BIOAVAILABILITY & BIOEQUIVALENCE TRIALS

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STRUCTURE OF THE TALK

- Definitions
- Rationale For Conducting Bioavailability (BA) & Bioequivalence (BE) Studies
- Key Consideration For Conduct Of Bioavailability & Bioequivalence Trials
- Evolution of Bioequivalence Criteria
- Present Issues In Bioequivalence Studies
- Conclusions

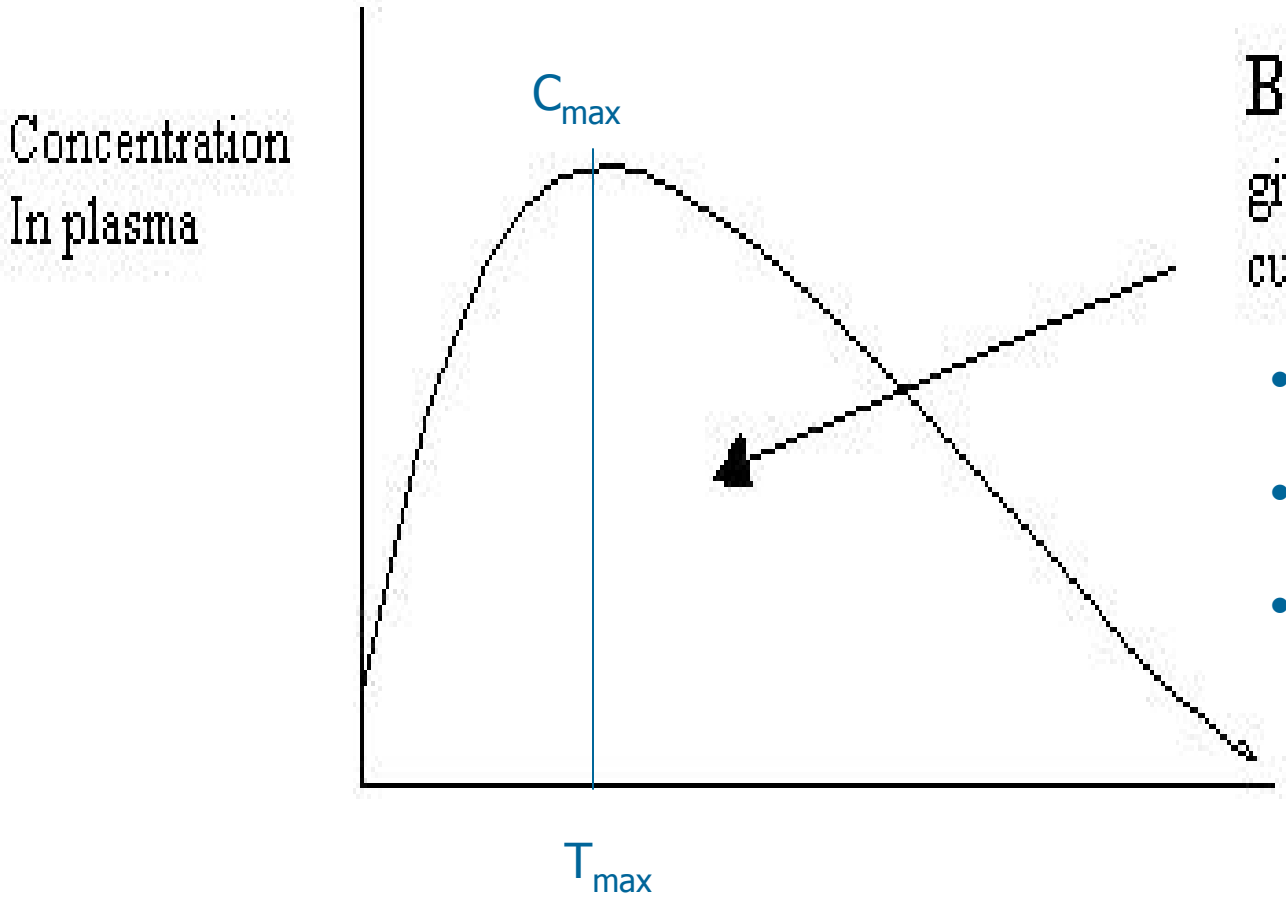
Definition Of Bioavailability (BA)

FDA Official statement (1997)

The rate and extent to which the active drug ingredient of therapeutic moiety is absorbed from a drug product and becomes available at the site of action

- The extent of bioavailability: AUC , C_{max}
- Rate of availability: C_{max}, T_{max}

Definition Of Bioavailability (BA)



Bioavailability (for a drug given orally) is the area under the curve.

- AUC - Area under the concentration- time curve
- C_{max} - Maximum concentration
- T_{max} - Time to maximum concentration

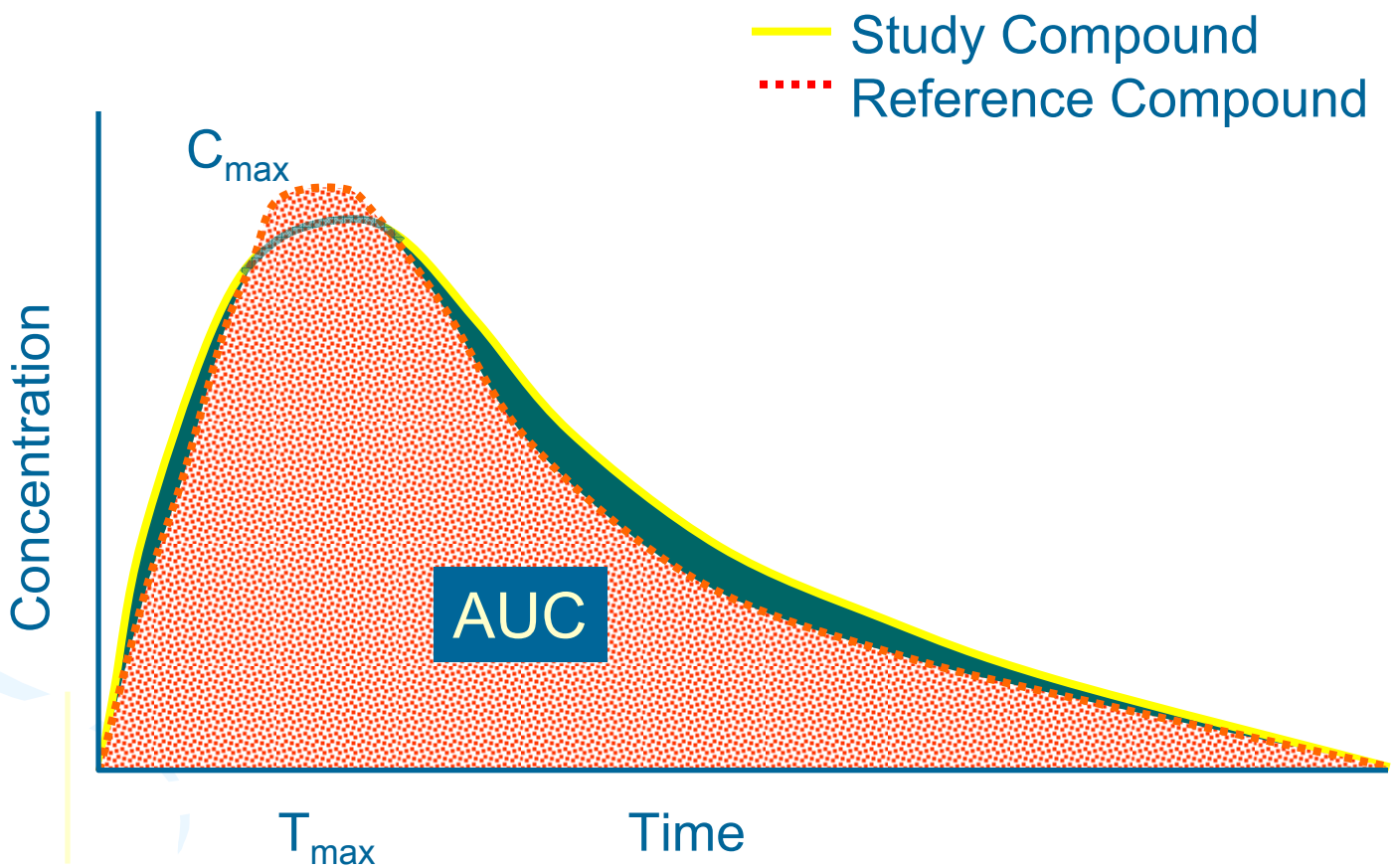
Definition Of Bioequivalence (BE)

FDA Official statement (1997)

Two formulations are said to be bioequivalent if

"The rate and extent of absorption of the test drug do not show a significant difference from the rate and extent of absorption of the reference drug, when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either single dose or multiple doses"

Definition Of Bioequivalence (BE)



Approved Drug Products With Therapeutic Equivalence Evaluations. 23rd ed. 2003. FDA/CDER Web site. Available at: http://www.fda.gov/cder/ob/docs/preface/ecpreface.htm#Therapeutic Equivalence-Related Terms. Accessed September 29, 2003.

Need for Conducting Bioavailability & Bioequivalence Studies

BA

- To evaluate the absolute systemic availability of active drug substance from a dosage form
- To determine the linearity of the bioavailability parameters over the proposed clinical dose range
- To estimate the inter and intra subject variability
- To study the effect of food on bioavailability

Need for Conducting Bioavailability & Bioequivalence Studies

BE

- When the proposed marketed dosage form is different from that used in pivotal clinical trials
- When significant changes are made in the manufacture of the marketed formulation
- When a new generic formulation is tested against the innovator's marketed product

Definition of Generic drugs

Generic drug is identical, or bioequivalent to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use.

Why Generic Products Are Required

- The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act) gave generic drug companies greater access to the market for prescription drugs, and gave innovator companies greater patent life.
- The patent gives a company the sole right to sell the drug while the patent is in effect. When patents or other periods of exclusivity expire, manufacturers can apply to the FDA to sell generic versions.

Why Generic Products Are Required

- Need by payers, including government, and formularies to reduce healthcare costs
  - Congressional Budget Office estimates generics save consumers $8 to $10 billion a year at retail pharmacies (http://www.fda.gov/cder/ogd/)
- Expense of brand name drugs for patients, such as seniors on fixed income, can be substantial

Why Generic Products Are Required

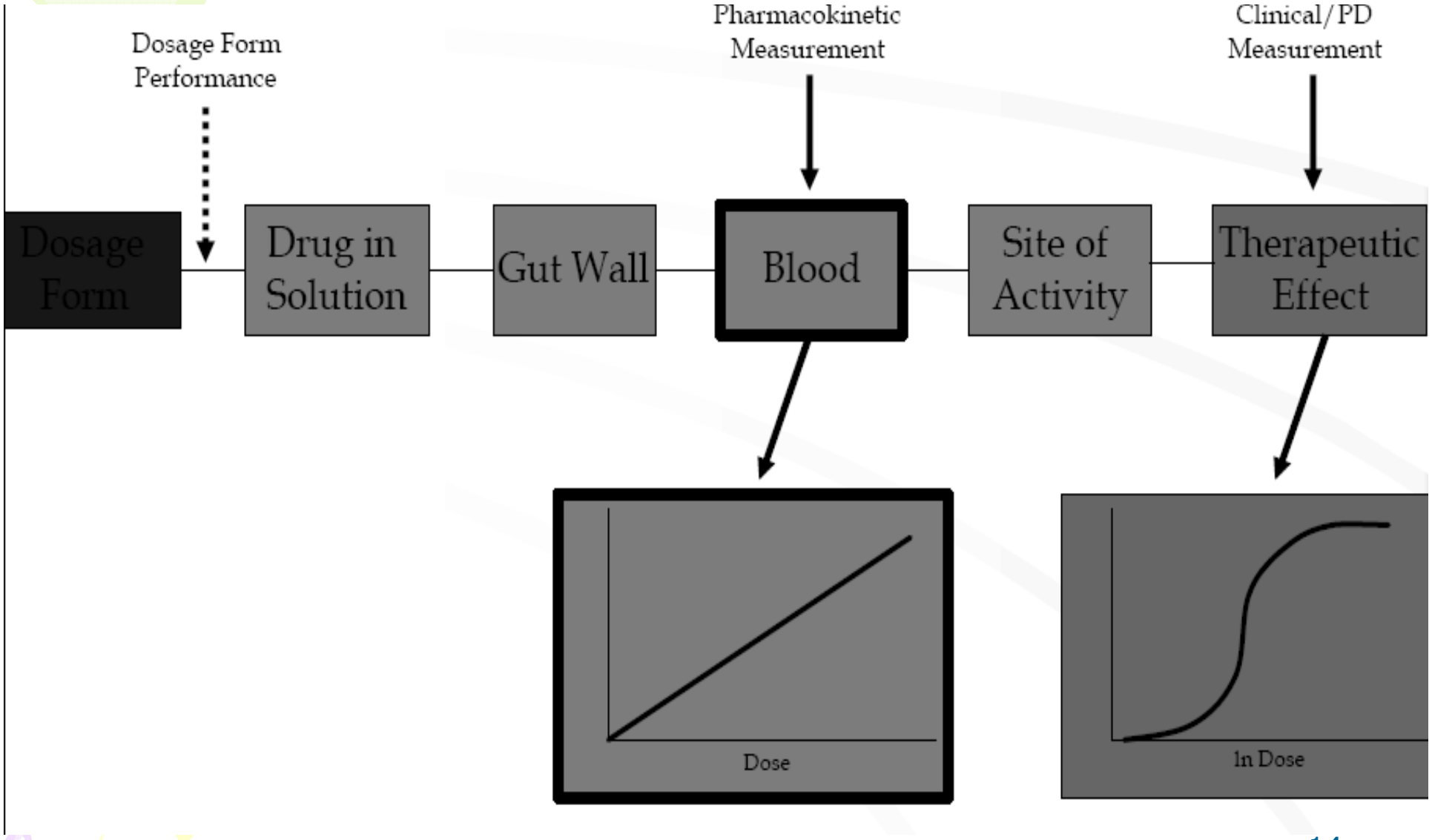
- Save an average of $45.50 for every prescription sold
- Currently used in 44% of all prescriptions dispensed
- Currently save $56.7 billion/year to consumers
- Can save customers an additional $1.32 billion/year for every 1% increase in the use of generic drugs

Can help both consumers and the government to reduce the cost of prescription drug

Approaches to Determining Bioequivalence (21 CFR 320.24)

- In vivo measurement of active moiety or moieties in biologic fluid
- In vivo pharmacodynamic comparison
- In vivo limited clinical comparison
- In vitro comparison
- Any other approach deemed appropriate by FDA

Model of Oral Dosage Form Performance



Key Consideration for Conduct of Bioavailability & Bioequivalence Studies

Designing the Bioavailability and Bioequivalence Trials

- Sufficient number of healthy volunteers are recruited
- PK sampling for at least 3.3 half-life of the drug
- 3-4 points in each phase of the PK profile
- More number of PK samples around T_{max}

Key Inclusions and Exclusion Criteria for the Selection of Volunteers

Typical Inclusion Criteria:

- Male, 20-40 years of age
- Body weight + 10% of the desirable weight for height and frame
- Stable health (ECG, physical examination, blood and urine tests)
- Signed Informed Consent Form

Key Inclusions and Exclusion Criteria for the Selection of Volunteers

Typical Exclusion Criteria

- History of drug abuse
- Any finding in the medical history, physical examination or clinical laboratory tests giving reasonable suspicion of a disease/condition that would contraindicate taking the investigational drug, or that might affect the interpretation of results of the study
- Conditions requiring concomitant medication

Key Inclusions and Exclusion Criteria for the Selection of Volunteers

Typical Exclusion Criteria

- Medication or drug use within 1 month prior to study initiation with any agent known to induce or inhibit drug-metabolizing enzymes
- Medications or drug use of any kind, including OTC medication within one week prior to study initiation

Key Inclusions and Exclusion Criteria for the Selection of Volunteers

Typical Exclusion Criteria

- A positive laboratory test for Hepatitis B surface antigen or urine screen for drugs of abuse
- Smokers
- Donation of blood within 60 days prior to study initiation
- Significant psychiatric disorders
- A history of hypertensitivity of intolerance, that in the opinion of the investigator, would compromise the study or safety of the subject

Standard Designs used in Bioavailability and Bioequivalence Trials

- Single-dose, two-way crossover, fasted
- Single-dose, two-way crossover, fed
- Multiple-dose, two-way crossover, fed
- Alternatives
  - Single-dose, parallel, fasted
  - Single-dose, replicate design
  - Multiple-dose, two-way crossover, fasted
  - Clinical endpoint study

(http://www.fda.gov/cder/guidance/3615fnl.pdf)

Standard Designs used in Bioavailability and Bioequivalence Trials

Cross Over Design

	Period	
VOL. No.	1st phase	2nd phase
1	A	B
2	B	A
3	A	B
4	A	B
5	B	A
6	A	B
7	B	A
8	B	A
9	A	B
10	B	A
11	B	A
12	A	B

Standard Designs used in Bioavailability and Bioequivalence Trials

Parallel Group Design:

Group 1	Group 2
A	B
1	2
3	4
5	6
8	7
9	10
12	11

Standard Designs used in Bioavailability and Bioequivalence Trials

Latin Square Design:

	Periods	
	1	2
1	A	B
2	B	A

Evolution of Bioequivalence Criteria

Criterion for Bioequivalence

For many years, ANOVA was the test of choice

$H_0 : \mu_T = \mu_R$ or formulations are bioequivalent

vs

$H_1 : \mu_T \neq \mu_R$ or formulations are bioinequivalent

Criterion for Bioequivalence

Drawbacks of ANOVA

A small difference, probably of no therapeutic importance, may be shown to be statistically significant if

- the trial is run under tightly controlled conditions
- the number of subjects is large enough

A large difference may shown to be statistically insignificant if

- there are sloppy designs
- assay variability is large
- within formulation variability
- the number of subjects is not enough

Contd.

Criterion for Bioequivalence

Drawbacks of ANOVA

FDA requirements:

Test at 5% level of significance with 80% power

Level of significance = Manufacturer's risk

Power = 1- Consumer's risk

$\Rightarrow$ Consumer's risk = 1 - Power

Contd

Criterion for Bioequivalence

Drawbacks of ANOVA

FDA guidelines (1978) for bioavailability studies states that

"Products whose rate and extent of absorption differ by 20% or less are generally bioequivalent"

Criterion for Bioequivalence

$-0.2\ \mu_R$ $+0.2\ \mu_R$

$\mu_T - \mu_R$

$-0.2\ \mu_R$ $+0.2\ \mu_R$

$\mu_T - \mu_R$ $\mu_T - \mu_R$

μ_T and μ_R are bioequivalent if

$-0.2\ \mu_R < \mu_T - \mu_R < 0.2\ \mu_R$

Criterion for Bioequivalence

EQUIVALENCE

Does Not Mean

EQUALITY

Criterion for Bioequivalence Confidence interval approach

In 1981, Westlake gave 90% Classical confidence interval for difference as

$$\bar{\mu}_T - \bar{\mu}_R \pm s\sqrt{2/n}.t_{0.05(1),v}$$

Criterion for bioequivalence

$$-0.20\bar{\mu}_R < \bar{\mu}_T - \bar{\mu}_R - s\sqrt{2/n}.t_{0.05(1),v}$$

$$\bar{\mu}_T - \bar{\mu}_R + s\sqrt{2/n}.t_{0.05(1),v} < 0.20\mu_R$$

Criterion for Bioequivalence Testing Of Hypothesis

Schuirmann (1987)

$H_{01} : \mu_T - \mu_R \leq -0.2\ \mu_R$ vs $H_{11} : \mu_T - \mu_R > -0.2\ \mu_R$

$H_{02} : \mu_T - \mu_R \geq 0.2\ \mu_R$ vs $H_{12} : \mu_T - \mu_R < 0.2\ \mu_R$

H_{01} and H_{02} will be rejected if

$$t_1 = \frac{\overline{\mu_T} - \overline{\mu_R} - 0.2\ \overline{\mu_R}}{s.\sqrt{2/n}} \geq t \quad \& \quad t_2 = \frac{0.2\ \overline{\mu_R} - (\overline{\mu_T} - \overline{\mu_R})}{s.\sqrt{2/n}} \geq t$$

H_0 : Products are bioinequivalent

H_1 : products are bioequivalent

Level of Significance

= Consumer's risk

Power = 1 - Manufacturer's risk

Additive Versus Multiplicative Model

The major health authorities recommend the logarithmic transformation for AUC and C_{max}.

RATIONALE

- In the cross over design, the usual assumption is that the observation is a function of additive effects due to subject, period and treatment. But fundamental pharmacokinetic equations are of multiplicative character for example,

  $AUC = Clearance^{-1}.f.dose$

  Taking logarithms, transforms multiplicative character into additive model equation i.e.

  ln AUC = ln Clearance + ln f + ln dose, where ln denotes the natural logarithm.

- AUC and C_{max} have skewed distribution. Logarithmic transformations turn them into symmetrical distributions

Criterion for Bioequivalence
Confidence interval approach after Logarithmic Transformation

$$0.8 < \text{Exp}\left(\hat{\mu}_T - \hat{\mu}_R - s\sqrt{\frac{2}{n}}.t_{0.05(1),v}\right)$$

$$\text{Exp}\left(\hat{\mu}_T - \hat{\mu}_R + s\sqrt{\frac{2}{n}}.t_{0.05(1),v}\right) < 1.25$$

Parametric Vs. Non-parametric Tests

- If the assumptions of log-normality of data, homogeneity and independence of errors are valid, parametric tests are more powerful than non-parametric tests.
- But if the assumptions are in doubt, non-parametric confidence intervals and tests such as Mann Whitney-Wilcoxon tests Wilcoxon-signed rank test, etc, depending upon the design should be used.
- As T_{max} does not follow normal or log-normal distribution, non-parametric tests are recommended for T_{max}.

International Harmonization Of Regulatory Requirements For Bioequivalence Studies

- 90% confidence interval for the difference of bioavailability of test and reference formulations should lie in *Bioequivalence range*
- Bioequivalence range is
  - **(0.8, 1.20) for untransformed data**
  - **(0.8, 1.25) for log transformed data**
- Logarithmic transformation for AUC and C_{max}
- Parametric tests are recommended if the assumptions of log-normality of data, homogeneity and independence of errors are valid
- But if the assumptions are in doubt, non-parametric confidence intervals should be used

Present Issues in Bioequivalence Trials

Present Issues in Bioequivalence Trials

Bioequivalence Range

- A single bioequivalence criterion 80 - 125 % at present is applicable to all drugs
- The equivalence range should be based on the clinical relevant differences.
- It should be individualized at least to the class of drugs.

Present Issues in Bioequivalence Trials

Pharmacokinetic Metrics For Rate Of Absorption

Table : Mean ratios and % of studies demostrating / not demonstrating (BE) for the simulated data sets (50% increase in ka from 0.150 to 0.255 h^{-1})

Metric	Mean Ratio	*BE(yes)	*BE(no)
Cmax	1.06	62	38
Cmax/AUCt	1.07	100	0
AUCe	1.04	71	29
AUCr	1.02	80	20
AUCe/AUCt	1.05	100	0
AUCr/AUCt	1.03	100	0
%PTF	1.30	0	100

Present Issues in Bioequivalence Trials

Pharmacokinetic Metrics For Rate Of Absorption

Table : Mean ratios and % of studies demonstrating / not demonstrating (BE) for the simulation data (no difference between formulations in terms of ka)

Metric	Mean Ratio	*BE(yes)	*BE(no)
Cmax	1.00	74	26
Cmax/AUCt	1.00	100	0
AUCe	1.00	80	20
AUCr	0.98	81	19
AUCe/AUCt	1.01	100	0
AUCr/AUCt	0.99	100	0
%PTF	0.99	38	62

Present Issues in Bioequivalence Trials

HIGHLY VARIABLE DRUGS

Drugs and drug products that exhibit intra subject variability of greater than 30% ANOVA CV in bioavailability parameters

Present Issues in Bioequivalence Trials

High Inter Subject Variability/Genetic Polymoriphism

With drugs under genetic polymorphic metabolism, different pharmacokinetic parameter values are produced

In any case, these procedures involve high costs

Present Issues in Bioequivalence Trials

Gender Differences In Pharmacokinetics

Present Issues in Bioequivalence Trials

Bioequivalence of Biopharmaceuticals

- In the near future, the patents of some RECOMBINANT-DNA-derived pharmaceuticals will expire
- We lack the technology to establish whether the structures of two biopharmaceuticals are completely identical

Present Issues in Bioequivalence Trials

Bioequivalence of drugs with long half-life

Present Issues in Bioequivalence Trials

Bioequivalence of endogenous substances

Present Issues in Bioequivalence Trials

Use of healthy volunteers in Bioequivalence

Conclusions

- During the last few years, there is a major progress in policies and procedures concerning the determination of bioequivalence
- Presently, there is international harmonization of regulatory requirements for bioequivalence studies
- However, the trend in the near future appears towards achieving the appropriate choice of clinically relevant bioequivalence ranges based on therapeutic ranges, rate of absorption metrics, designs to resolve the issue of intra and inter subject variabilities etc.