



Pharmacokinetics in Clinical Trials

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CDER Small Business Assistance Training

Outline

- Define pharmacokinetics
- Discuss types of pharmacokinetic studies performed in drug development
- Provide examples of different types of pharmacokinetic studies
- Illustrate the importance of bioequivalence studies
- Define the role of DSI to ensure data integrity

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Pharmacokinetics (PK)

- Defined as the quantitative analysis of the time course of a drug
- Pharmacokinetics describes what the body does to a drug
- Commonly referred to as “ADME”
 - absorption
 - distribution
 - metabolism
 - excretion

Pharmacokinetics (cont.)

- Provides a basis for dose selection in early clinical trials
- Identifies the linearity and dose-proportionality across a range of doses
- Supports dose adjustments for specific populations
- Supports dose adjustments with drug interactions (either perpetrator or victim drug)

Relationship Between Pharmacokinetics (PK) and Pharmacodynamics (PD)



- Absorption
- Distribution
- Metabolism
- Excretion

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Goals of Initial Pharmacokinetic Studies

- Provide an assessment of the safety and tolerability in healthy subjects (may be a first in human study)
- Provide an understanding of the pharmacokinetics of the drug
- Identify possible sources/determinants of between-subject variability

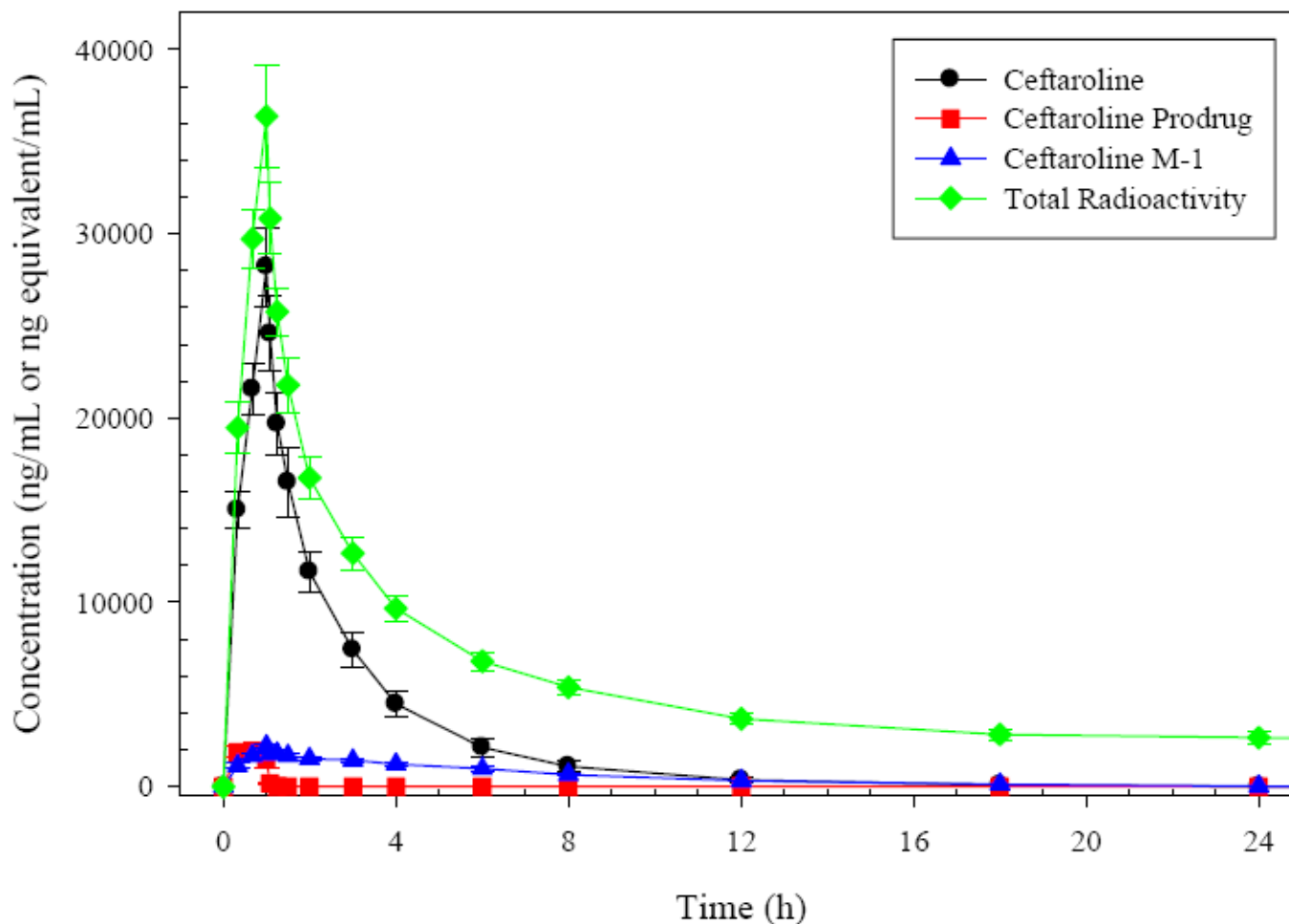
Types of Phase 1 Pharmacokinetic Studies

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

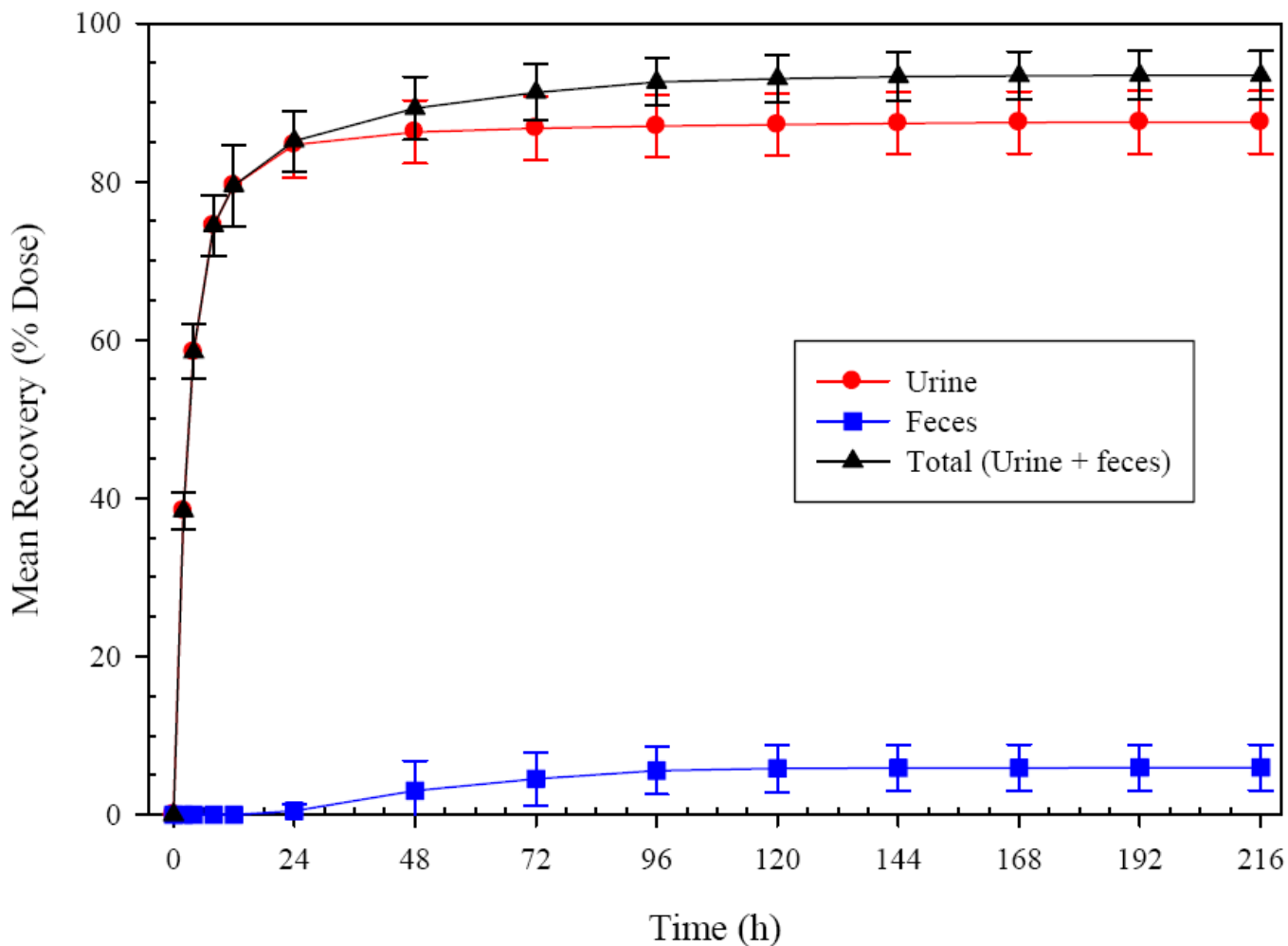
Mass Balance (ADME)

- Commonly ^{14}C -radiolabeled drug
- Usually single dose
- Usually healthy male subjects
- Provides valuable information regarding metabolism and excretion, especially for drugs that are metabolized and excreted via renal & hepatic mechanisms
- Can be performed early in development, but may be performed at any stage

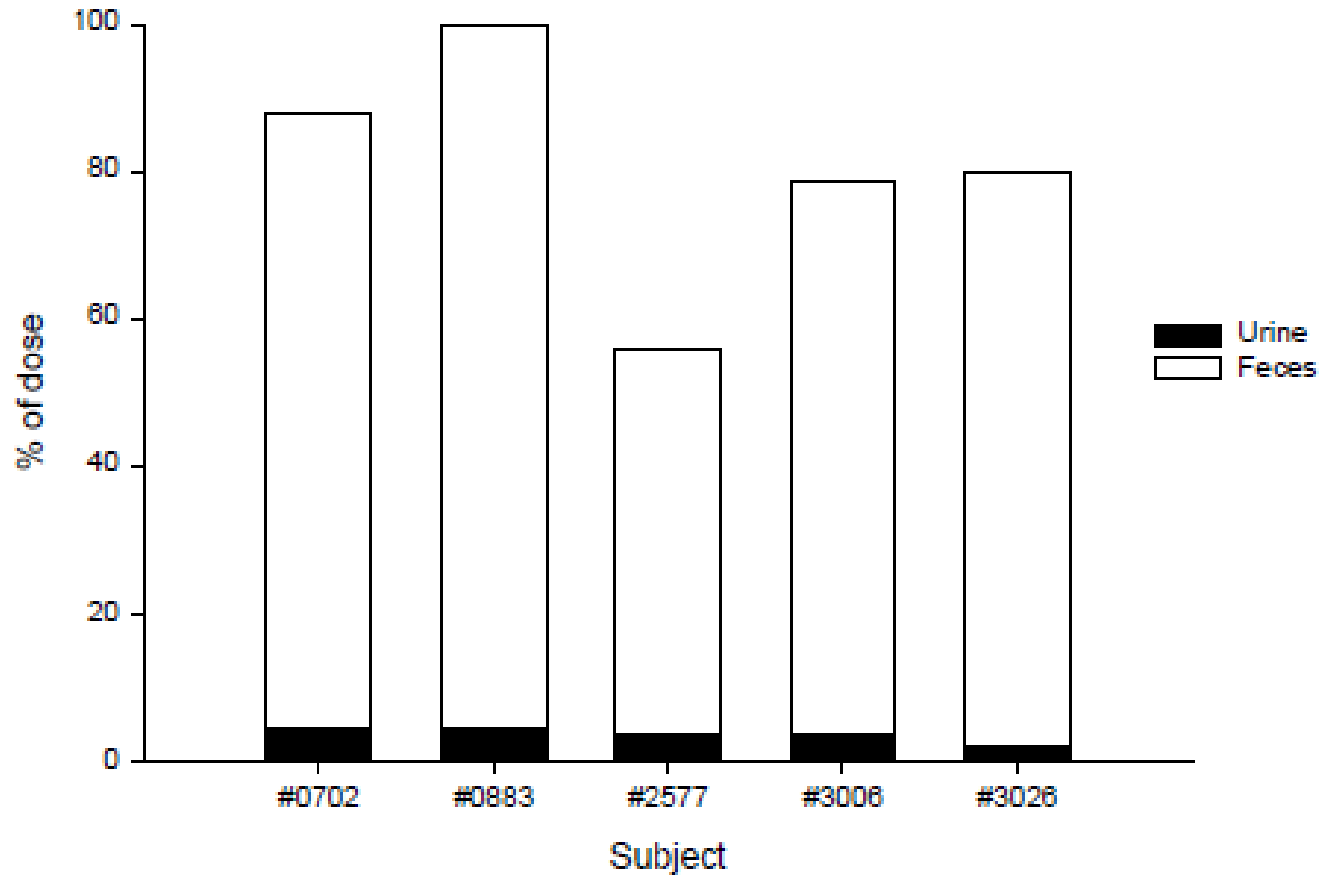
Mass Balance (ADME)



Mass Balance (ADME)



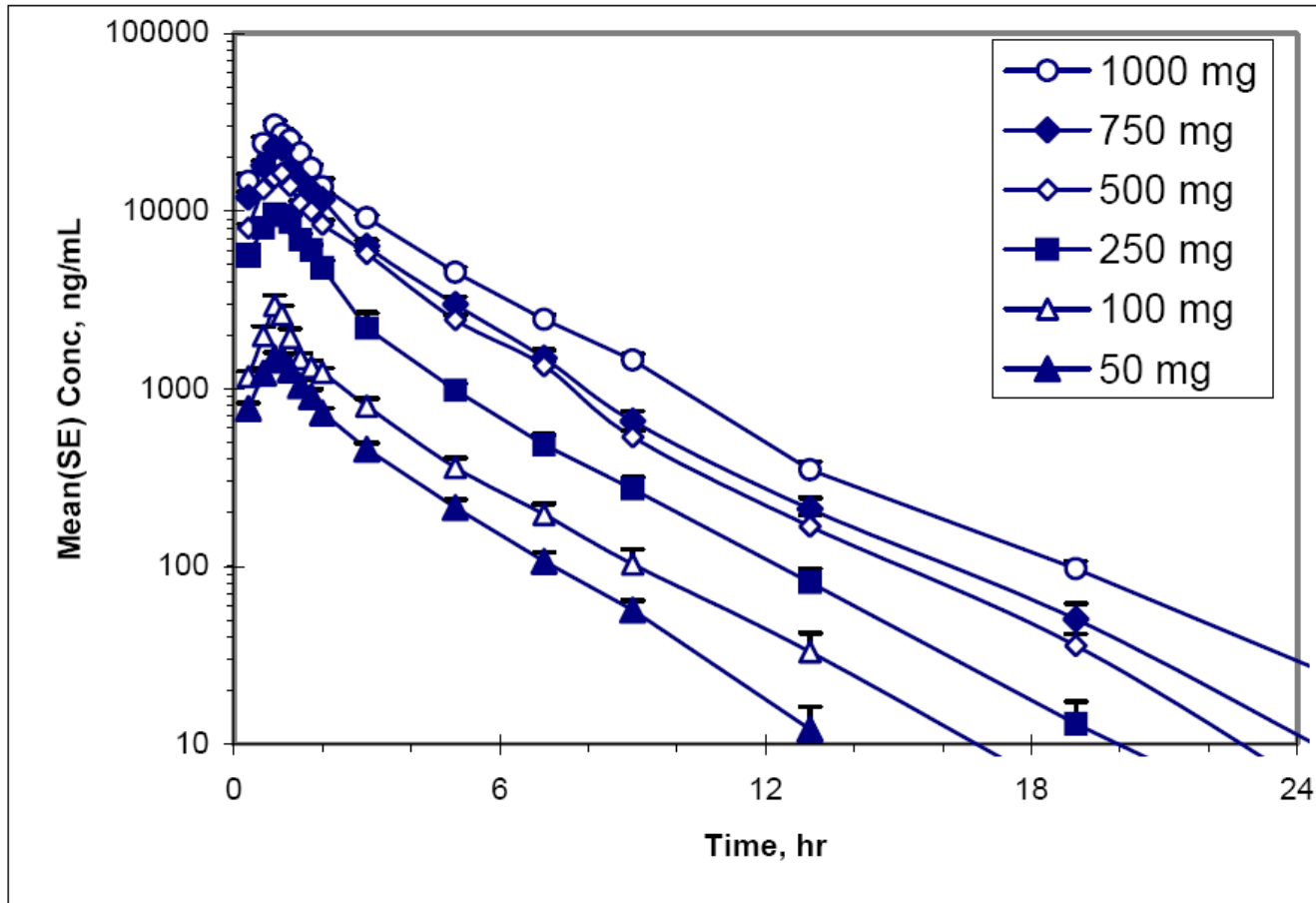
Mass Balance (ADME)



Single Dose/Multiple Dose Pharmacokinetics

- Assesses the pharmacokinetics of the compound across a range of doses (including clinically relevant doses)
- Assesses linearity and dose proportionality
- Multiple dosing can assess time-dependent effects
- Usually performed in healthy male and female subjects

Single-Dose Concentration-Time Profiles

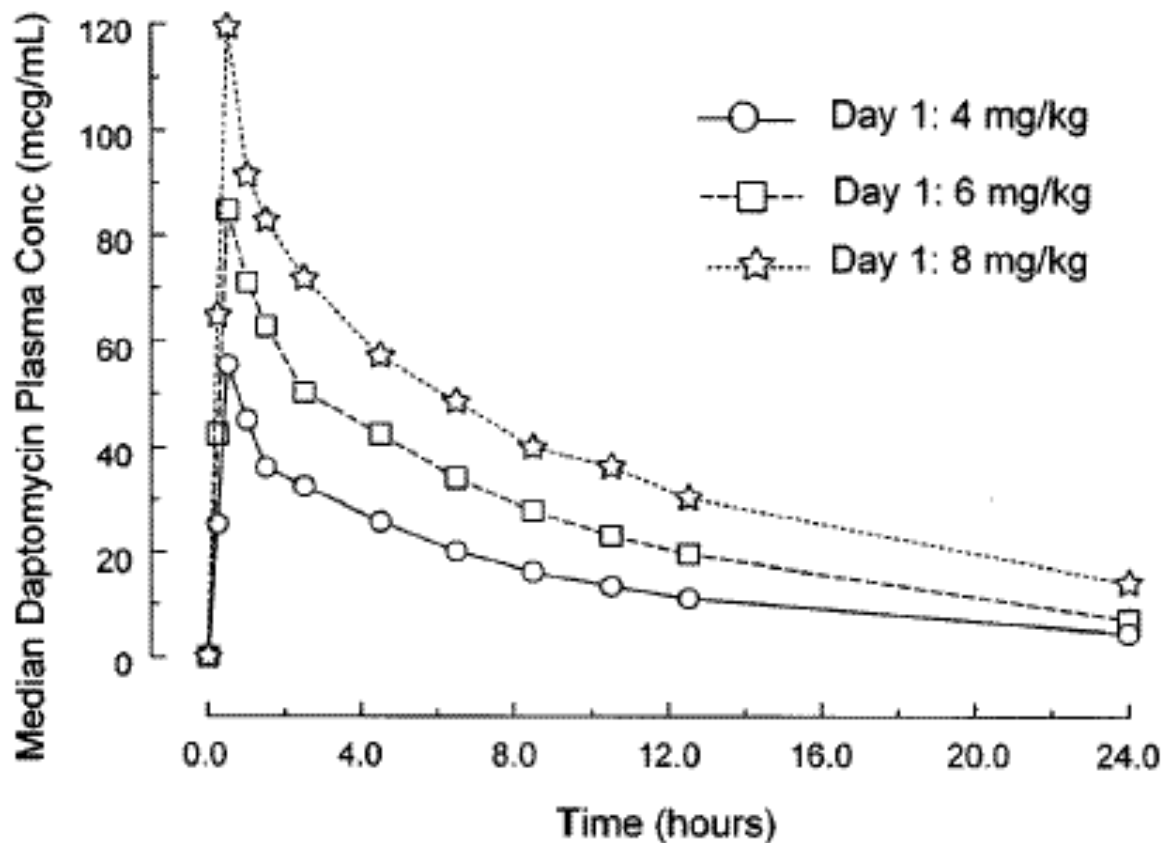


Single-Dose PK Parameters

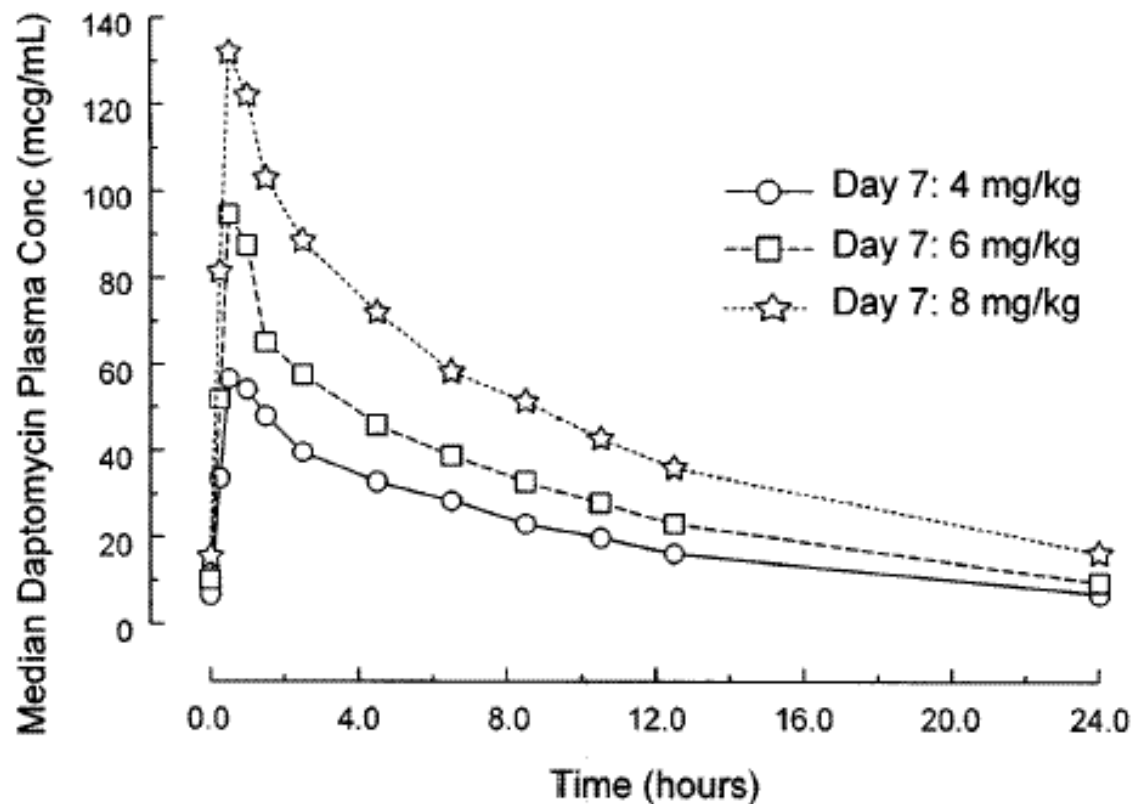
Parameter	50 mg (N=6)	100 mg (N=6)	250 mg (N=6)	500 mg (N=6)	750 mg (N=6)	1000 mg (N=6)
C_{max} ($\mu\text{g/mL}$)	1.51 \pm 0.25	3.08 \pm 0.96	10.1 \pm 1.68	16.6 \pm 2.11	23.4 \pm 4.92	30.5 \pm 4.32
T_{max} (h)	0.92 (0.90-1.08)	0.92 (0.92-1.10)	0.92 (0.92-1.25)	1.08 (0.92-1.08)	1.00 (0.92-1.08)	0.92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

Multiple-Dose Concentration-Time Profiles (Day 1)



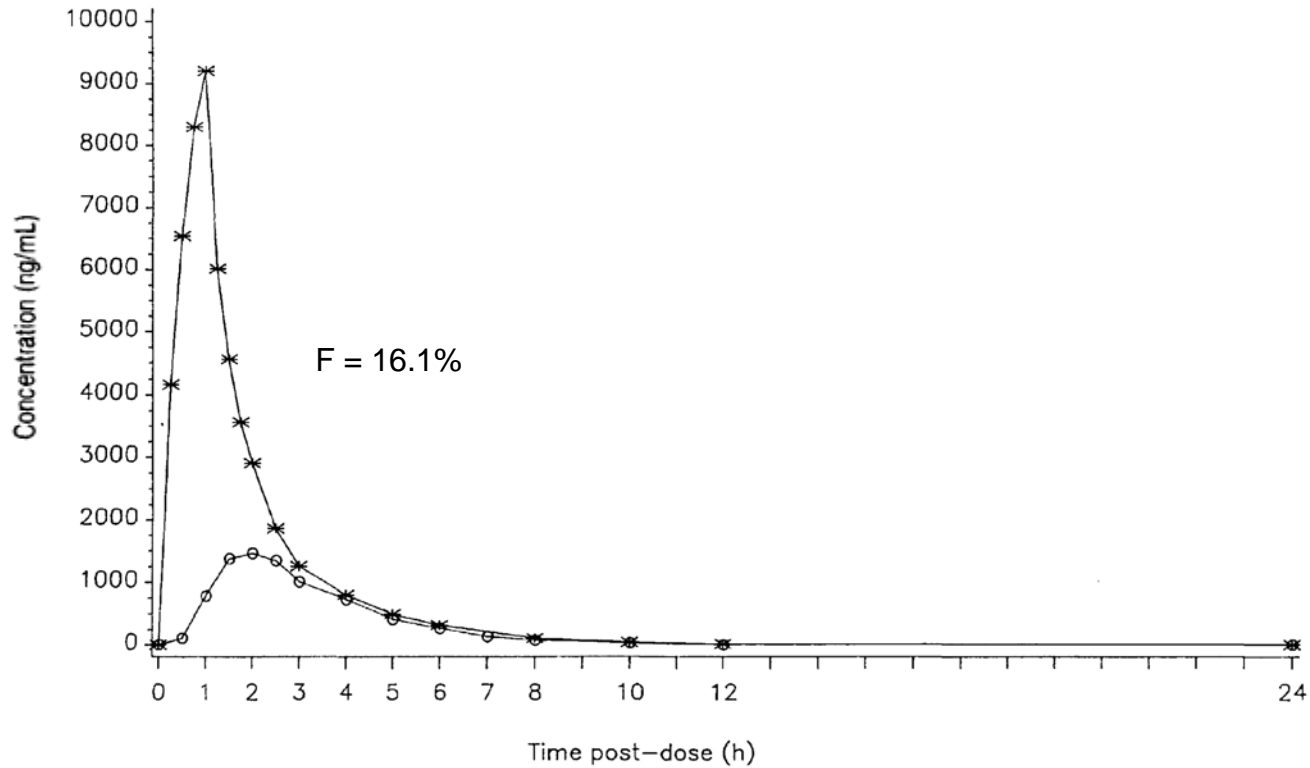
Multiple-Dose Concentration-Time Profiles (Day 7)



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)

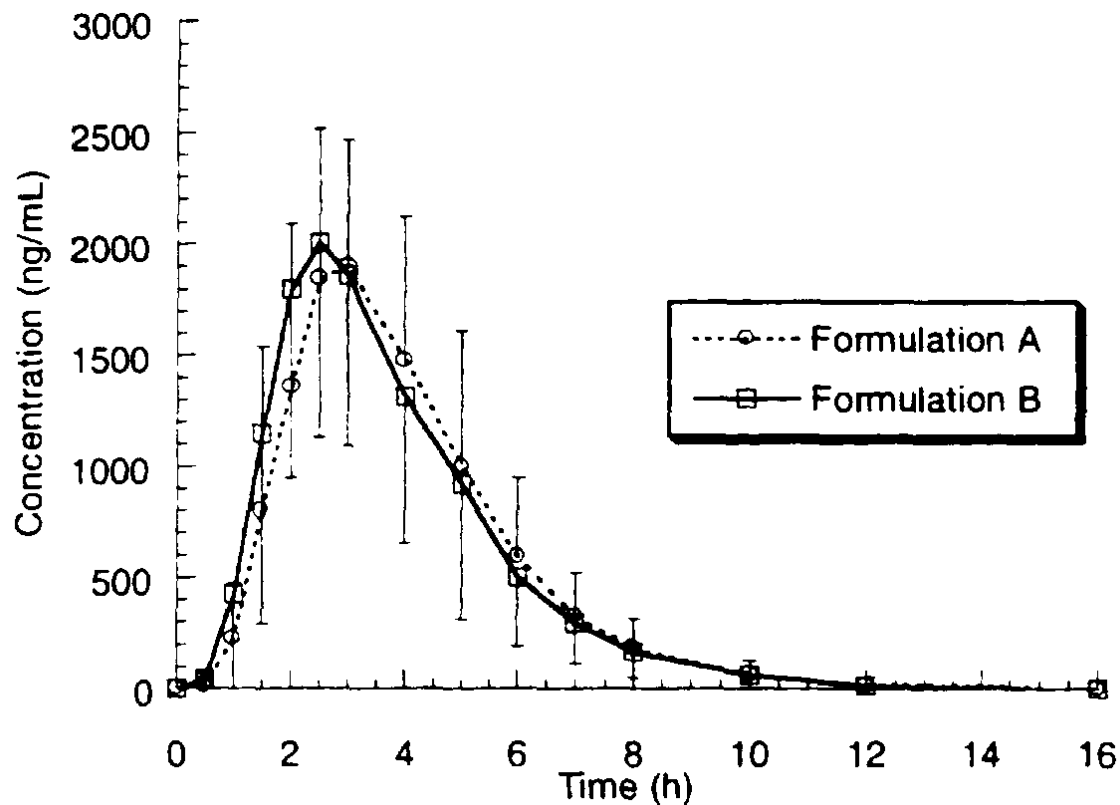
Absolute Bioavailability



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 active when administered at the same molar dose under similar conditions
- The approaches for demonstrating bioequivalence generally follows similar approaches for measuring bioavailability

Bioequivalence

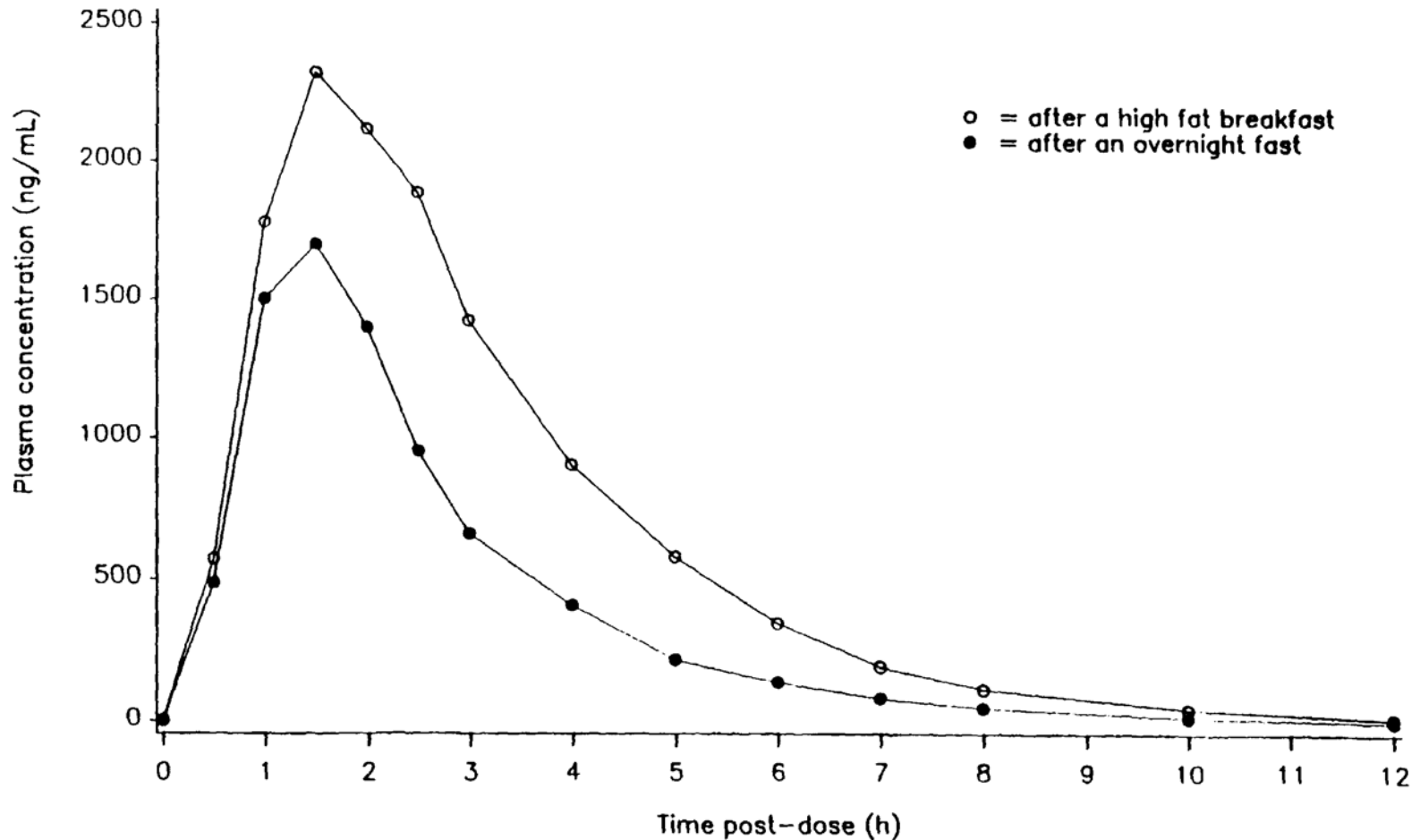


Parameter	Point Estimate	90% Confidence Interval
C_{max}	0.974	0.895 to 1.060
AUC_{0-t}	1.003	0.930 to 1.082
$AUC_{0-\infty}$	1.004	0.932 to 1.083

Food Effect

- Administration of food with oral drug products may influence the BA and/or BE
- Focus on the effects of food 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 meal and the fasted state
- High-fat meal = 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively

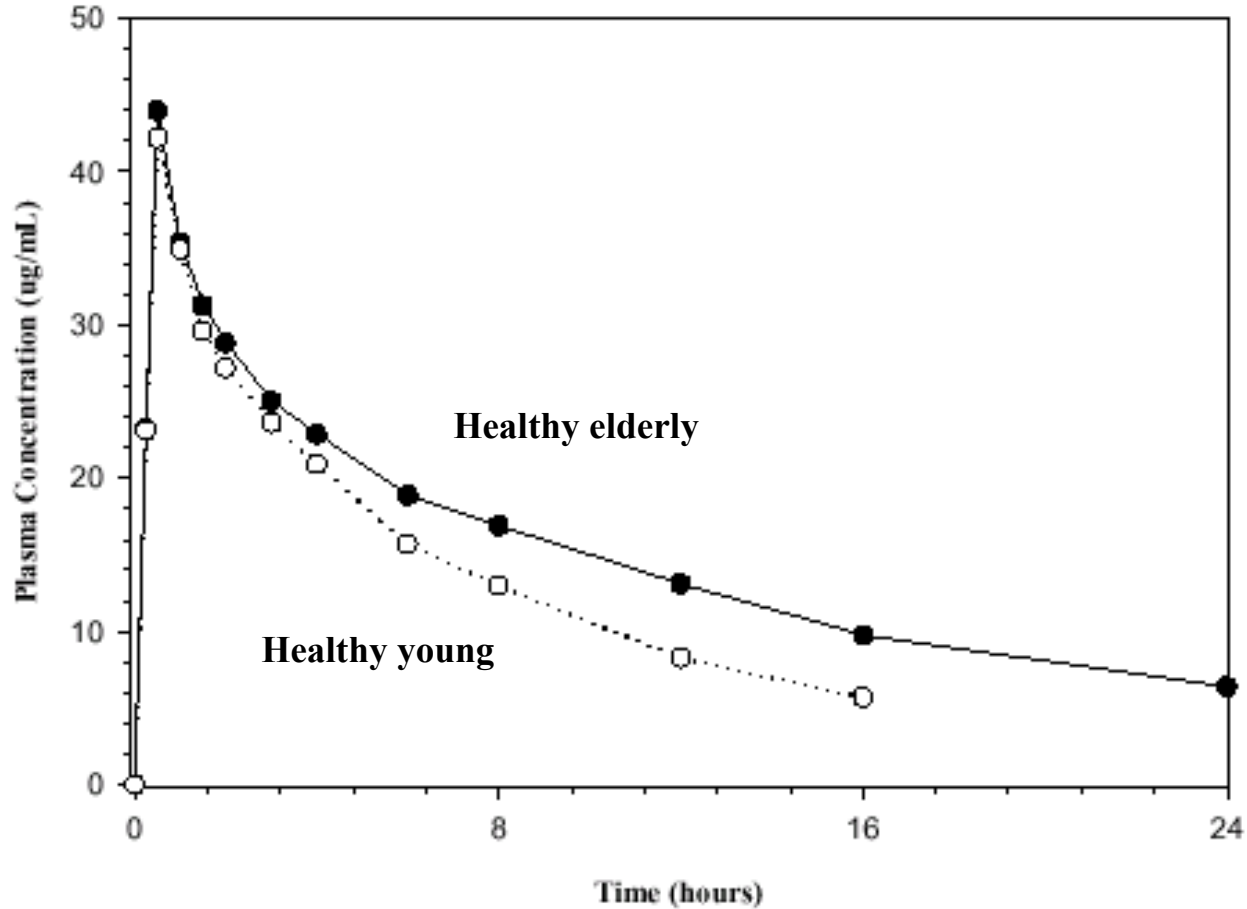
Food Effect - High Fat Meal



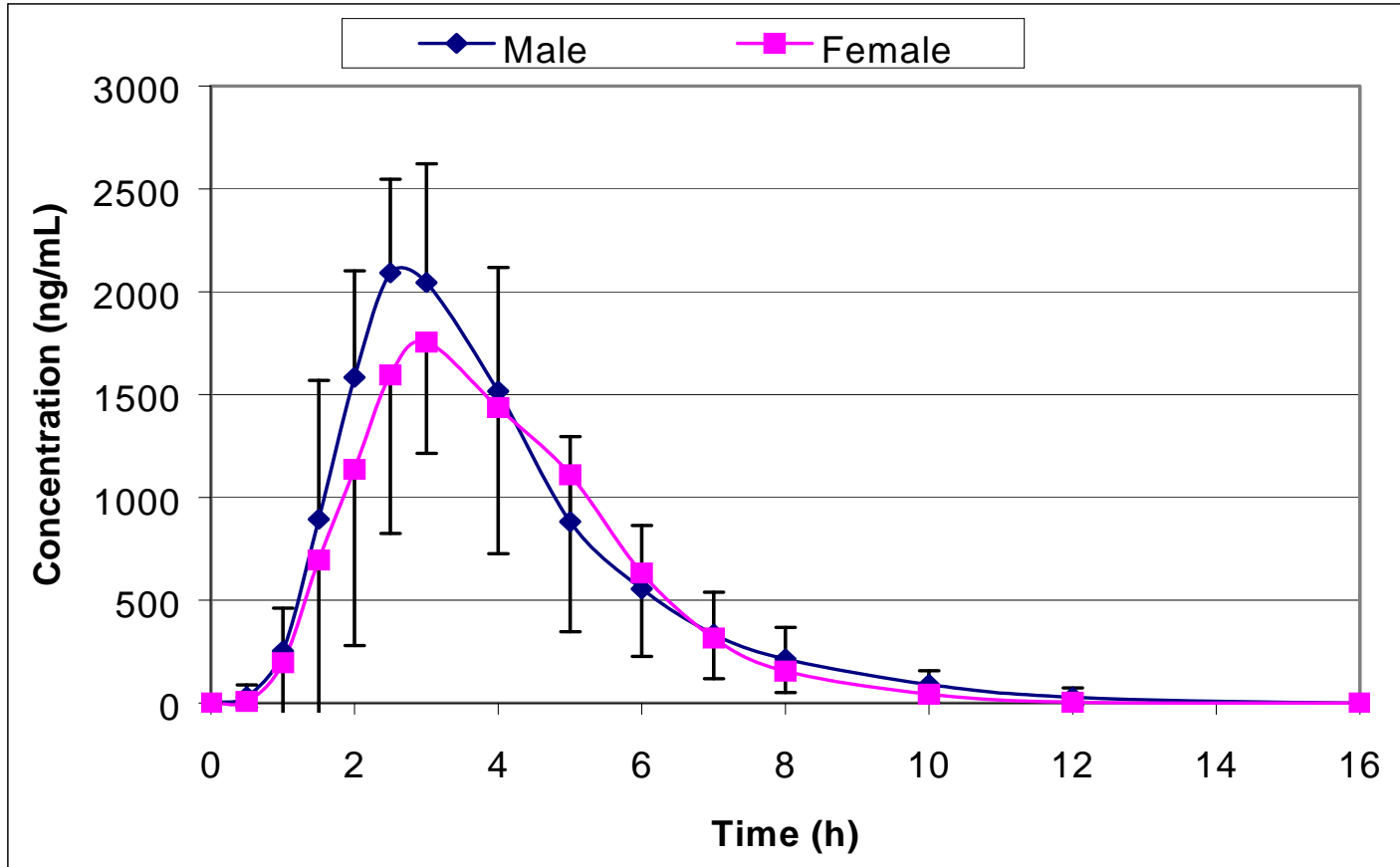
Specific Populations

- 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

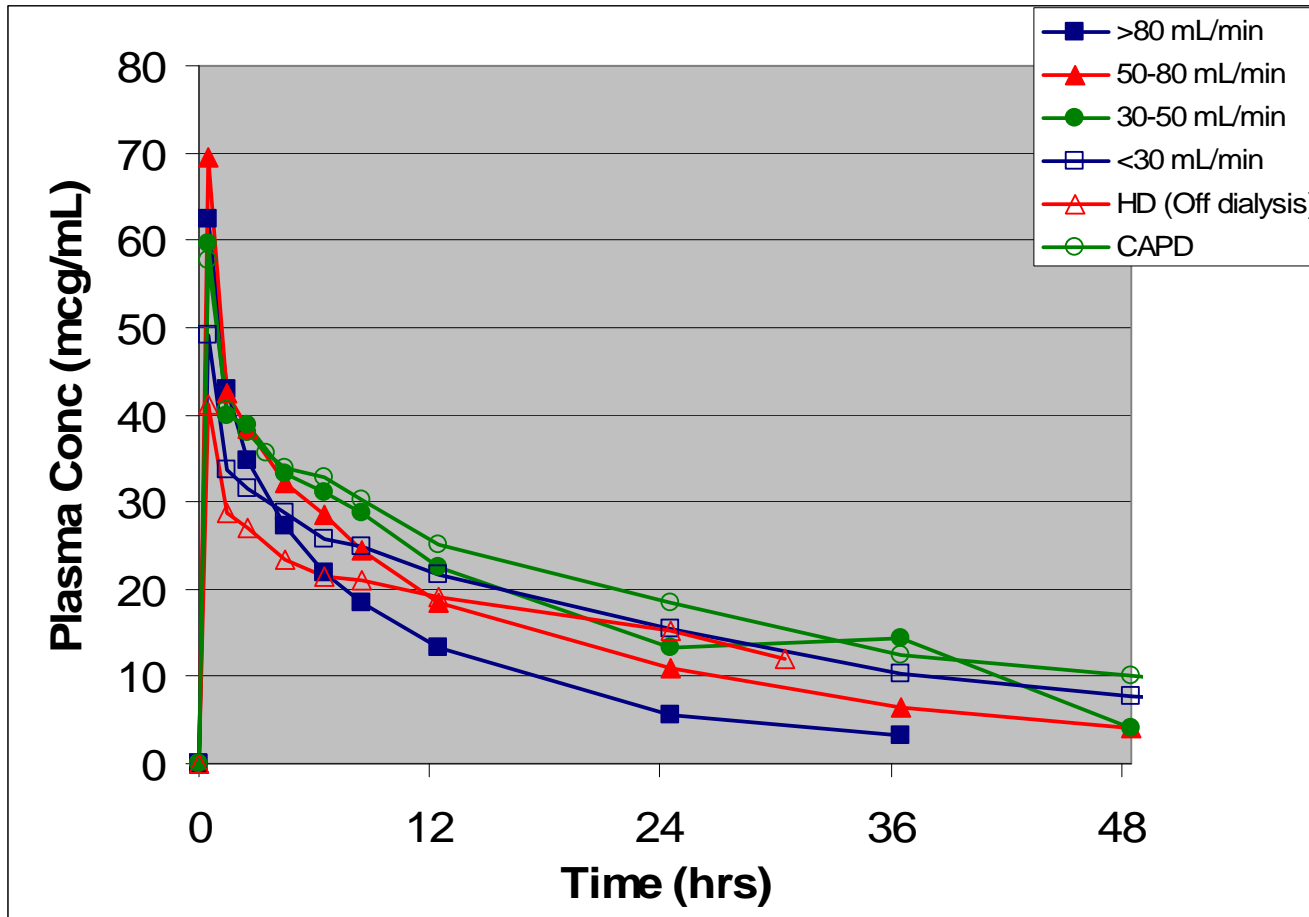
Specific Populations - Elderly



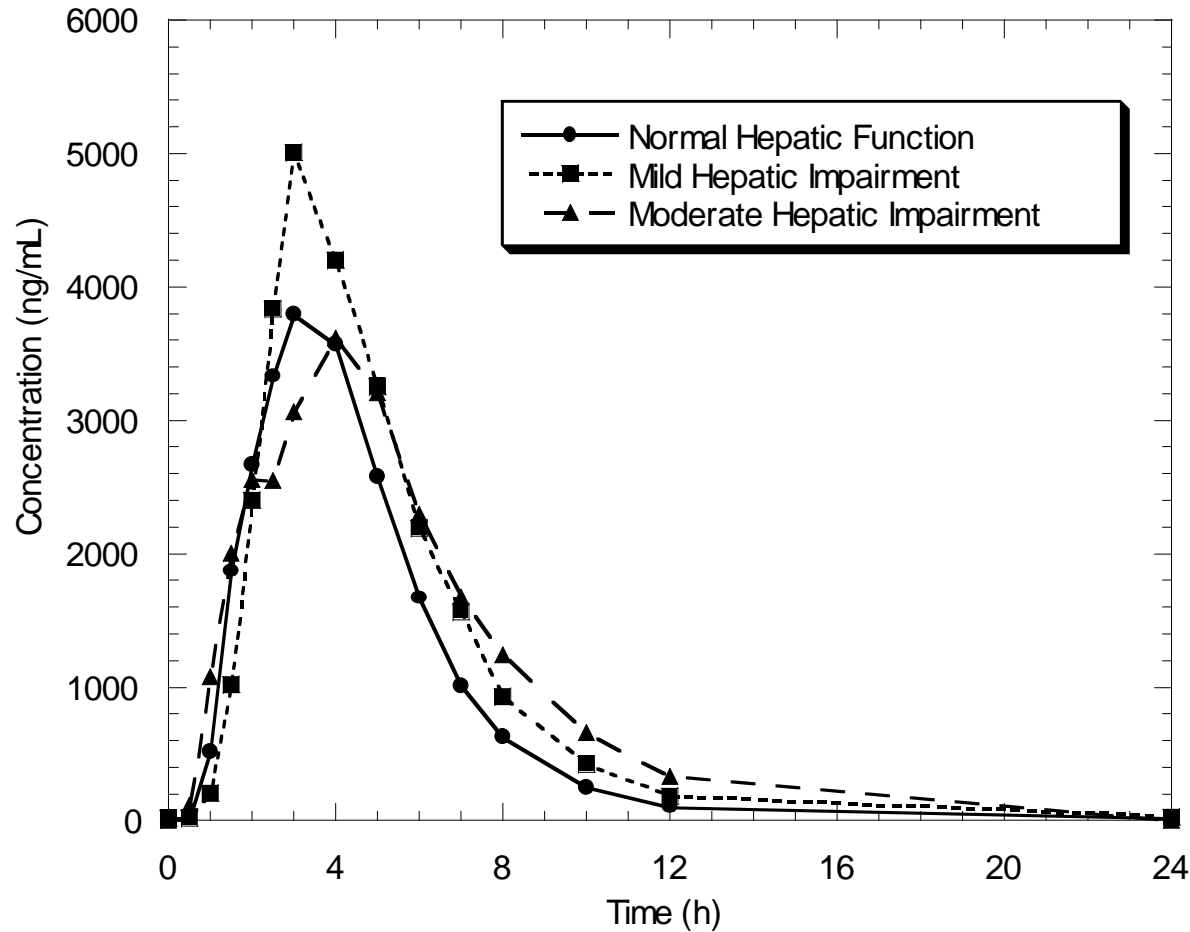
Specific Populations - Gender



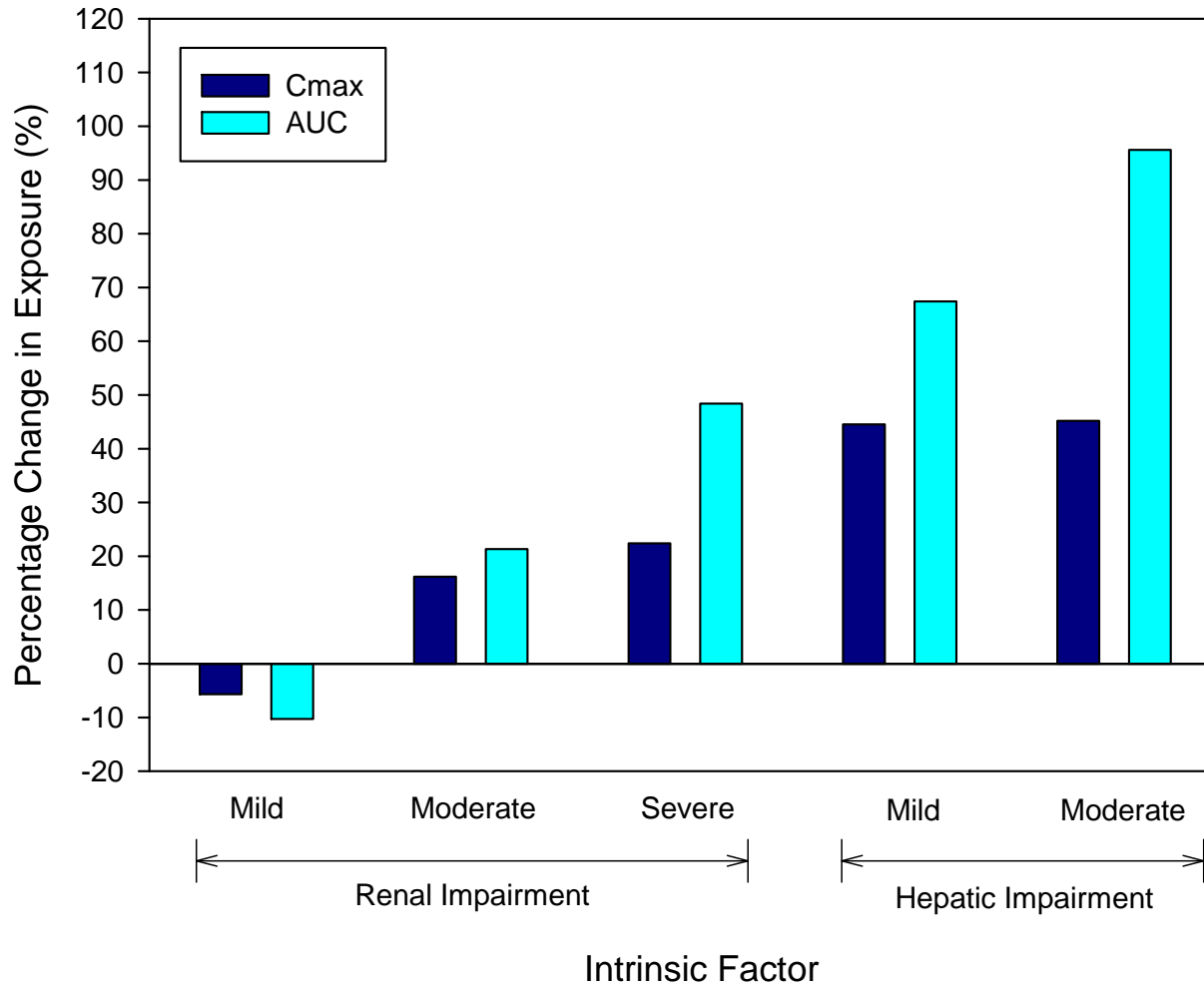
Specific Populations - Renal Impairment



Specific Populations - Hepatic Impairment



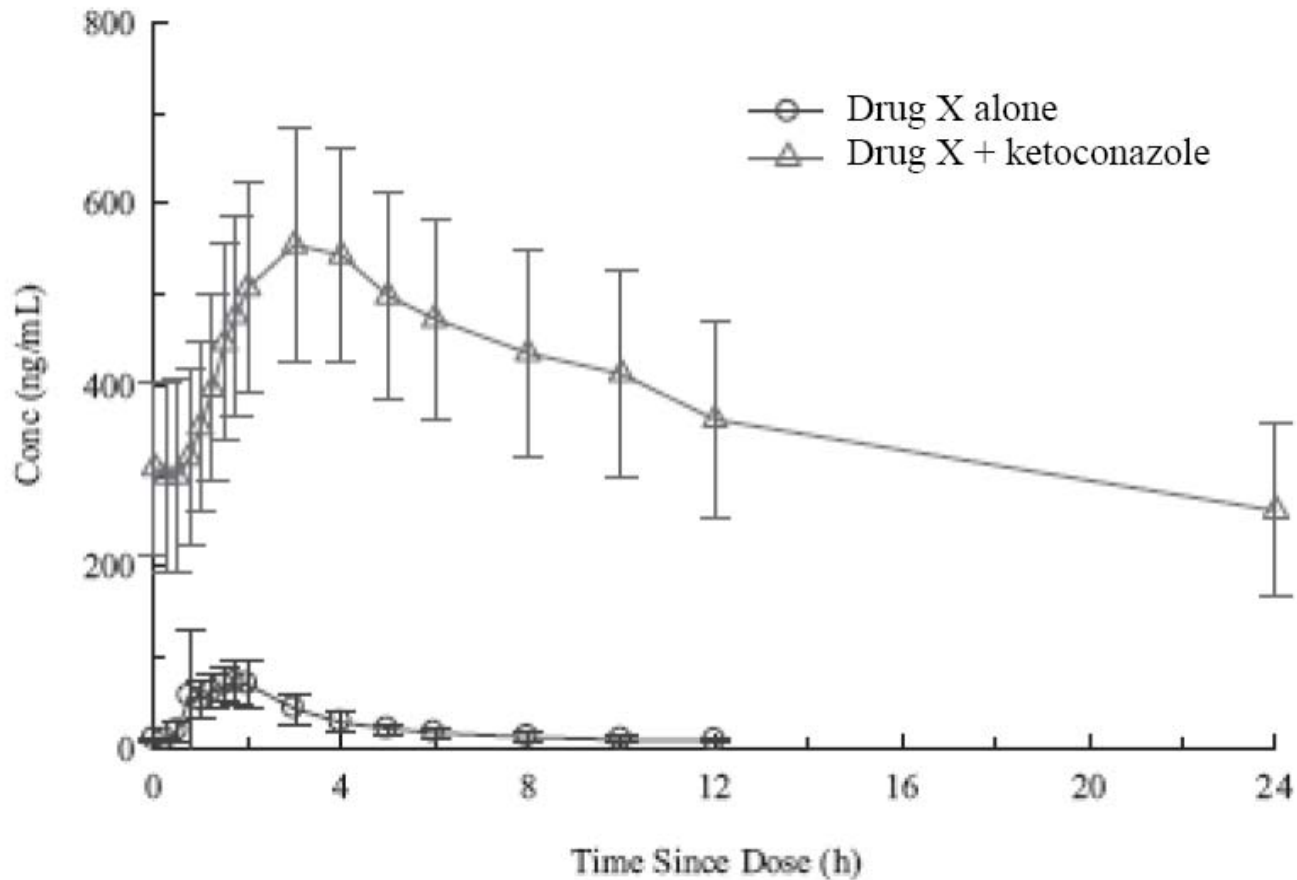
Impact of Renal and Hepatic Impairment



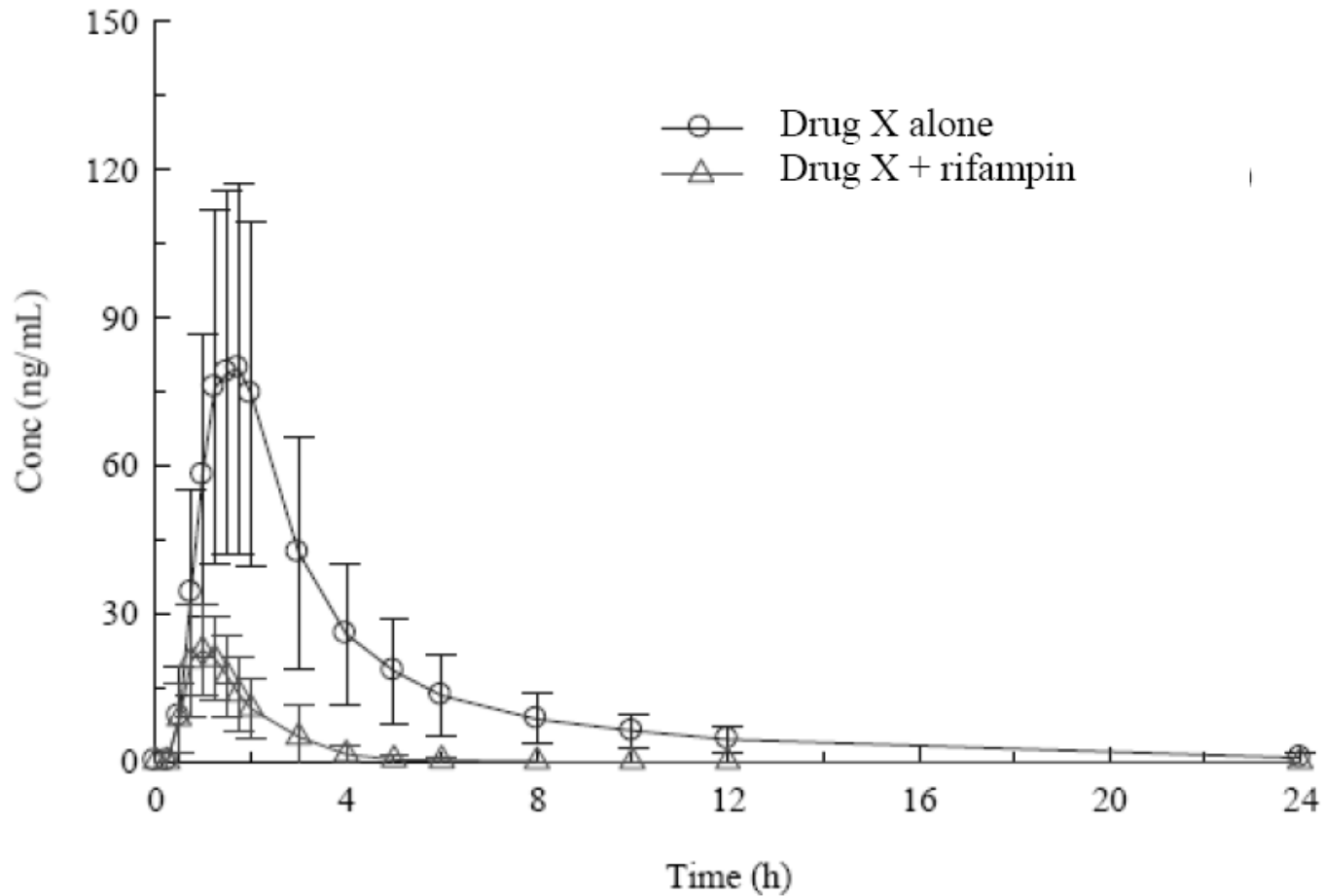
Drug-Drug Interaction Studies

- Evaluate the pharmacokinetics of both or either drug when two drugs are co-administered
- Supports dose adjustments when a drug interaction occurs (either perpetrator or victim drug)
- Can be single or multiple dose
- Usually performed in healthy male and female subjects

Impact of Ketoconazole



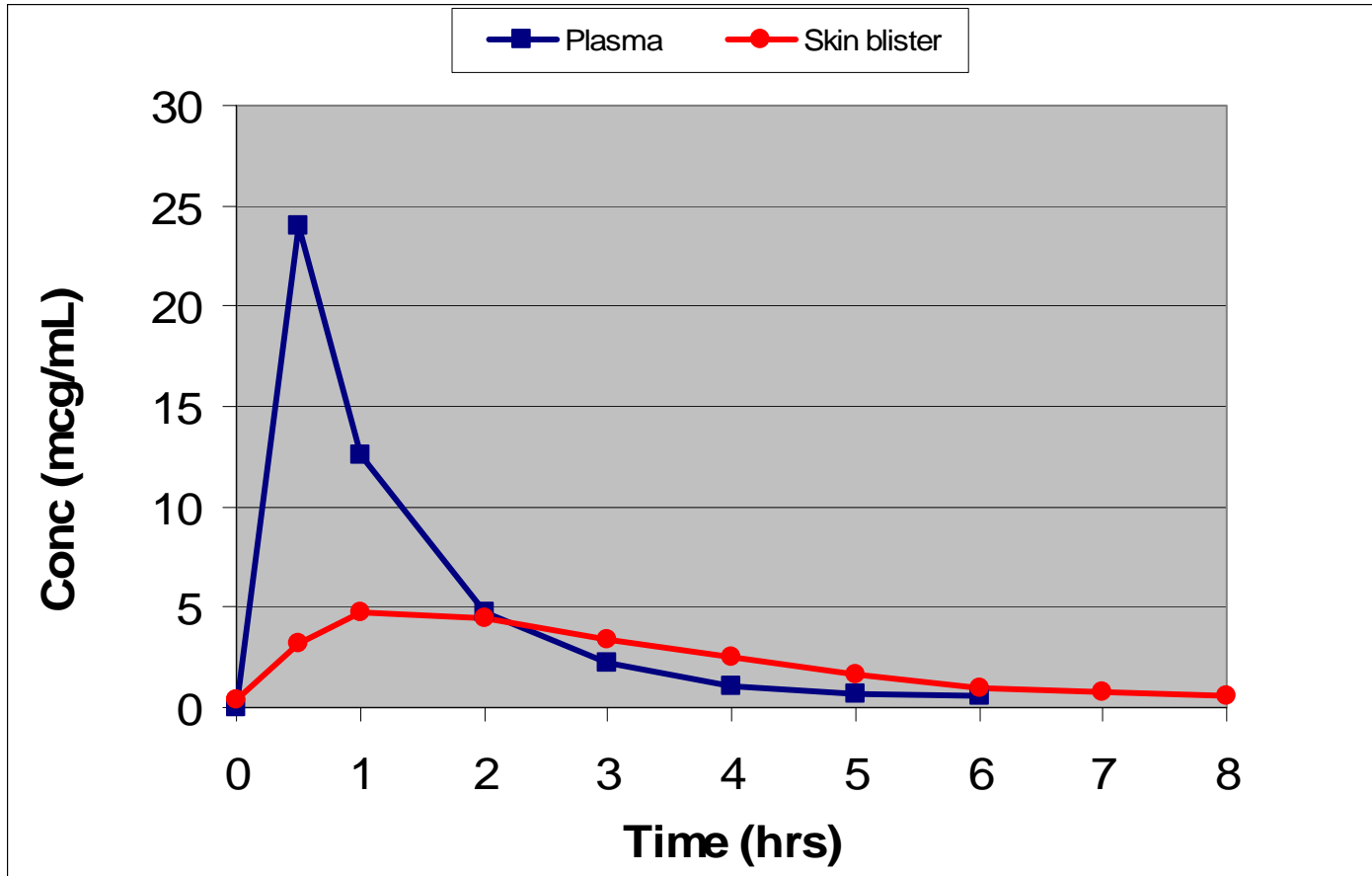
Impact of Rifampin



Tissue Penetration Studies

- Provide an assessment of drug concentrations at the site of action
- Type of study depends upon drug class/site of action (e.g., penetration into skin blisters, microdialysis, or bronchoalveolar lavage for anti-infectives)
- Can be single-dose or multiple-dose
- May be performed in healthy subjects or patients with the disease of interest

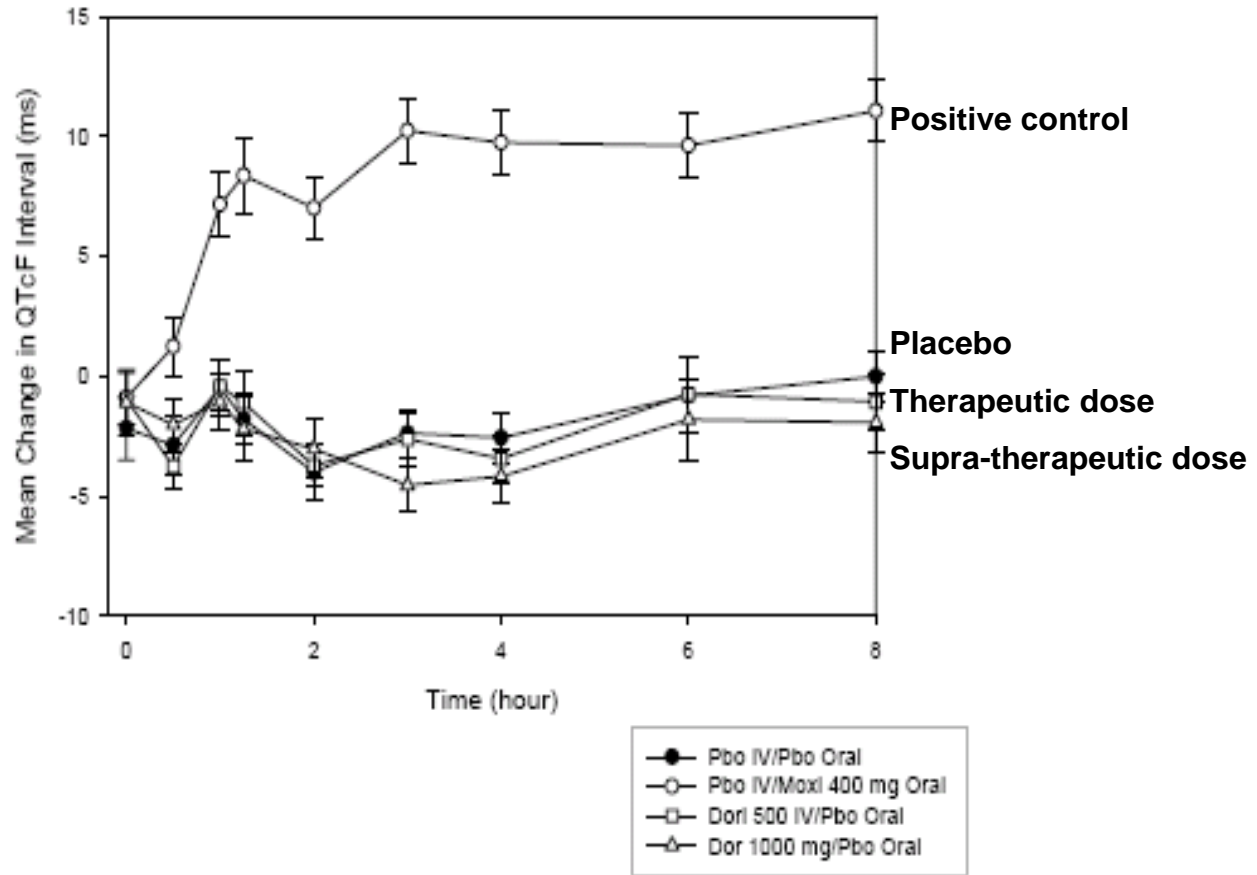
Tissue Penetration



Thorough QTc Studies

- Determines whether a drug has a threshold pharmacologic effect on cardiac repolarization
- The threshold for regulatory concern is an upper bound of the 95% CI around the mean effect on QTc of 10 ms
- Performed in healthy male and female subjects
- Usually single-dose (for drugs with short half lives and no metabolites)
- Usually a crossover study design (but can be parallel study)
- Should evaluate concentrations higher than those achieved following the anticipated clinical dose

Thorough QTc Study (4-Way Crossover)



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- **Illustrate the importance of bioequivalence studies**
- Define the role of DSI to ensure data integrity


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
- Links the clinical trial formulation with the to-be-marketed formulation (NDAs)
- Links the innovator formulation with the generic formulation (ANDAs)

How is BE Determined?


- Usually based on pharmacokinetic measures of C_{max} and AUC for systemically available drugs
- Test and Reference products are considered bioequivalent when the 90% CI of the geometric mean ratios (T/R) of C_{max} and AUC are within 80% to 125%

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 decreasing order of accuracy, sensitivity, and reproducibility


Bioequivalence Endpoints (cont.)

- 
- 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

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

Bioequivalence Endpoints (cont.)

- 
- 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

When is a Bioequivalence Study Necessary?

- For NDAs:
 - When the to-be-marketed formulation is different than the clinical trial formulation
 - When changes are made to the marketed formulation
- For ANDAs comparing the generic versus the innovator formulation

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- Define the role of DSI to ensure data integrity of BE studies

Role of the Division of Scientific Investigations (DSI)

- Upon request, DSI performs inspections with the Office of Regulatory Affairs (ORA) of the bioanalytical and/or clinical sites to verify the accuracy, quality, and integrity of the data
- Critical points of inspection of bioanalytical sites:
 - Analytical method validation
 - Acceptance criteria during in-study validation
 - Handling of samples
 - Repeat analysis of samples
 - Equipment logs, SOPs
 - Correspondence logs
 - Confirmation of data included in final study report

Inspections of Bioanalytical Sites

- Confirms that the data supporting a regulatory decision are valid and accurate

Role of the Division of Scientific Investigations (DSI)

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

Subject Safety

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

Dosing

- Who received what?
 - Actual treatment administered
 - Test versus reference
 - Was the randomization scheme adhered to?
- When did they receive it?
 - Actual dosing time

Drug Products

- Accountability
 - Number of tablets administered, returned, remaining
- Lot numbers
 - Verify information provided to FDA
- Control of drug storage area
 - Security, temperature, humidity

Blood Draw Time

- Were samples processed according to the protocol?
 - Temperature, centrifugation, within specified time frame
- Were processed samples (e.g., plasma, serum) stored appropriately?

Adverse Events

- Were all adverse events reported?

Protocol Adherence

- Including/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 prior to dosing

Reserve Samples

- Retained samples that are representative of the actual drug products used in the study
 - Reserve samples help the FDA to investigate instances of possible fraud in BE testing
- 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
 - Maintained in sufficient quantity to permit FDA to perform 5x all of the release tests required in the application

21 CFR 320.28 “Retention of bioavailability samples” and 21 CFR 320.63 “Retention of bioequivalence samples”

Reserve Samples (cont.)

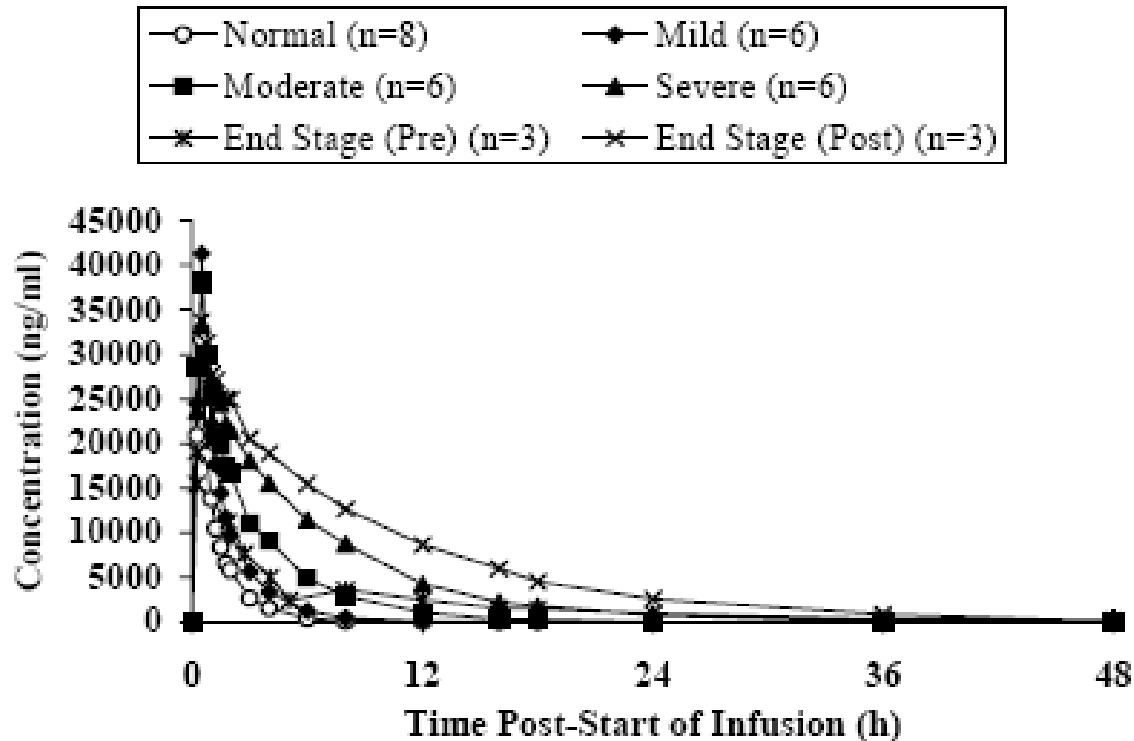
- Reserve samples must be:
 - Retained for a period of at least 5 years following the date on which the application or supplemental application is approved, or if the application is not approved, at least 5 years following the date of completion of the bioavailability study in which the sample from which the reserve sample was obtained was used.
 - Stored under conditions consistent with product labeling
 - Reserve samples are sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis

21 CFR 320.28 “Retention of bioavailability samples” and 21 CFR 320.63 “Retention of bioequivalence samples”

Questions???



Specific Populations - Renal Impairment



Specific Populations - Renal Impairment

		(Renal impairment /Normal)		
Renal impairment [Group]	AUC_{0-∞}	Estimate	90 % CI	p-value
Normal [A-D]	36929	.	.	.
Mild [A]	59455	1.61	(1.33, 1.95)	0.0003
Moderate [B]	104505	2.83	(2.33, 3.43)	<.0001
Severe [D]	188409	5.10	(4.20 6.19)	<.0001
End Stage (Pre) [C]	99659	2.70	(2.12 3.44)	<.0001
End Stage (Post) [C]	269541	7.30	(5.73 9.30)	<.0001

Tissue Penetration Studies

