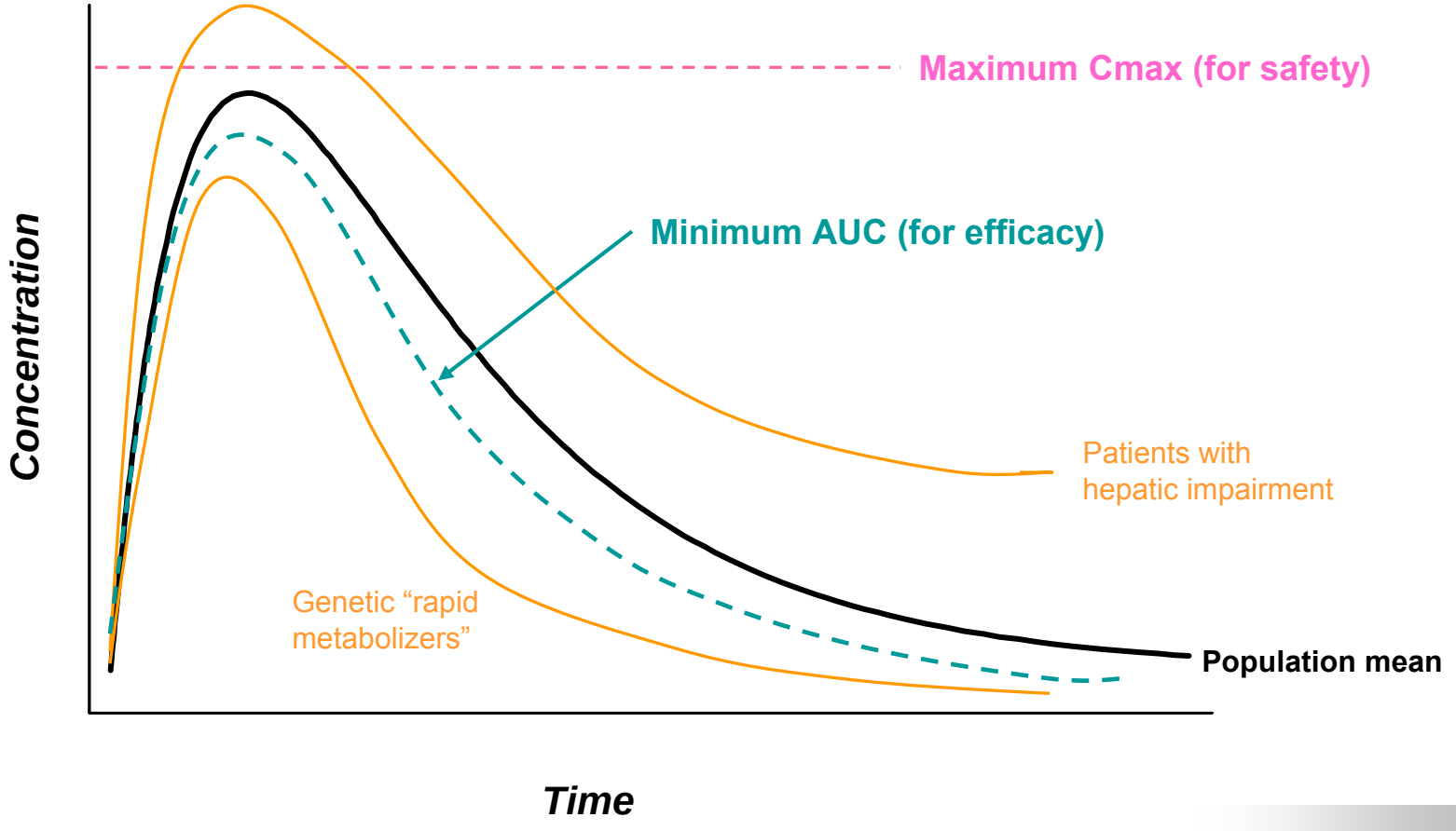


GOAL

RIGHT DOSE

RIGHT TIME

To determine the dose/dosing regimen that achieves target drug exposures in all relevant populations



How do we achieve the goal?

Clinical Pharmacology

- First-in-Human
- SAD and MAD PK Studies
- Healthy vs. Patient population
- ADME (Mass Balance)
- Specific Populations
  - Renal Impairment
  - Hepatic Impairment
  - Age, gender, etc.
  - Pediatrics
- Drug Interactions
- Population PK
- Biomarkers
- Pharmacogenomics
- Special Safety (e.g., TQTc study)

Exposure-response (PK/PD)

- Dose selection and optimization
- Efficacy vs. Safety
- Quantitative approaches
  - Clinical trial simulation
  - Disease models

Biopharmaceutics

- Bioavailability/Bioequivalence (BA/BE)
- Food Effect

***In Vitro* Studies**

- Protein Binding
- Blood to Plasma Partitioning
- In vitro drug metabolism, transport and drug interactions

Bioanalytical Methods

- Assay Validation & Performance Reports

Biologics only

- Immunogenicity
- Comparability

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Single Dose/Multiple Dose Escalation Studies

- Typically the first-in-human study (or studies)
- Randomized, placebo-controlled, healthy volunteers (or patients, in certain cases)
- Starting dose determined by preclinical toxicology studies
- Information gained:
  - Safety/tolerability, identify maximum tolerated dose (MTD)
  - General PK characteristics, variability, linearity, dose proportionality
  - Steady-state parameters (accumulation, time-dependency)
  - Preliminary exploration of drug elimination (urine PK, metabolite identification)

ADME (i.e. Mass Balance) Study*

- Objective: To understand the full clearance mechanisms of the drug and its metabolites in humans
- Typically single dose, healthy males (n=4-6), at intended route of administration
- Radio-labeled (C^{14}) drug molecule
- Measure concentrations of parent and metabolite(s) and determine amt of radioactivity in plasma, urine, feces
- Information gained:
  - Primary mechanism(s) of elimination and excretion from the body
  - Proportion of parent drug converted to metabolite(s)

* Not usually done with high MW therapeutic proteins

BA/BE Studies

- Objective: To evaluate the rate (Cmax, Tmax) and extent (AUC) of *absorption* of drug from a test formulation (vs. reference formulation)
- **BA**:Typically, crossover, single dose (if linear PK) study in healthy subjects; measure blood/plasma conc. of parent drug and major active metabolites for ≥ 3 t½

  BE: crossover study in fasted healthy subjects given single doses of test & reference products administered at same molar doses; measure blood/plasma conc. of parent drug only
- "Pivotal" BE study required to bridge the to-be-marketed formulation (test) to that used in Phase 3 clinical trials (reference)
- BE acceptance criteria: 90% CI of the geometric mean ratios of Cmax & AUC between test and reference fall within 80-125%
- Information gained:
  - Relative BA, Absolute BA of drug from a formulation
  - BE (no significant difference in BA) of test vs. reference

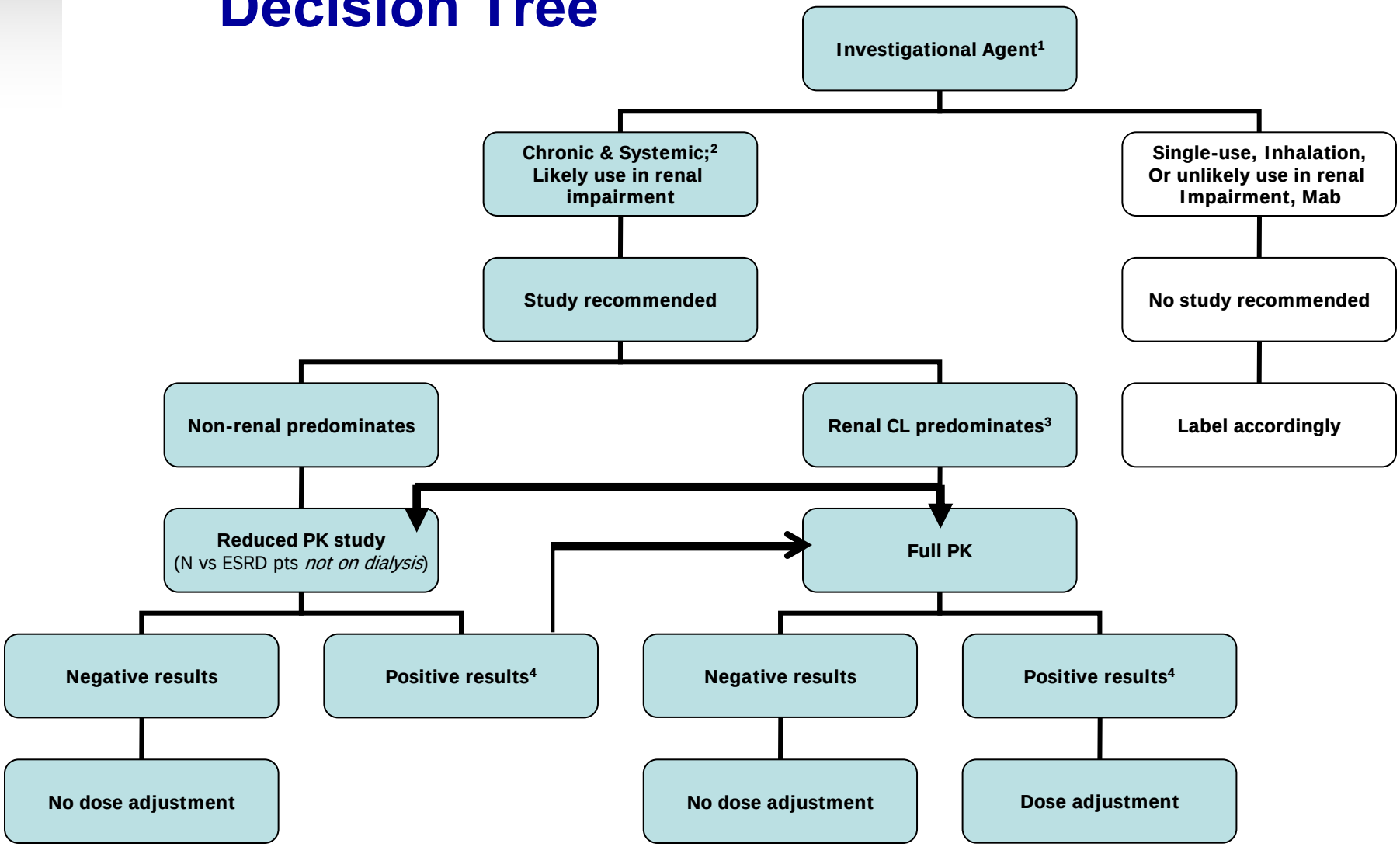
Food Effect Study

- Objective: To evaluate the effect of food on rate and extent of drug absorption from a given formulation
- Single dose, crossover, two-treatment (fed vs fasted), two-period, two-sequence study in healthy subjects (n ≥ 12 with data); use highest strength of drug product; fed: FDA high-fat high-calorie meal
- 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 could be determined based on drug's exposure-response profile.
- Information gained:
  - effect of food on the BA of oral drugs
  - Labeling instructions on whether to administer drug on empty stomach or without regard to meals

FDA

* Not usually done with therapeutic proteins

Renal Impairment Study Decision Tree



[1] Metabolites (active/toxic) – same decision tree

[2] Includes cytokines or cytokine modulators with MW <69 kDa

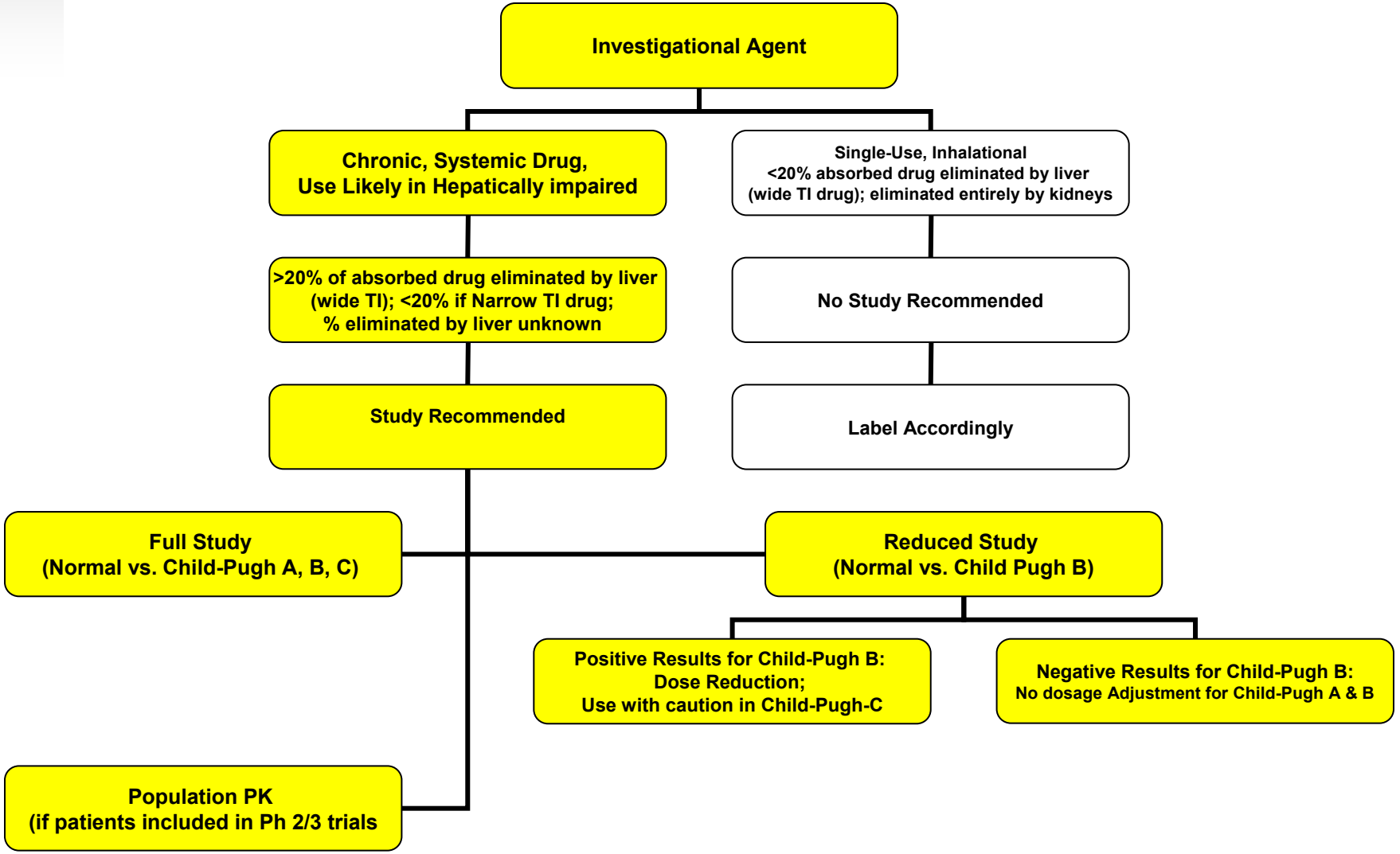
[3] Option to do either full or reduced study or Pop PK Analysis of Ph 2/3 data

[4] >50% increase in AUC; < for Narrow TI drugs

Renal Impairment Study
Full Study Design

- Single dose (if linear & time independent PK), parallel groups, “healthy” males and females with varying degrees of renal function (≥6 per group)
- Calculate CrCl via Cockcroft-Gault; eGFR via MDRD
- Stratification (based on CrCl): Normal (≥90 mL/min), Mild (60-89 mL/min), Moderate (30-59 mL/min) and Severe Impairment (15-29 mL/min), ESRD (<15 mL/min) dialysis and non-dialysis
- 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

Hepatic Impairment Study Decision Tree



Hepatic Impairment Study

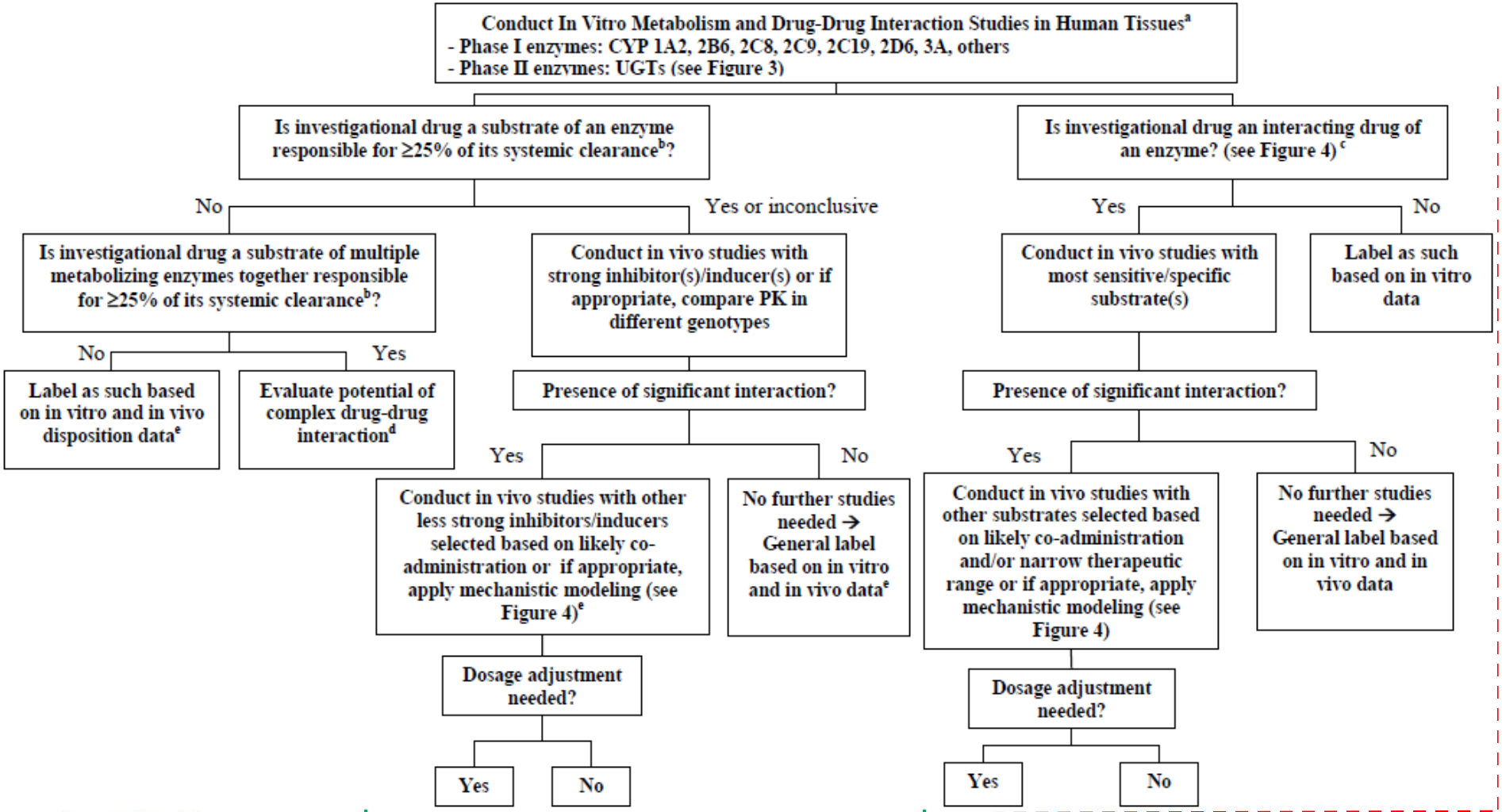
- **Study Designs:**

  (1) Full Study: Single dose (if linear & time-independent PK), parallel groups, males & females with varying degrees of hepatic impairment (≥6 per group)
  - Normal Hepatic Function (matched for age, gender & BW to subjects with hepatic impairment)
  - Child-Pugh Class A (Mild)
  - Child-Pugh Class B (Moderate)
  - Child-Pugh Class C (Severe)

  (2) Reduced Study: Normal vs. Child-Pugh B (Moderate) (≥8 per group)

  (3) Pop-PK approach
- If drug is metabolized by enzyme with genetic polymorphisms (e.g. CYP2C19, CYP2D6), genotype status of subjects should be assessed and considered during PK data analysis.
- **Information gained:**
  - Effect of hepatic impairment on PK of parent drug and metabolites
  - Dosage recommendations for various stages of hepatic impairment

Drug Interaction Studies -
Decision Tree for Metabolism-Based DDIs (Draft)



*"cocktail" approach OK

Drug Interaction Studies

- Objective: To evaluate potential of investigational drug as an inhibitor/inducer (I) and substrate (S) of certain metabolizing enzymes/transporters
- Preferably crossover design (parallel - if long t½ drug); healthy subjects (or patients for safety considerations or if desirable to evaluate PD endpoints)
- The choice of doses/dosing intervals/dosage forms of substrate and inhibitor/inducer, routes & timing of co-administration, number of doses should maximize possibility of detecting an interaction and mimic the clinical setting, with due consideration for safety of study population.
- 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.

Thorough QT Study (TQT)

- In vivo safety study required for all systemically available NMEs (regardless of *in vitro* or non-clinical findings)
- Objective: To identify drugs that prolong QT(95% CI upper bound ≥ 10 ms) that need a more thorough ECG monitoring in pivotal trials; TQT study conducted prior to Phase 3 trials
- Usually, single dose study in healthy subjects; evaluate therapeutic and "supratherapeutic" doses of drug versus positive control (e.g., moxifloxacin)
- ICH Guidelines, E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs
  - Recommendations for design, conduct, analysis, and interpretation of clinical studies
-

Desirable Clinical Pharmacology Properties of a Drug

- **ABSORPTION:**
  - High absolute bioavailability with low variability
  - Exhibits linear PK over therapeutic dose range, i.e. dose-proportional increases in Cmax, AUC
    - Single-dose study design sufficient: BA, PK in renal impairment, hepatic impairment & DDI
  - AUC, Cmax not significantly affected by concomitant food, pH-altering medications, grapefruit, alcohol, etc.
  - BCS Class I (high solubility + high permeability)
    - can qualify for biowaiver of future additional BA/BE studies

Desirable Clinical Pharmacology Properties of a Drug

- **DISTRIBUTION:**
  - Reaches the target site(s) of action immediately and at effective/nontoxic concentrations; doesn't accumulate in non-target organs
    - Local (targeted) application advantageous over systemic administration
  - Not significantly (>80 to >95%) bound to plasma proteins; extent of protein binding not concentration- and time-dependent
    - only free or unbound drug is active
    - less prone to DDI with highly-protein drugs (e.g., warfarin)
    - PK in terms of total drug concentrations often sufficient (e.g., in PK studies in renal and hepatic impairment)

Desirable Clinical Pharmacology Properties of a Drug

- **METABOLISM/EXCRETION:**
  - Not extensively metabolized or not exclusively metabolized by a CYP450 enzyme
    - CL less likely to be affected by hepatic impairment and/or concomitant administration of other drugs that affect one or more metabolizing enzymes
  - Not metabolized by polymorphic enzymes (e.g., CYPs 2D6, 2C19, 2C9, NAT2)
    - does not require genotyping in PK and other clinical studies
  - CL not highly variable depending on 'covariates' as age, race, gender, disease/comorbidities
  - CL not time-dependent (e.g., metabolic auto-induction, diurnal variation)
    - may require longer duration of studies for PK profiling

Desirable Clinical Pharmacology Properties of a Drug

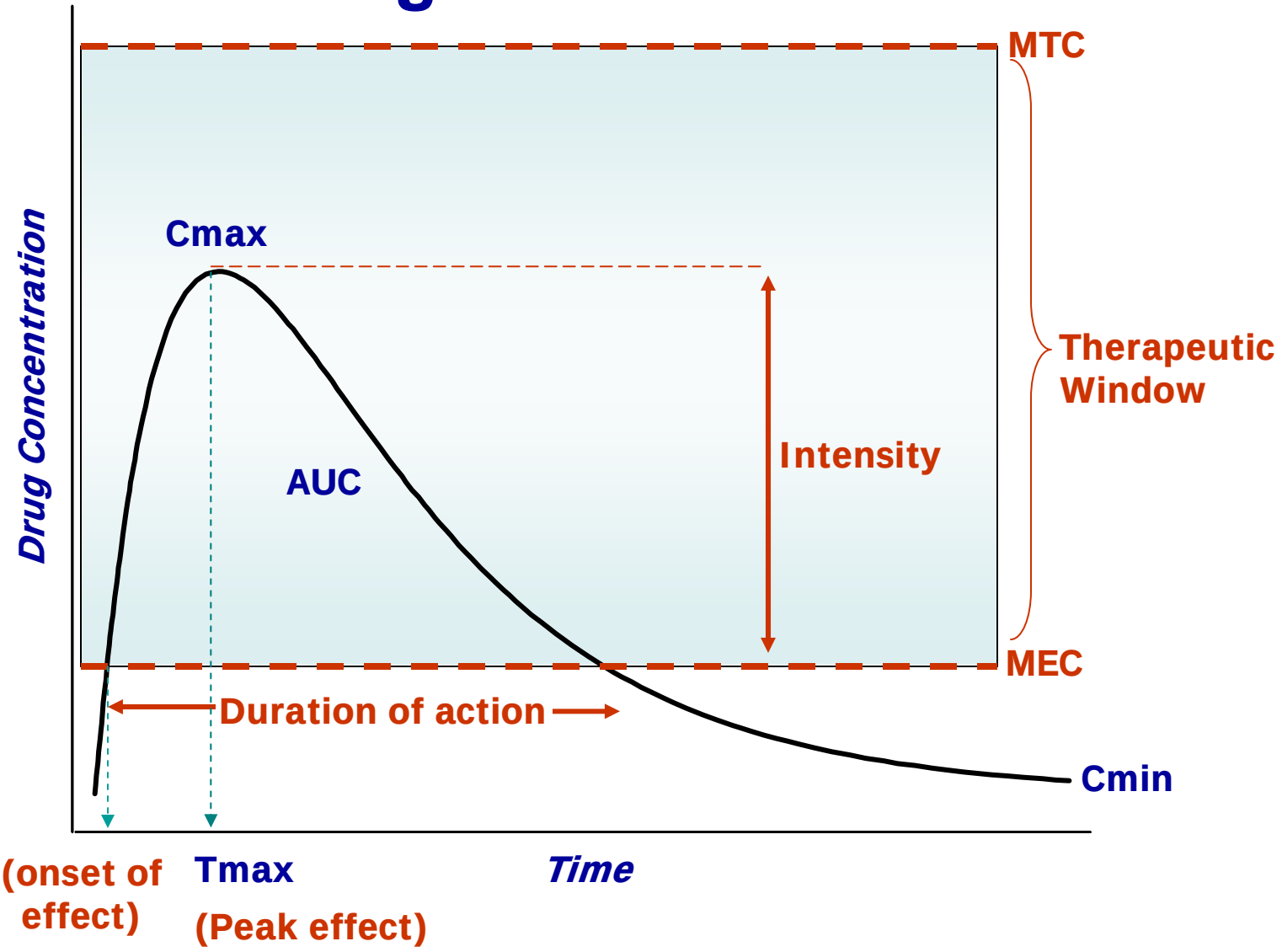
- **OTHERS:**
  - Not a Narrow Therapeutic Index Drug
    - slight changes in drug exposure less likely to impact efficacy/safety
    - less likely to require therapeutic drug monitoring in clinical trials and clinical practice to minimize toxicities and lack of efficacy
  - Does not prolong the QT interval
    - less likely to have TdP risk
  - Not a significant inhibitor or inducer of CYP3A, P-gp, etc.
    - less likely to have DDI with concomitantly administered drugs
  - Does not trigger formation of neutralizing anti-drug antibodies or organ-damaging immune complexes (immunogenicity)

PK Parameters and Design of Phase 2/3 Trials

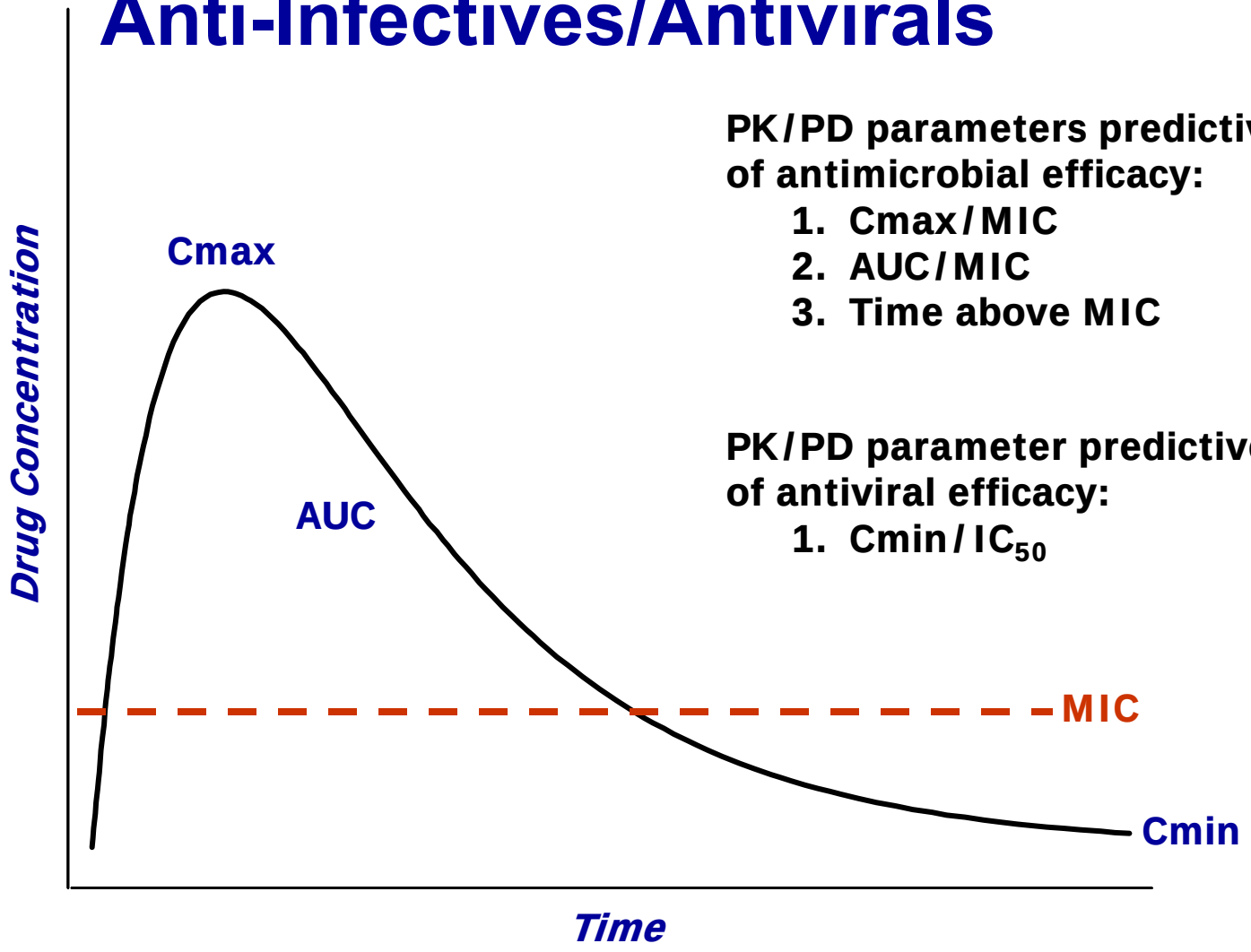
Parent Drug and Active Metabolites:

- T_{max}
  -represent 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 (viewed relative to MEC and MTC)
    eg. PK/PD parameters predicting efficacy of anti-infectives

PK and Drug Effect



PK and Drug Effect EXAMPLE: Anti-Infectives/Antivirals



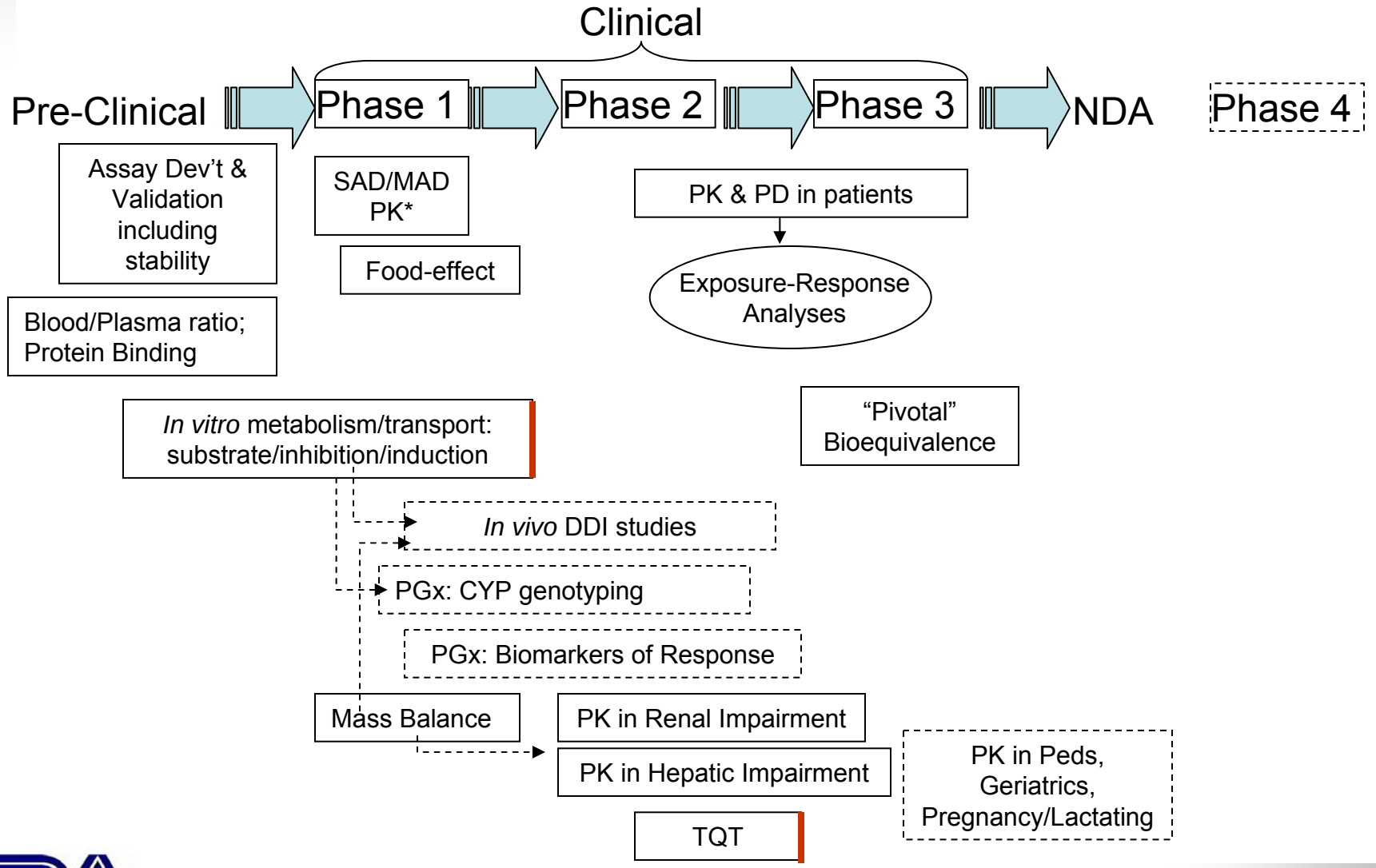
PK/PD parameters predictive of antimicrobial efficacy:

1. Cmax/MIC
2. AUC/MIC
3. Time above MIC

PK/PD parameter predictive of antiviral efficacy:

1. Cmin/IC_{50}

Timing of Early and Clinical Pharmacology Studies



Phase 1 Studies: Impact on Labeling

FULL PRESCRIBING INFORMATION:

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
- **8.1 Pregnancy**
- **8.2 Labor and Delivery**
- **8.3 Nursing Mothers**
- **8.4 Pediatric Use**
- **8.5 Geriatric Use**

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Clinical Pharmacology Guidance Documents

- Clinical Lactation Studies (2005*)
- Clinical Pharmacogenomics (2011*)
- Drug Interaction Studies (2012*, 2006,1999,1997)
- Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro (1997)
- General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products (1998*)
- In Vivo Drug Metabolism/Drug Interaction Studies (1999)
- Pharmacokinetics in Patients with Impaired Hepatic Function (2003)
- Pharmacokinetics in Patients with Impaired Renal Function (2010*, 1998)
- Pharmacokinetics in Pregnancy (2004*)
- Population Pharmacokinetics (1999)
- Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications (2003)

FDA

* Draft

Biopharmaceutics Guidance Documents

- Bioanalytical Method Validation (2001)
- Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action (2003*)
- Bioavailability and Bioequivalence Studies for Orally Administered Drug Products (2003)
- Dissolution Testing of Immediate Release Solid Oral Dosage Forms (1997)
- 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)
- Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (2000)

FDA

* Draft

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 a meal or snack.

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

- In a radiolabeled ADME study, approximately 93% of the dose was excreted in the urine by 12 hours. Less than 1% of the total radioactivity was recovered in feces after one week.
- Because doripenem is primarily eliminated by the kidneys, a Full PK study in patients with renal impairment was conducted.
- 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.

Hepatic Impairment Example: ISENTRESS® (raltegravir) oral tablets

- *In vitro* metabolism studies using human liver microsomes indicated that raltegravir is not a substrate of CYP450 enzymes but is metabolized mainly by UGT1A1. 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 PK-Hepatic Impairment Study (Reduced Study Design), there were no clinically important 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 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.

Drug Interaction Example: BOSULIF® (bosutinib) oral tablets

- Bosutinib is extensively metabolized; only 3% of the dose is excreted unchanged in the urine.
- *In vitro,* bosutinib was shown to be a CYP3A substrate but not a CYP3A inhibitor or inducer.
- *In vivo*, bosutinib AUC ↑ 9x with ketoconazole (a strong CYP3A inhibitor), ↓ by 93% with rifampin (strong CYP3A inducer).
- PBPK Modeling *predicted* bosutinib AUC ↑ 2-4x with moderate CYP3A inhibitors and no change with weak CYP3A inhibitors.
- Since bosutinib is a sensitive* CYP3A substrate, the labeling states: Avoid concomitant use with all strong or *moderate* CYP3A inhibitors or inducers.
- PMR study with erythromycin recommended to determine dosage adjustment needed when given with moderate CYP3A inhibitors

* Sensitive CYP substrate – ↑AUC ≥ 5x by CYP inhibitor