U.S. Food and Drug Administration

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Principles and Applications of Pharmacokinetics in Drug Development

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Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research

Small Business Assistance Workshop, September, 2011

Outline

- What is pharmacokinetics
- Different types and applications of pharmacokinetic studies
- Bioequivalence studies
- Data quality check and Biomedical Monitoring (BIMO) program in Office of Scientific Investigations

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Pharmacokinetics (PK)

- A study of movements of drugs within biologic systems over a period of time; a quantitative analysis of the time course of a drug disposition
  - Absorption
  - Distribution
  - Metabolism
  - Excretion
- Often described as “what the body does to a drug” (vs. “what a drug does to the body”)

Pharmacodynamics (PD): How it is related to PK

- Study of the effects of drugs in the body and their mechanisms of action
  - "What a drug does to the body"
- Pharmacodynamic markers in drug development

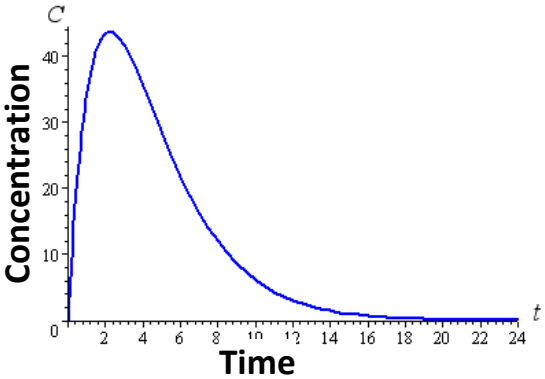
- Absorption
- Distribution
- Metabolism
- Excretion

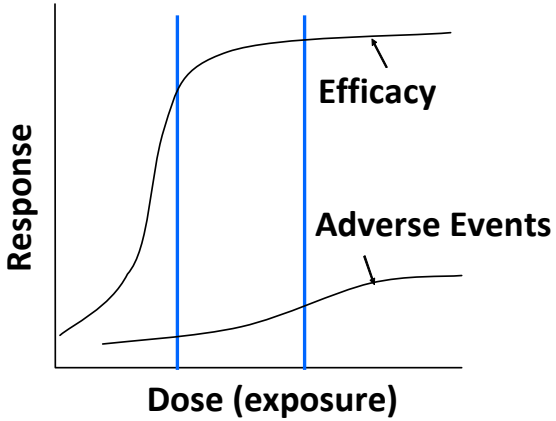
Right Drug

Right Patients

Safe and Effective
Personalized
Medicine

Right Dose





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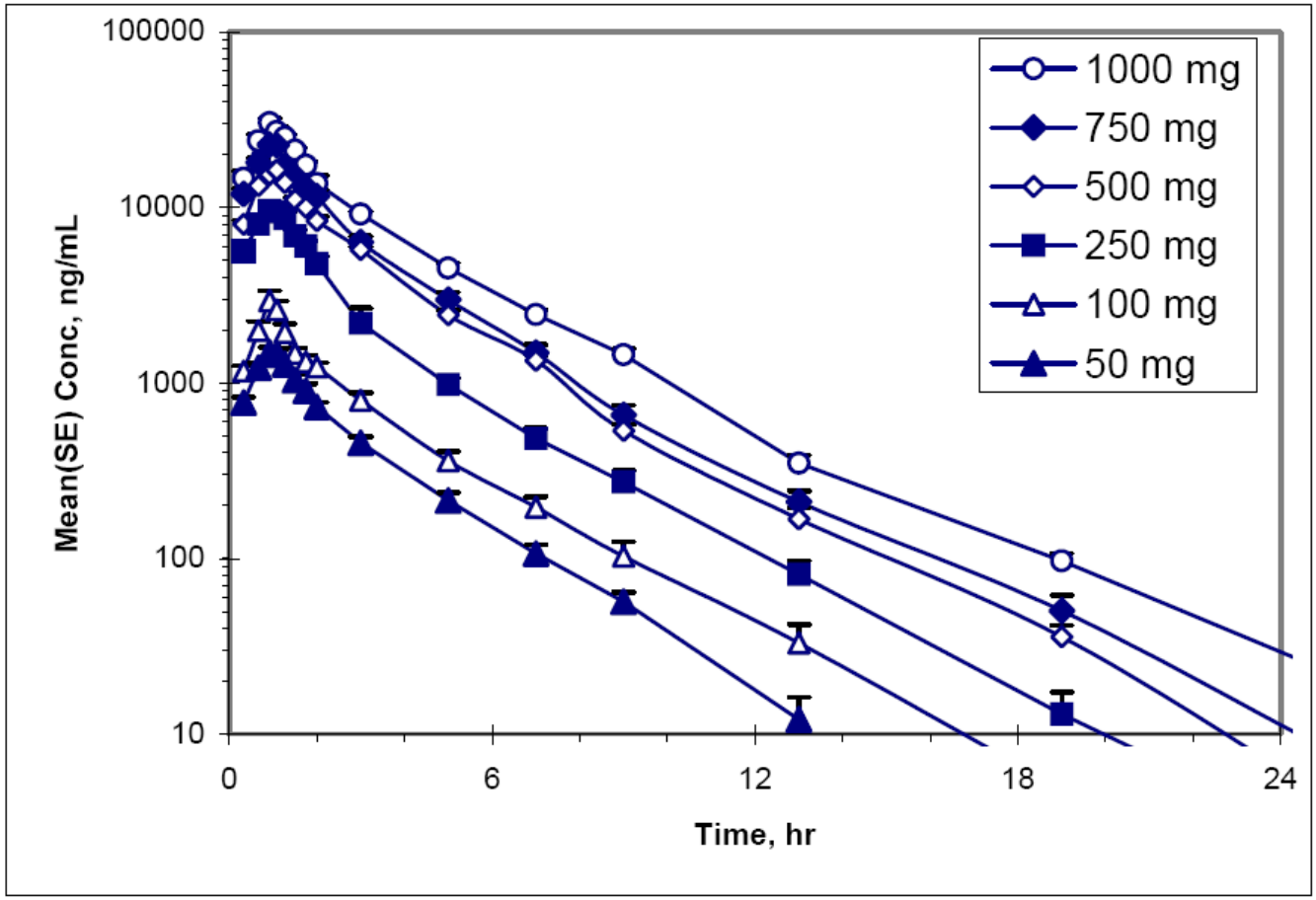
Types of Phase 1 PK Studies

- Single dose/multiple dose PK
- Mass balance (ADME)
- Bioavailability/bioequivalence
- Food effect (oral formulations)
- Specific populations
  - age/gender
  - renal impairment
  - hepatic impairment
  - obesity
- Drug-drug interactions
- Thorough QTc (cardiac repolarization)

Single Dose PK Study

- Often a fist-in-human study
- Usually performed in healthy male and female subjects
- To assess the pharmacokinetics of the compound across a range of doses (including clinically relevant doses)
- Determine linearity and dose proportionality

Single-Dose Concentration-Time Profiles

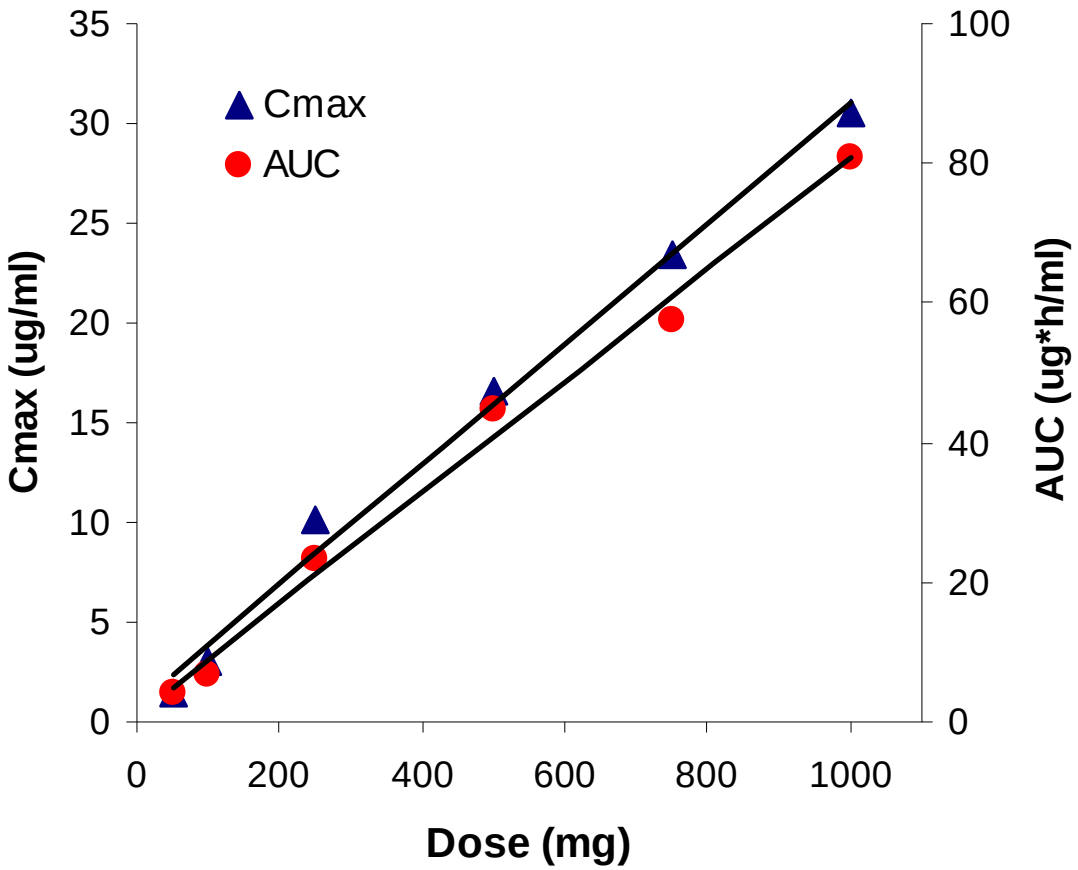


Single-Dose PK Parameters

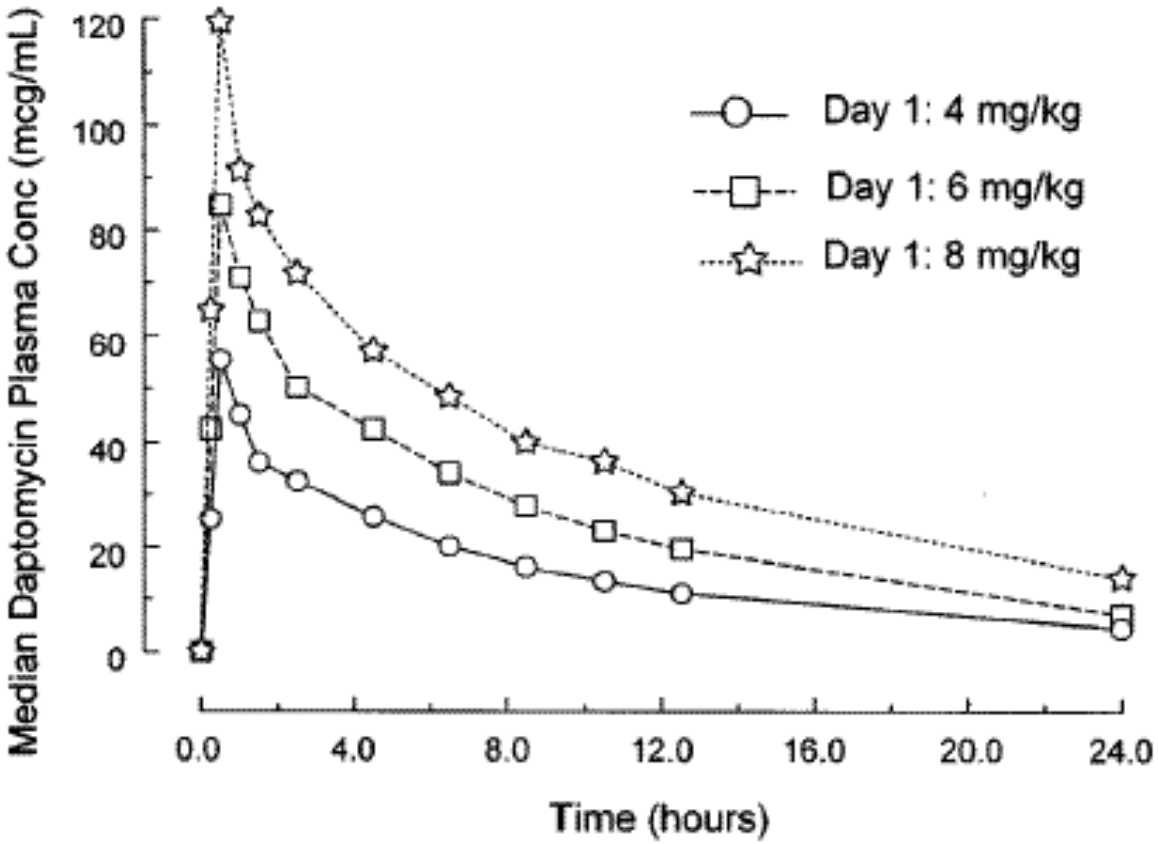
Parameter	**50 mg** (N=6)	**100 mg** (N=6)	**250 mg** (N=6)	**500 mg** (N=6)	**750 mg** (N=6)	**1000 mg** (N=6)
C_{max} (µg/mL)	1.51 ± 0.25	3.08 ± 0.96	10.1 ± 1.68	16.6 ± 2.11	23.4 ± 4.92	30.5 ± 4.32
T_{max} (h)	0.92 (0.90-1.08)	0.92 (0.92-1.10)	0.92 (0.92-1.25)	1.08 (0.92-1.08)	1.00 (0.92-1.08)	0.92 (0.92-1.02)
AUC_{inf} (ug*h/mL)	3.95 ± 0.73	6.72 ± 1.67	23.4 ± 5.38	44.8 ± 2.86	57.6 ± 9.75	80.9 ± 8.63
$t_{1/2}$ (h)	2.03 ± 0.15	2.23 ± 0.42	2.33 ± 0.26	2.53 ± 0.28	2.62 ± 0.29	2.90 ± 0.14
CL (L/h)	11.5 ± 2.33	13.7 ± 2.94	9.87 ± 2.35	9.89 ± 0.63	11.8 ± 2.07	11.0 ± 1.17
V_z (L)	33.4 ± 4.46	42.9 ± 4.19	32.8 ± 7.17	35.9 ± 3.45	44.4 ± 8.08	46.0 ± 5.23

AUC_{inf}; area under concentration-time curve from time 0 to infinity; C_{max}, maximum observed concentration; CL, plasma clearance; $t_{1/2}$, elimination half-life; T_{max}, time of C_{max}; V_z, volume of distribution of terminal phase

Dose proportionality



Multiple-Dose Concentration-Time Profiles (Day 1)



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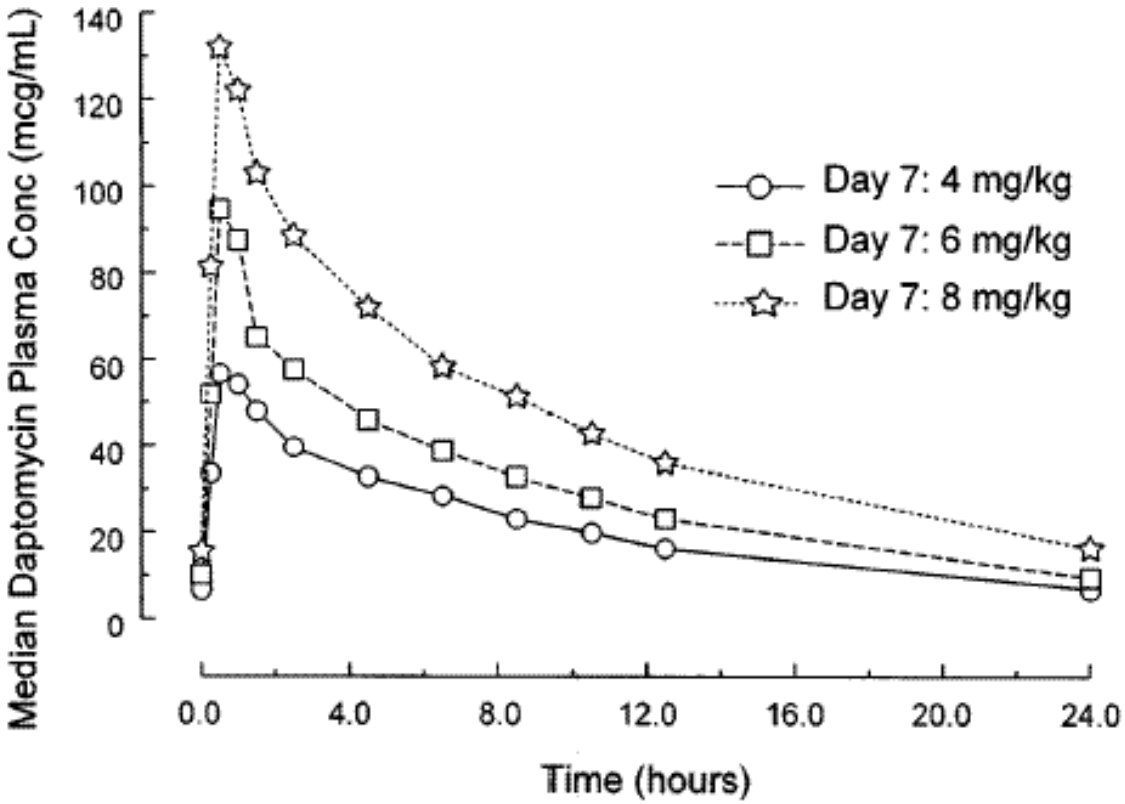
Multiple-Dose Concentration-Time Profiles (Day 7)



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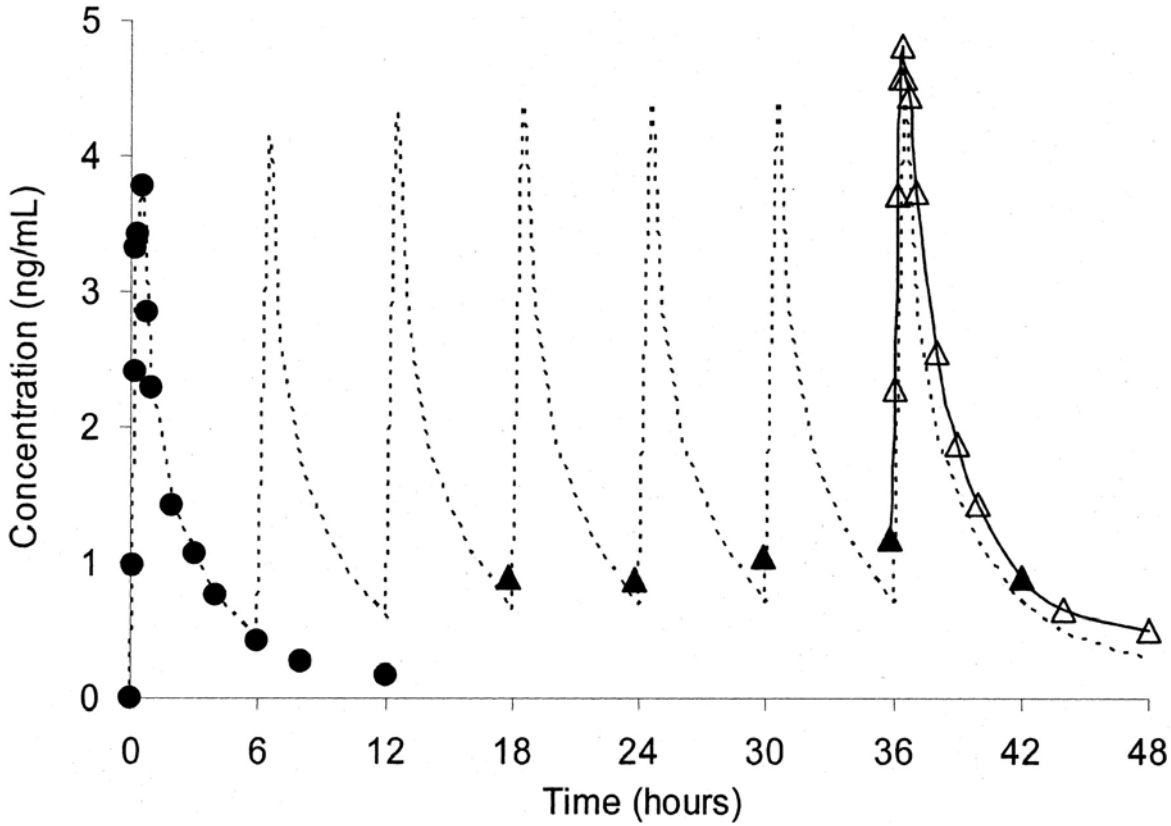
Multiple-Dose PK

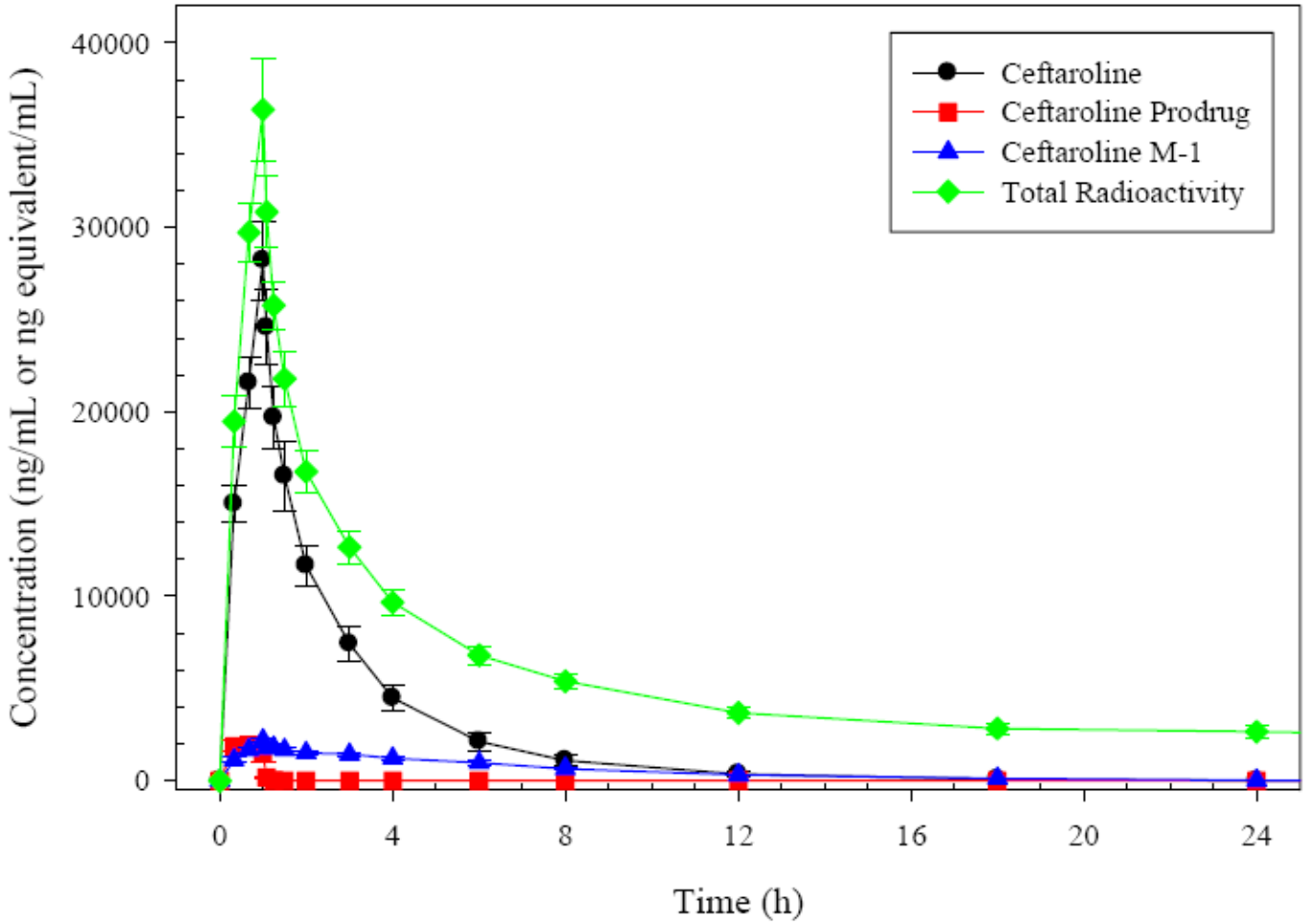


Anesth Analg 2004; 99:1379–86

Mass Balance Study (ADME)

- To understand the routes of elimination of a drug and to identify its circulatory and excretory metabolites
- Commonly ^{14}C-radiolabeled drug
- Usually single dose
- Usually healthy volunteers
- Provides valuable information not only on metabolism and excretion pathways, but also insights on how renal or hepatic impairment might affect drug clearance, especially for those metabolized and excreted via renal & hepatic mechanisms
- Can be performed early in development, but may be performed at any stage

Mass Balance (ADME)



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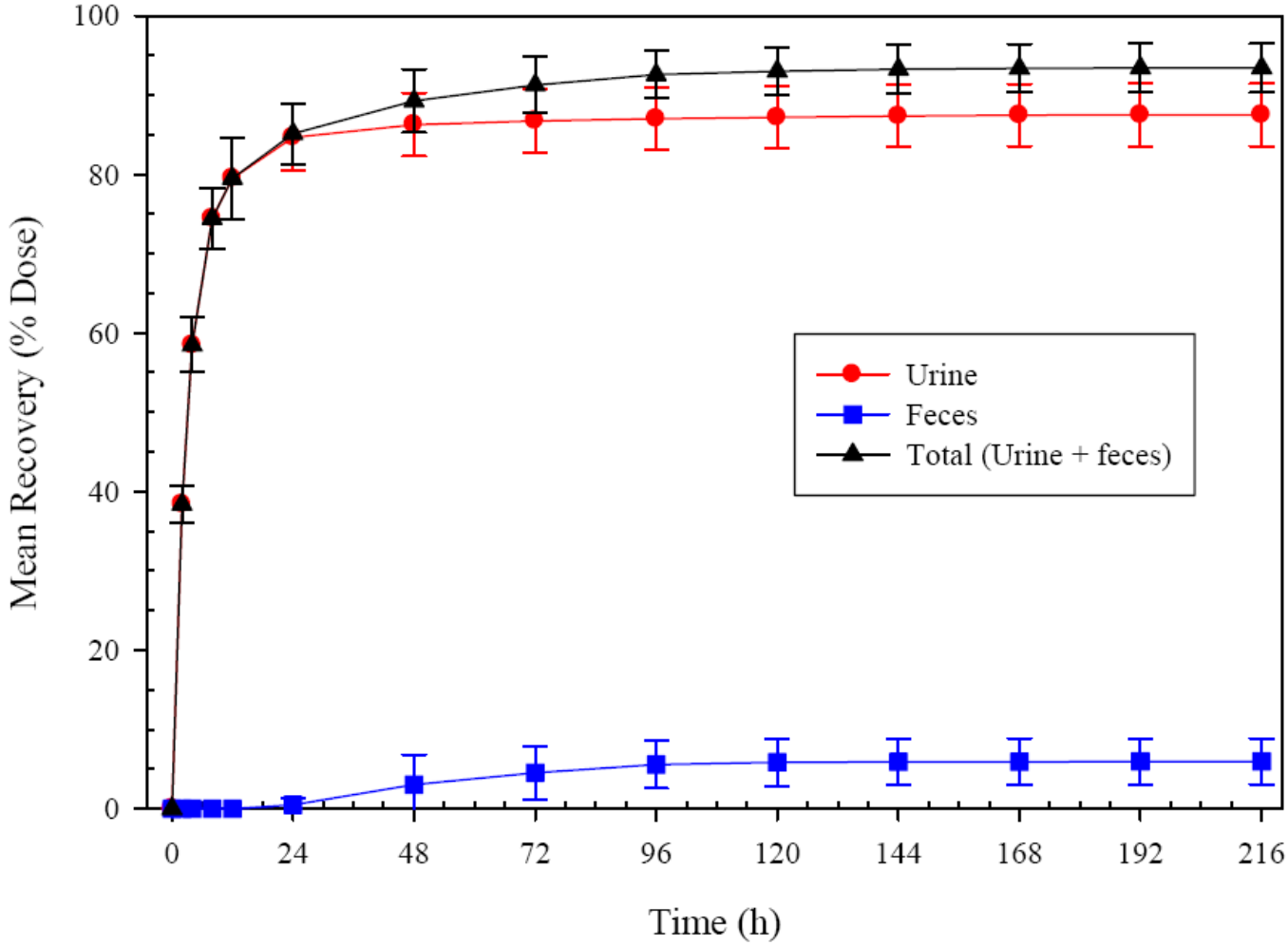
Mass Balance (ADME)



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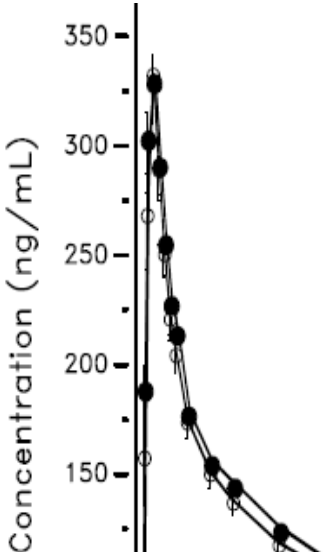
Bioavailability (BA)

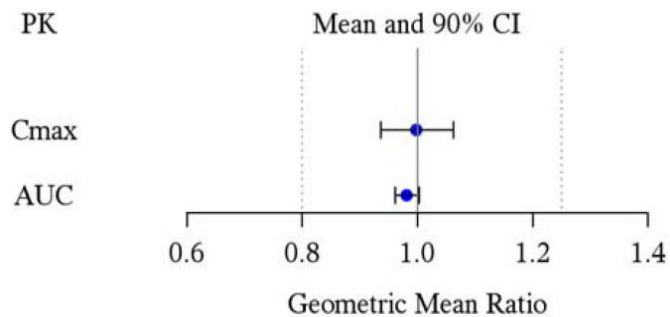
- The rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action
- Can provide an estimate of the relative fraction of the orally administered dose that is absorbed into the systemic circulation compared to a reference material (i.e., solution, suspension, or intravenous dosage form)

Bioequivalence (BE)

- The absence of a significant difference in the rate and extent to which the active ingredient or active moiety becomes available at the site of action when administered at the same molar dose under similar conditions
- In plain English...
  - When two drug products achieve similar drug concentration-time profile in the systemic blood circulation following administration of a same dose

BE Example



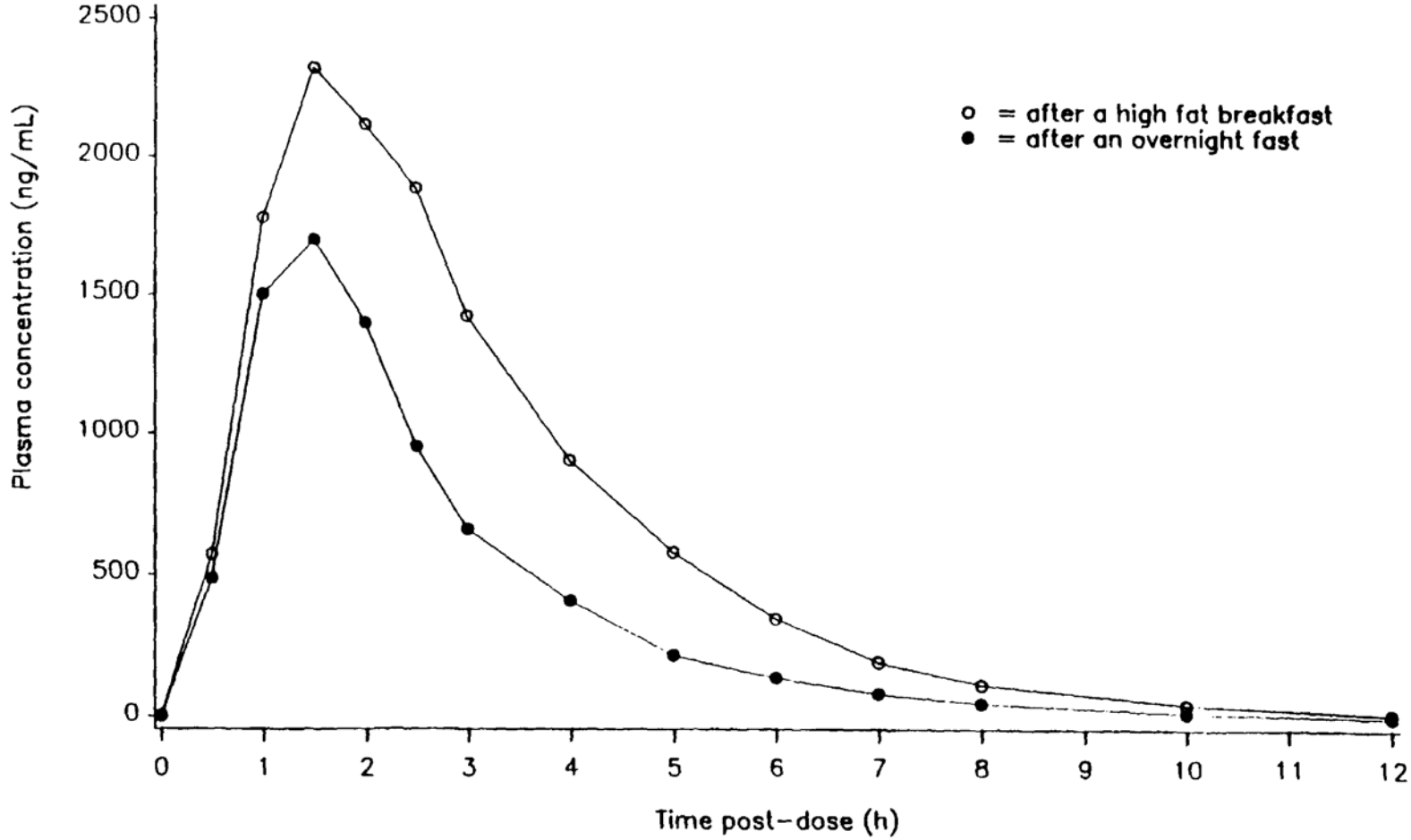


Pharmacokinetic Parameters (units)	Formulation Least Squares Mean		Ratio of Means Test/Reference	90% CI of Ratio
	Catalent Test	PharmaScience Reference		
AUC0-lqc (h•ng/mL)	10261	10431	0.984	(0.965, 1.003)
AUC0-inf (h•ng/mL)	10635	10840	0.981	(0.961, 1.002)
Cmax (ng/mL)	357.7	358.5	0.998	(0.936, 1.063)

Food Effect

- Administration of food with oral drug products may affect the BA and/or BE
- Food can have influences on the release of the drug substance from the drug product as well as the absorption of the drug substance
- Usually a single-dose, two-period, two-treatment, two-sequence crossover study comparing a high-fat high-calorie meal to the fasted state
- High-fat high-calorie meal = 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively

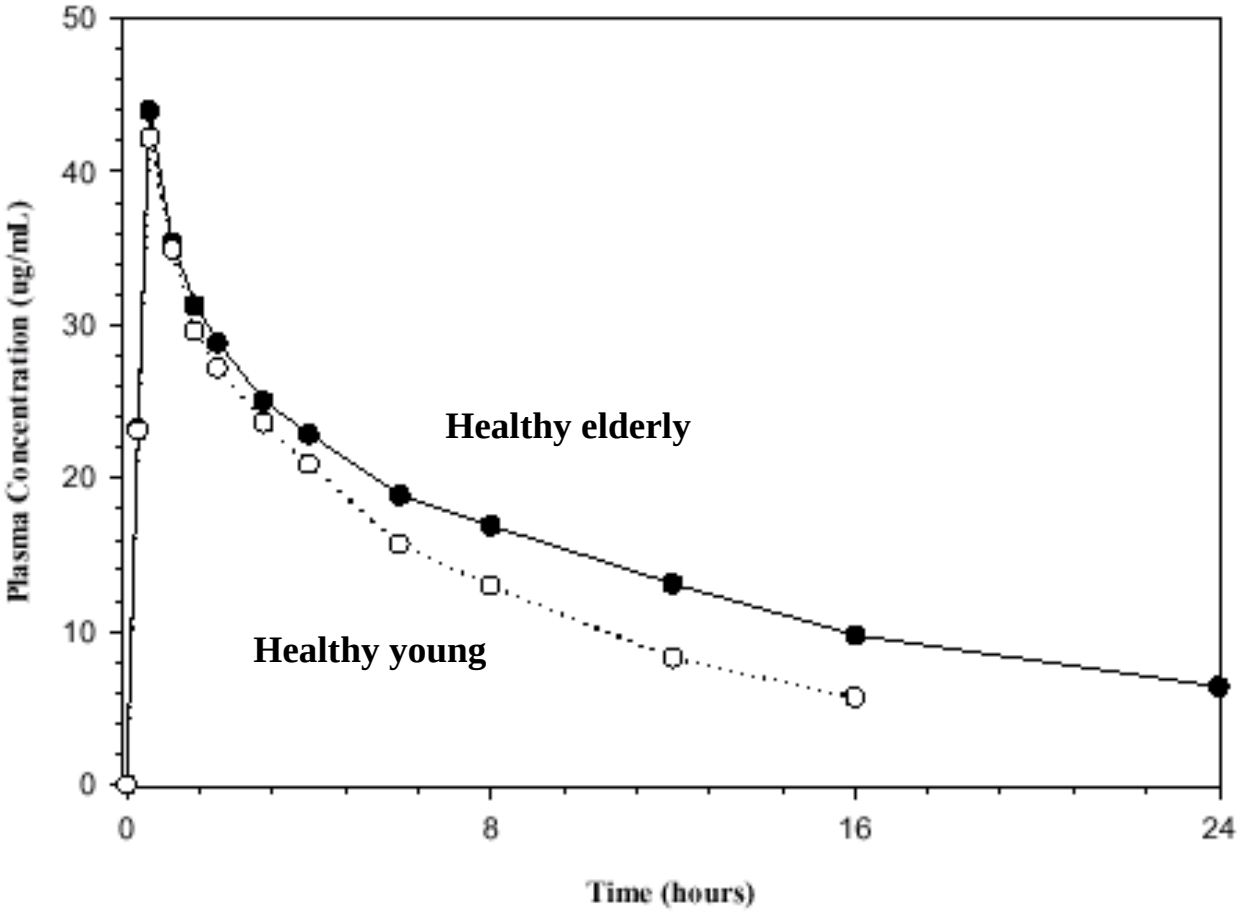
Food Effect - High Fat Meal



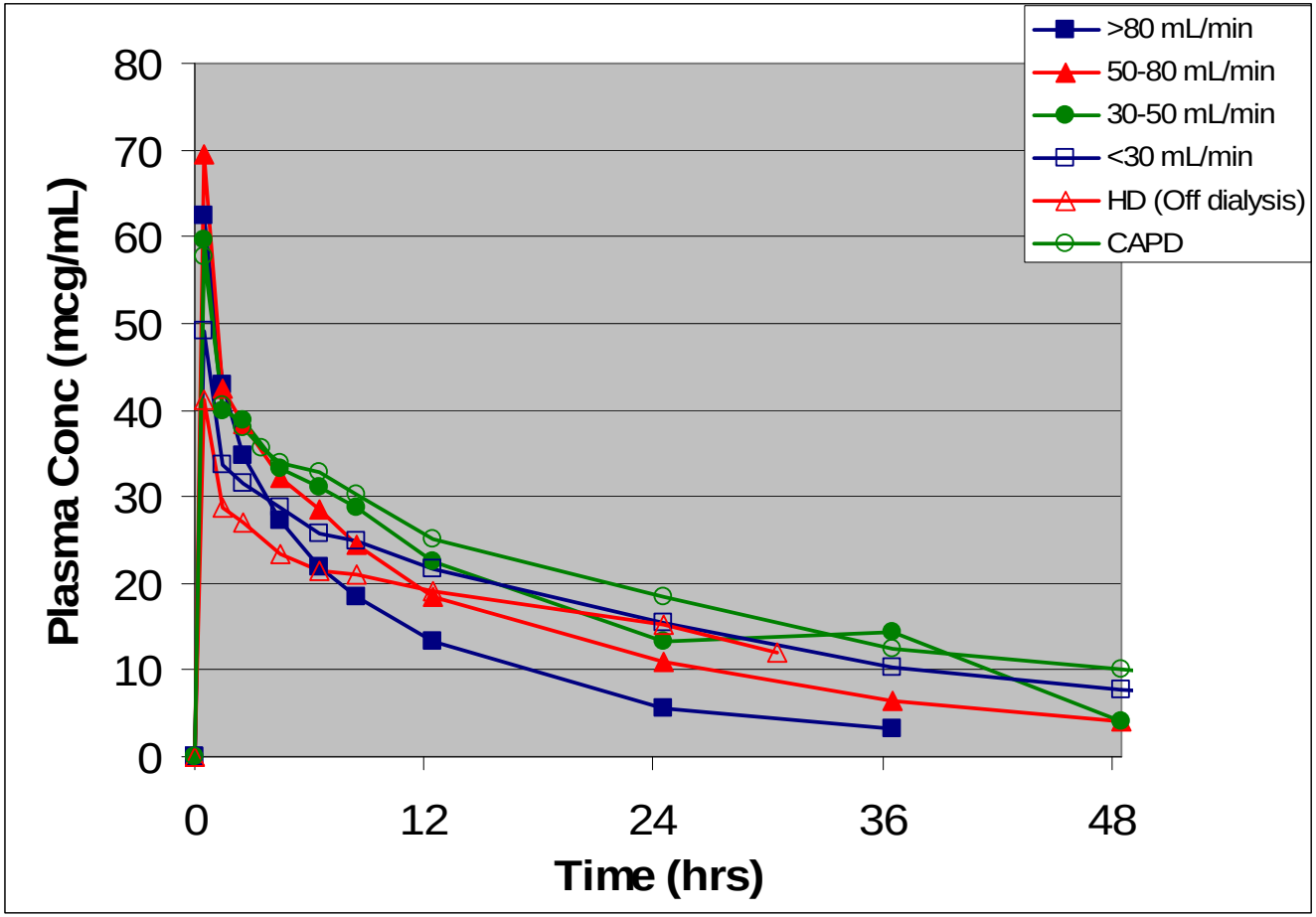
Specific Populations

- Evaluates the impact of an intrinsic factor on the PK of the drug
  - Age (elderly and pediatrics)
  - Gender (male and female subjects)
  - Renal or hepatic impairment
  - Obesity
  - Pregnancy
- Usually a single-dose study
- Recommended to perform study prior to Phase 3
- Supports dose adjustments of the drug in the specific population

Specific Populations - Age



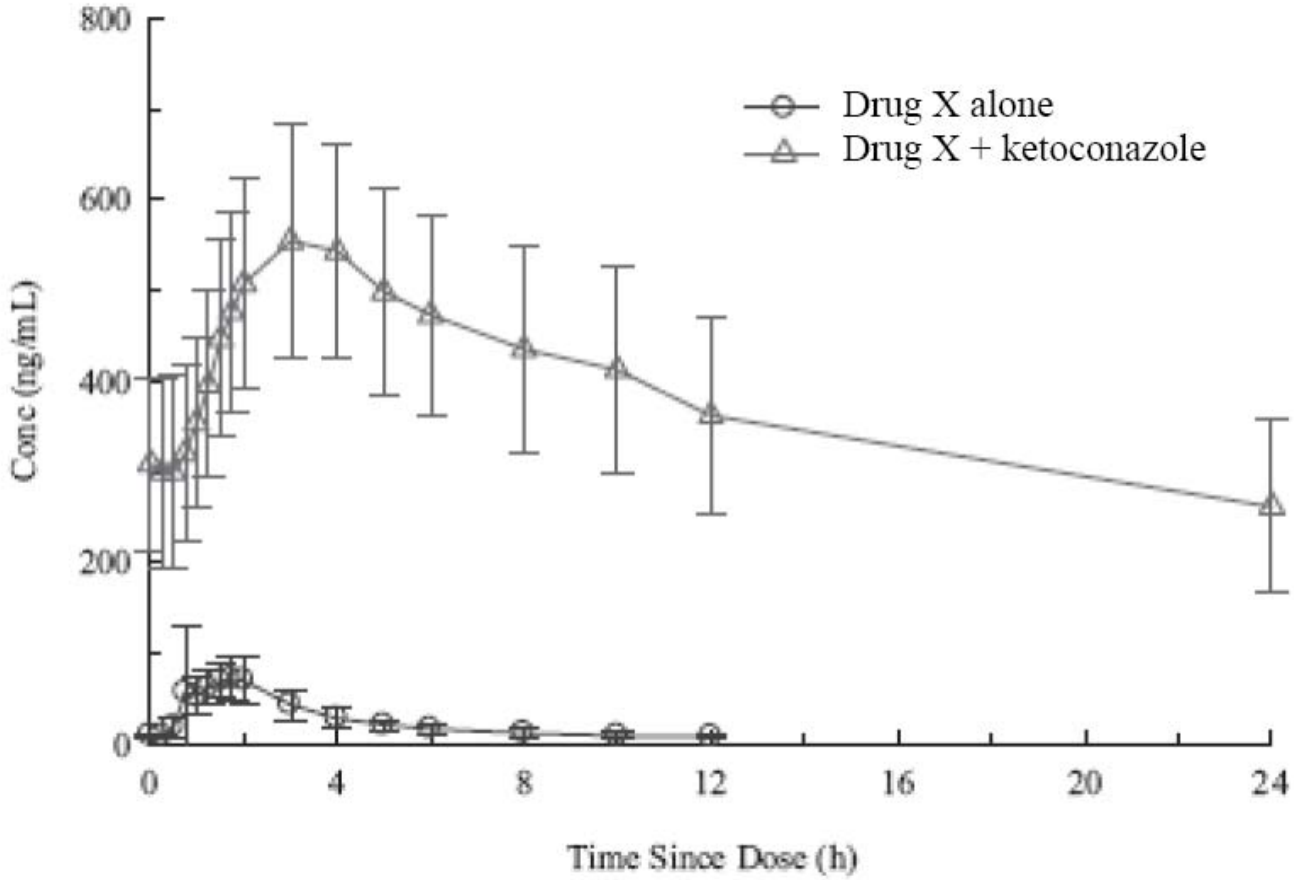
Specific Populations - Renal Impairment



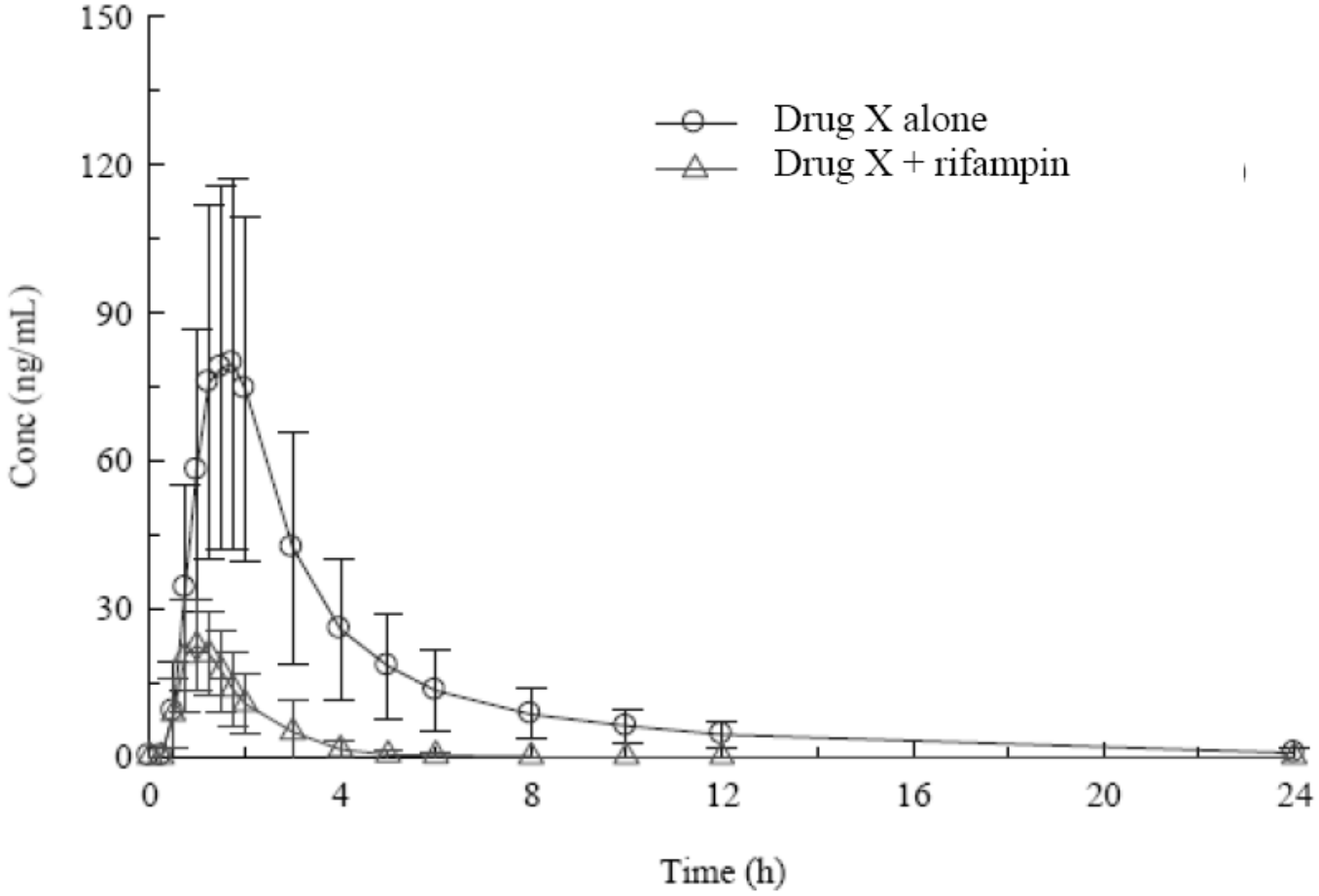
Drug-Drug Interaction Studies

- Evaluates the potential of the drug acting as either a pharmacokinetic perpetrator or a victim when two drugs are co-administered
- Supports dose adjustments when drug interactions observed (either perpetrator or victim drug)
- Usually performed in healthy male and female subjects
- Study design depends on the mechanisms of drug interactions, half life, clinical dosing regimen, etc

Impact of Ketoconazole



Impact of Rifampin



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Bioequivalence

- The absence of a significant difference in the rate and extent to which the active ingredient or active moiety becomes available at the site of action when administered at the same molar dose under similar conditions
- Studies are conducted to assess the sameness of two drug products, different dosing regimens, etc (eg., formulation change, food effects, crushed tablets)

When is a Bioequivalence Study Pivotal?

- For New Drug Applications (NDA):
  - When the to-be-marketed formulation is different than the clinical trial formulation
  - When changes are made to the marketed formulation (eg., switch to capsule, suspension or ER formulation)
- For Abbreviated New Drug Applications (ANDA):
  - To compare the generic versus the innovator formulation

How is BE Determined?

- Typically based on pharmacokinetic measures of Cmax and AUC for systemically available drugs
- Test (T) and Reference (R) products are considered bioequivalent when the 90% CI of the geometric mean ratios (T/R) of Cmax and AUC are within 80% to 125%
- Typically, a group of subjects (n=18-36) are administered test and reference drug products sequentially in two dosing periods, which are separated by a washout period
- Serial samples of biologic fluid (eg., plasma, serum, urine) are collected at pre-dose and at various time points after dosing and are analyzed for determination of drug and/or active metabolite concentrations

Bioequivalence Endpoints*

- In vivo test in humans in which the concentration of the active moiety in whole blood, plasma, serum or other appropriate biological fluid is measured as a function of time
- In vivo test in humans in which the urinary excretion of the active moiety is measured as a function of time
  - This is not appropriate if urinary excretion is not a significant mechanism of elimination

*In decreasing order of accuracy, sensitivity, and reproducibility

Bioequivalence Endpoints (cont.)

- In vivo test in humans in which an appropriate acute pharmacological effect of the active moiety is measured as a function of time if such effect can be measured with sufficient accuracy, sensitivity, and reproducibility
  - This approach may be applicable to dosage forms that are not intended to deliver the active moiety to the bloodstream for systemic distribution
- Well-controlled clinical trials that establish the safety and effectiveness of the drug product, for purposes of measuring bioavailability, or appropriately designed comparative clinical trials, for purposes of demonstrating bioequivalence

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CDER Bioresearch Monitoring (BIMO) Program

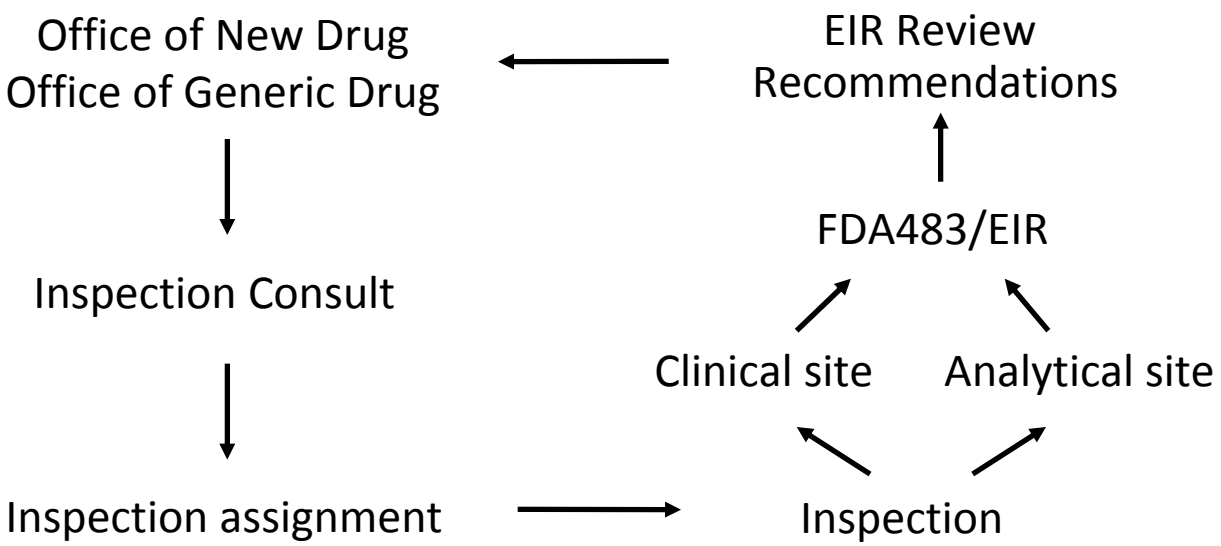
- On-site inspections of clinical investigators, sponsors, IRBs, CROs, GLP and BE studies
- Ensure adherence to applicable regulations
  - Good Laboratory Practice (GLP)
  - Bioequivalence (BE)
  - Good Clinical Practice (GCP)
- Objectives
  - To verify the quality and integrity of data submitted to the Agency
  - To ensure the rights and welfare of human research subjects are protected
  - To ensure that FDA regulated research is conducted in compliance with applicable regulations

BIMO Program

- Inspection Types
  - For-Cause (directed)
  - Surveillance
  - Prescription Drug User Fee Act (PDUFA)-related
- Compliance Classification
  - NAI (No Action Indicated): Inspected entity is in compliance
  - VAI (Voluntary Action Indicated): Minor deviation(s) from the regulations. Voluntary correction is requested
  - OAI (Official Action Indicated): Requires regulatory or administrative action by FDA due to serious non-compliance issues

BE program: Office of Scientific Investigations (OSI)

- Upon request, OSI performs inspections with the Office of Regulatory Affairs (ORA) of the bioanalytical and/or clinical sites of the BE study to verify the quality and integrity of the data submitted to the Agency



Inspections of Bioanalytical Sites

- Critical points of inspection of bioanalytical sites:
  - Pre-study analytical method validation
  - Run acceptance criteria during subject sample analysis
  - Documentation of sample handling
  - Repeat analysis of samples
  - Equipment logs, SOPs
  - Correspondence logs
  - Confirmation of data included in final study report
- Confirms that data a regulatory decision is replied upon are valid and accurate

Points to Consider: Method Validation

- Precision and Accuracy (inter- and intra-batch)
- Selectivity – interference from endogenous/ exogenous substances
- Stability under study conditions
  - Freeze/thaw
  - Long term frozen storage
  - Bench-top, auto-sampler
  - Stock solution
- Report all study results during validation

Points to Consider: SOP

- Written procedures with a priori criteria
  - Run acceptance/rejection criteria
  - Chromatography acceptance/reintegration criteria
  - Repeat analysis, data reporting

Inspections of Clinical Sites

- Critical points of inspections of clinical sites:
  - Subject safety
  - Dosing
  - Drug products
  - Blood draw times
  - Sample processing
  - Adverse events
  - Protocol adherence
  - Reserve samples

Points to Consider: Subject Safety

- Were the rights, health, and welfare of the subjects protected
  - Was informed consent obtained?
  - Was adequate medical supervision provided?
- Were all adverse events reported?

Points to Consider: Dosing and Blood Sampling

- Who received what and when?
  - Test versus reference
  - Actual treatment administered
  - Was the randomization scheme adhered to?
  - Actual dosing time
- Were samples processed and stored according to the protocol?
  - Temperature, processed within specified time frame, etc.

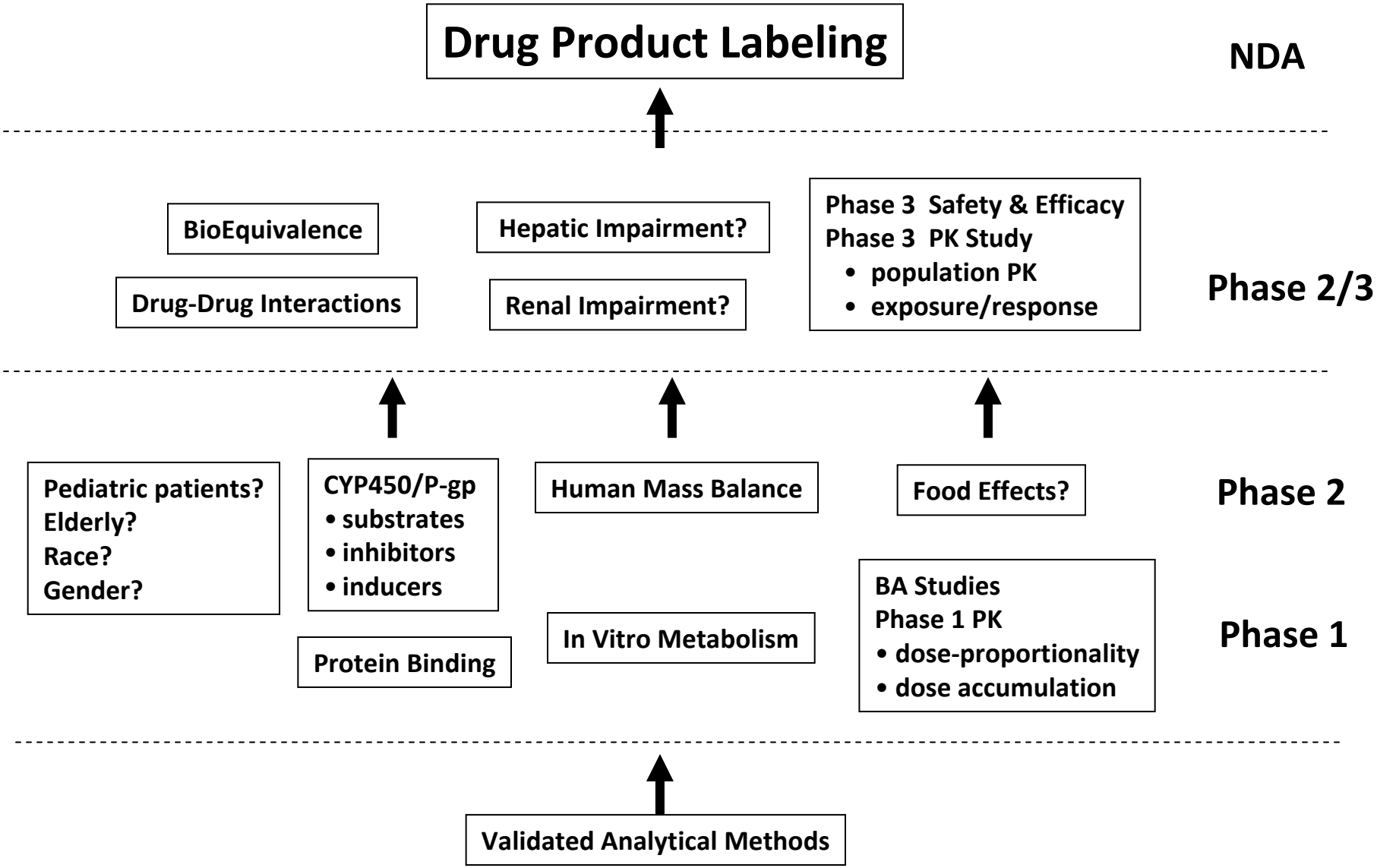
Points to Consider: Protocol Adherence

- Inclusion/exclusion criteria
  - Were inclusion/exclusion criteria met?
- Were protocol-required screening activities conducted?
  - e.g., clinical chemistry, hematology, pregnancy tests, vital signs, ECGs, physical exams, etc.
- Was adherence to protocol restrictions documented at each dosing period?
  - Rx and OTC drugs prior to dosing and throughout study
  - Caffeine/alcohol restrictions prior to dosing

Points to Consider: Reserve Samples

- Retained samples that are representative of the actual drug products used in the study
- Reserve samples must be:
  - Randomly selected at the study site
  - Positively identified as having come from the same sample used in the specific BE study
  - Retained for at least 5 years following an approval, or if the application is not approved, at least 5 years following the date of completion of the study

21 CFR 320.28 "Retention of bioavailability samples" and 21 CFR 320.63 "Retention of bioequivalence samples"


Drug Product Labeling
NDA
BioEquivalence
Drug-Drug Interactions
Hepatic Impairment?
Renal Impairment?
Phase 3 Safety & Efficacy
Phase 3 PK Study
• population PK
• exposure/response
Phase 2/3
Pediatric patients?
Elderly?
Race?
Gender?
CYP450/P-gp
• substrates
• inhibitors
• inducers
Protein Binding
Human Mass Balance
In Vitro Metabolism
Food Effects?
Phase 2
BA Studies
Phase 1 PK
• dose-proportionality
• dose accumulation
Phase 1
Validated Analytical Methods

Thank you