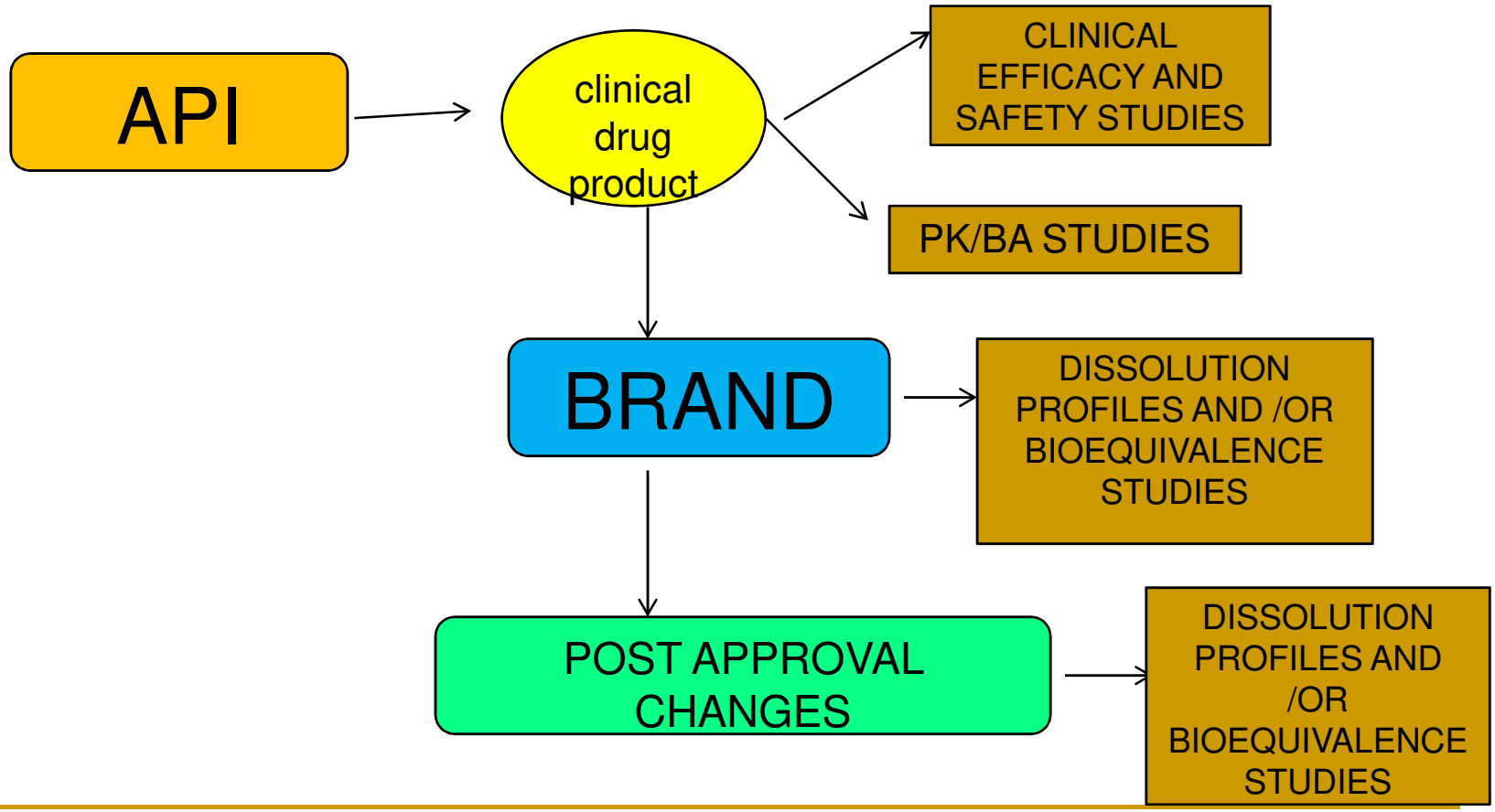
BIOAVAILABILITY/ BIOEQUIVALENCE

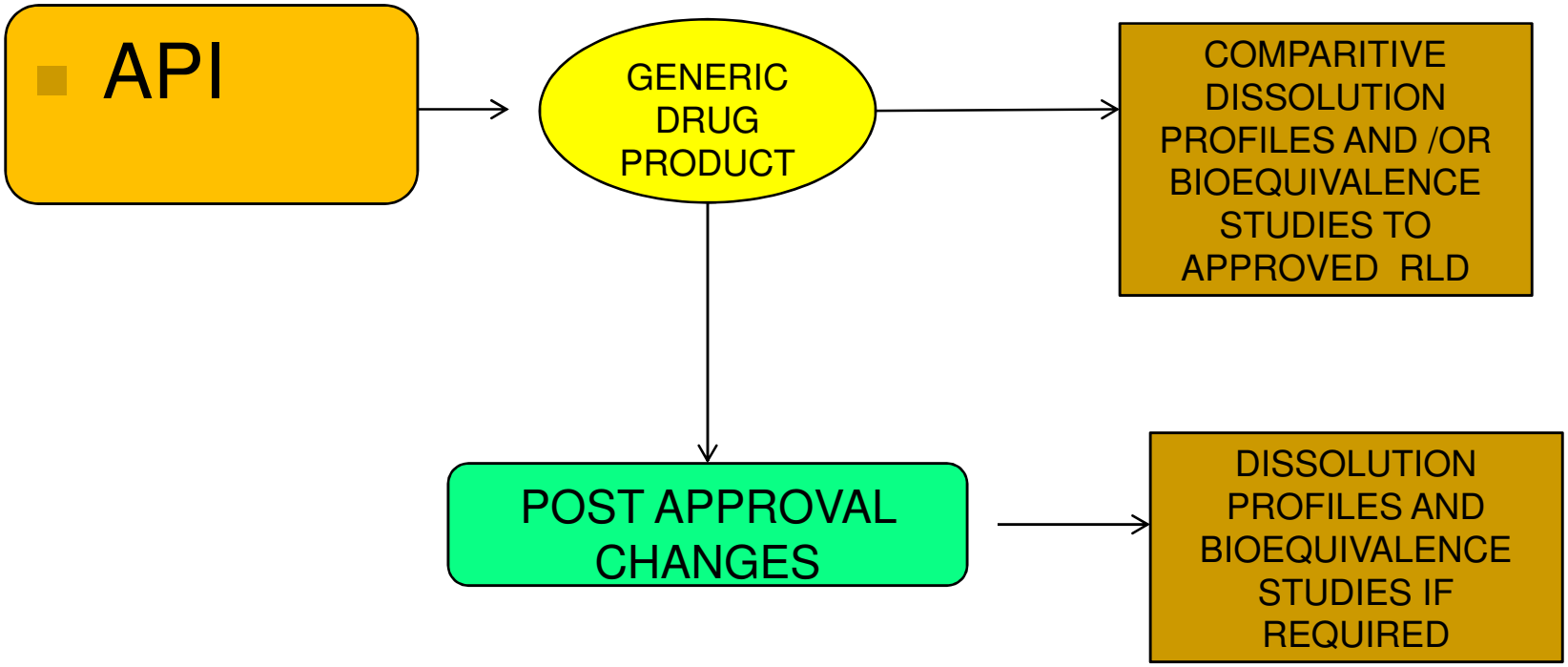
Dr.K.Latha

- Time course of drug
- Route of administration
- Characteristics of drug
- Solubility, permeability
- Presence of other materials
- Lipid soluble-prodrugs
- Poor water solubility-change of dosage form, particle size reduction, prodrugs
- Chemical degradation
- Preabsorptive metabolism

DRUG PRODUCT PERFORMANCE AND DRUG PRODUCT DEVELOPMENT



DRUG PRODUCT PERFORMANCE AND GENERIC PRODUCT DEVELOPMENT



- **Generic -** A generic drug is generally comparable to the brand-name drug in dosage, strength, and intended use. Generic drugs typically cost less than brand name drugs. Multi source drug product
- Multi-source drugs are those that are available both as the brand-name drug, and as generic equivalents or generic alternatives.

- Single source drug
- When a patent expires for a brand drug, the FDA sometimes grants a period of exclusivity (typically lasting six months) to one company to make the generic form of the drug.
- The company may be the same maker as the brand drug or an entirely different company.
- During this time, there is a “single source” for the generic drug and no other company can produce the generic until the exclusivity period expires.

- source drugs are those brand-name drugs that do not have a generic equivalent or generic alternative.
- Drug product selection and generic product substitution are major responsibilities for physicians, pharmacists and others who prescribe, dispense or purchase drugs.
- To facilitates decision, the US food and drug administration (FDA) publishes annually, in print and on the internet.

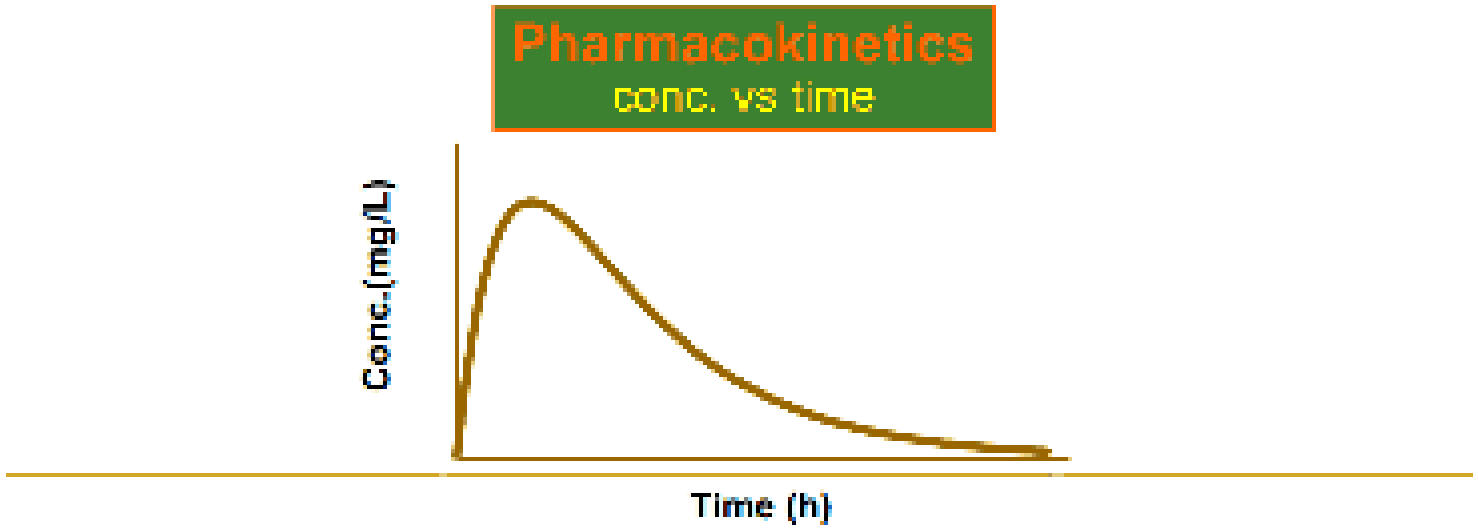
- Approved drug products with therapeutic equivalence evaluations----known as orange book.

  (www.fda.gov/cder/ob/default.htm)
- Bioavailability: rate and extent of drug absorption.
- Bioequivalence requirement
- Bioequivalent drug product

Bioavailability

(quantifies ABSORPTION = ?, Reasons for poor F)

- The extent and rate at which its active moiety is delivered from pharmaceutical form and becomes available in the systemic circulation



- Brand name
- Chemical name
- Abbreviated new drug application (ANDA)
- Drug product
- Drug product selection
- Drug substance
- Equivalence
- Generic name

- Generic substitution
- Pharmaceutical alternatives
- Pharmaceutical equivalents
- Pharmaceutical substitution
- Reference listed drugs
- Therapeutic alternatives
- Therapeutic equivalents
- Therapeutic substitution

Why do we care about BIOAVAILABILITY?

The "true dose" is not the drug swallowed;
BUT is the drug available to exert its effect.

- Dissolution
- Absorption
- Survive metabolism

May have a drug with very low bioavailability

- Dosage form or drug may not dissolve readily
- Drug may not be readily pass across biological membranes (i.e. be absorbed)
- Drug may be extensively metabolized during absorption process (first-pass, gut wall, liver)

Important component of overall variability

- Variable bioavailability may produce variable exposure

Rate versus Extent of Absorption

Extent of absorption is reflected by AUC
Rate of absorption, ka, is reflected by Tmax
Both Rate and Extent of absorption affect Cmax

Leads to 4 possible relative scenarios:

- (R) Rapid, (E) Complete Absorption
yields a short Tmax, high Cmax, high AUC
- (R) Rapid, (E) incomplete absorption
yields a short Tmax, low Cmax, low AUC
- (R) Slow, (E) complete absorption
yields a long Tmax, high Cmax, high AUC
- (R) Slow, (E) incomplete absorption
yields a long Tmax, low Cmax, low AUC

Purpose

- Approved active drug ingredients
- Therapeutic moieties not yet approved for marketing by FDA.
- *In vivo* studies---- for clinical studies, safety and efficacy.
- For unmarketed drugs—not have full NDA approval by FDA, *in vitro/in vivo* bioequivalence studies must be performed for marketing as generic product.

- Bioavailability studies are performed to define physical changes of drug & drug product on pharmacokinetics of drug.
- Bioequivalence studies are used to compare the bioavailability of the same drug (salt or ester) from various products.
- For in vivo performance of drug product.
- If the drug products are bioequivalent and therapeutic equivalent, then clinical efficacy and safety profile of these are assumed to be similar and are used for substitution for each other.

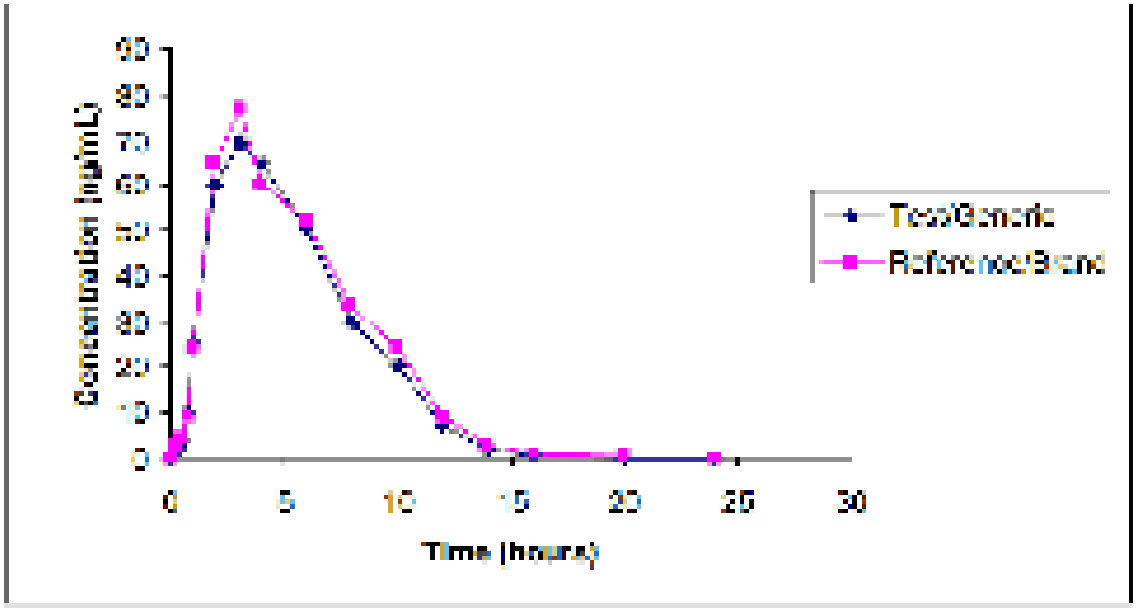
FDA Draft-Guidance for Industry (1997)

Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products

New Dosage Form of a Previously Studied Drug

In some cases, modified release dosage forms may be approved on the basis of pharmacokinetic data linking the new dosage form from a previously studied immediate-release dosage form. Because the pharmacokinetic patterns of controlled-release and immediate release dosage forms are not identical, it is generally important to have some understanding of the relationship of blood concentration to response to extrapolate to the new dosage form.

Bioequivalence



Why do we need Bioequivalence studies?

- No clinical studies have been performed in patients with the Generic Product to support its Efficacy and Safety.
- With data to support similar in vivo performance (= Bioequivalence)
  Efficacy and Safety
  data can be extrapolated from the Innovator Product to the Generic Product.

Approaches to Determining BE (21 CFR 320.24)

- In vivo measurement of active moiety in biologic fluid
- In vivo pharmacodynamic comparison (Topical Corticosteroid)
- In vivo clinical comparison (Nasal suspensions)
- In vitro comparison (Nasal Solution, Topical solution, Oral solution)

- Bioavailability
- Relative bioavailability
- Absolute bioavailability
- Methods for assessment of bioavailability

1. direct method: drug conc. In blood or serum

Tmax,cmax,AUC.

2. Indirect method: urine drug excretion data
3. Acute pharmacodynamic effect
4. Clinical observations
5. in vitro studies
6. bioequivalence studies

Problems with drug products for BA/BE

1. Low solubility
2. slow dissolution rate
3. particle size/surface area
4. structural forms
5. drug products have a high ratio of excipients to active ingredients (>5:1)
6. specific inactive ingredient (excipient)
7. absorption site
8. degree of absorption is poor (<50%)

9. Rapid metabolism & excretion
10. Special coating and formulations.
11. if it is dose-dependent kinetics, rate & extent are important to bioequivalence.

Design:

Design and evaluation requires co-operative input from pharmacokineticists, statisticians, bioanalytical chemists and others.

Basic design is determined by

1. scientific questions to be answered
2. nature of reference & dosage form
3. analytical methods
4. benefit-risk & ethical considerations

- Principal investigator should prepare a detailed protocol for the study.

1. title

A) principal investigator (study director)

B) project/protocol no& date.

2. study objective

3. study design

A) design

B) drug product

i) test ii) reference

C) dosage regimen
D) sampling collection schedule
E) housing/confinement
F) fasting/meals schedule
G) analytical methods
4) study population
A) subjects
B) subject selection
1) medical history
2) physical examination
3) laboratory tests

C) inclusion/exclusion criteria

i) inclusion criteria

ii) exclusion criteria

D) restrictions/prohibitions

5) clinical procedures

A) dosage & drug administration

B) biological sampling schedule & handling procedures

C) activity of subjects

6. Ethical considerations

A) Basic principles

B) institutional review board

C) informed consent

D) indications for subject withdrawal

E) adverse reactions & emergency procedures

7) facilities

8) data analysis

A) analytical validation procedure

B) statistical treatment of data

9) drug accountability

10) appendix

- Before beginning the study , the institutional review board (IRB) of clinical facility must approve the study.
- IRB consists of both professional and lay persons with diverse backgrounds---clinical experience, ethical issues and community attitudes.
- IRB is responsible for safe guarding the rights and welfare of human subjects.
- It’s principle not to do unnecessary human research

- Study is performed in healthy male or female volunteers who have given informed consent
- Critically ill patients are not included unless the attending physician determine the potential benefit to the patient.
- No. of subjects depends on variability---intra, intersubject.
- Patient selection is made.
- Exclusions with known allergies, overweight, under medication (1 week)

- Smokers are often included in the studies.
- Subjects are generally fasted for 10-12 hrs (overnight) prior to drug administration and continue to fast for 2-4 hr after dosing.
- Analytical methods:
- Accurate, precise, sensitive.
- Both parent drug and metabolite are to be measured--- for bioavailability.
- For bioequivalence--- parent drug is measured.
- Active metabolite may be measured for high hepatic clearance drugs, parent drug conc. Is too low.

- Reference standard:
- Is reference listed drug (RLD)---listed in orange book.
- Proposed generic drug product is ‘test’
- RLD– formulations currently marketed with a fully approved NDA for which valid scientific safety and efficacy data are available.
- RLD--- innovator’s or original manufacturer’s brand name product.

Study design

- Three for solid oral dosage forms

1. fasting study
2. food intervention study
3. multi dose (steady state) study

1. fasting study

Single dose, two period, two treatment, two sequence, open labeled, randomized cross over design comparing equal doses of the test and reference products in fasted, adult healthy subjects for both IR and MR oral dosage forms

- Blood sampling, just before (zero time) the dose and at appropriate intervals after dose to get plasma drug conc. time profile.
- Parallel design --- drugs containing long half lives.
- Replicate design--- drugs has high intrasubject variability.

Study Designs

- Single-dose, two-way crossover, fasted
- Single-dose, two-way crossover, fed

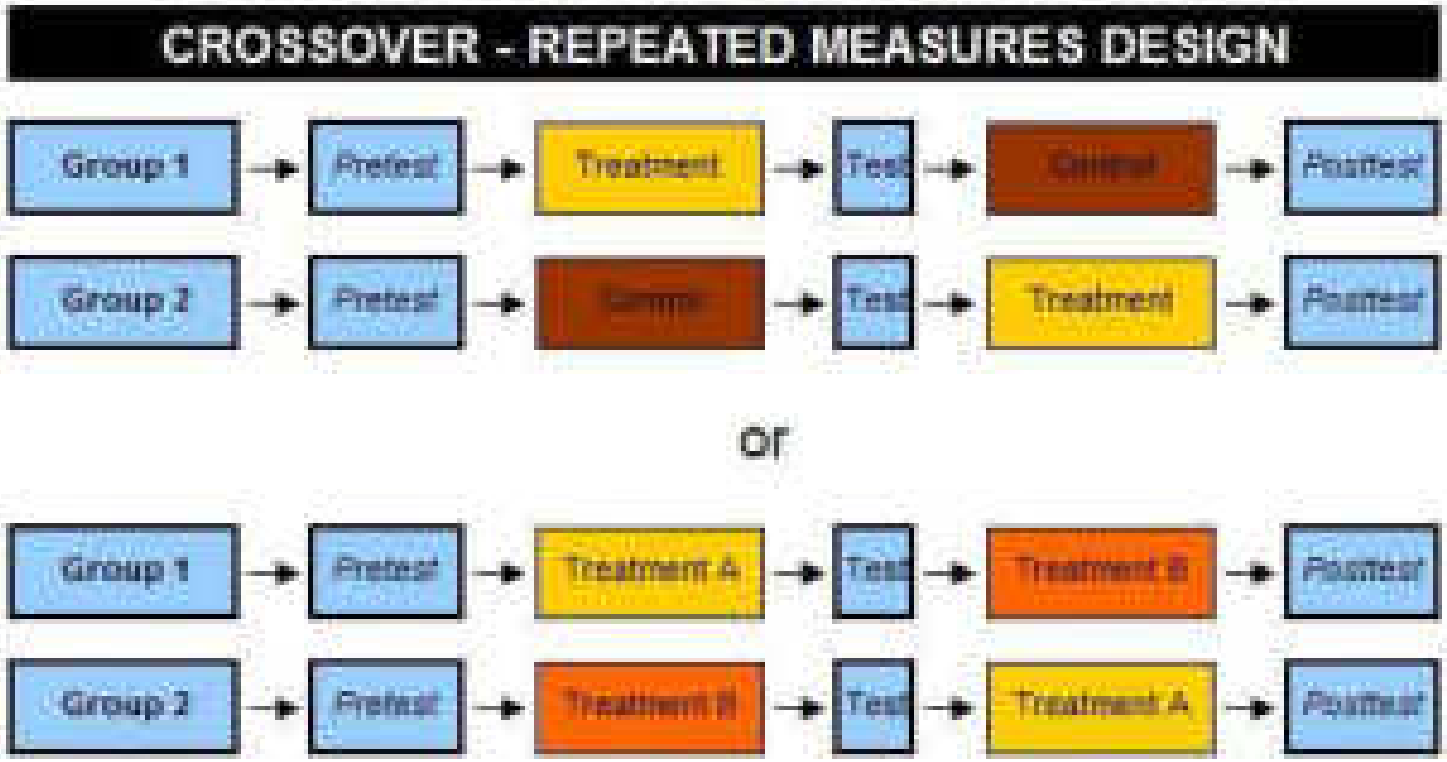
Alternative

- Single-dose, parallel, fasted (Long half-life)
- Single-dose, replicate design (Highly Variable Drugs)
- Multiple-dose, two-way crossover, fasted (Less Sensitive, non-linear kinetic)

Parallel or crossover?, Fasted or Fed?, Single or Multiple?, Replicate or nonreplicate?

Study Designs

- Duration of washout period for cross-over design
- should be approximately > 5 times the plasma apparent terminal half-life
- However, should be adjusted accordingly for drugs with complex kinetic model


CROSSOVER - REPEATED MEASURES DESIGN
Group 1
Pretest
Treatment
Test
Posttest
Group 2
Pretest
Test
Treatment
Posttest
or
Group 1
Pretest
Treatment A
Test
Posttest
Group 2
Pretest
Test
Treatment A
Posttest

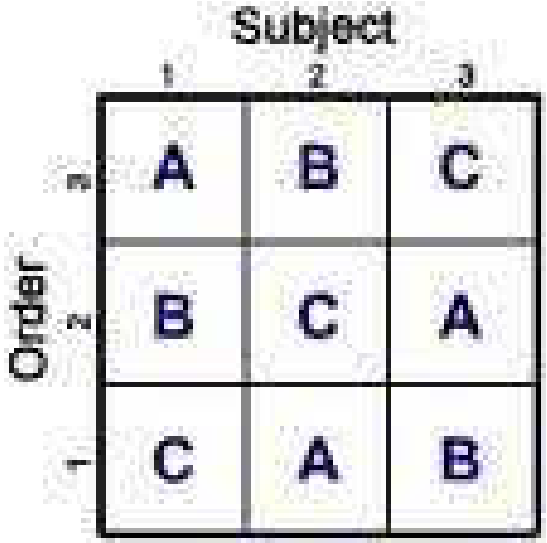
Food intervention study

- Test meal– high fat (approx 50% of total caloric content), high calorie (800-1000 calories)
- Typical test meal is two eggs fried in butter, two strips of bacon, two slices of toast with butter, 4 ounces of brown potatoes, 8 oz of milk.
- After overnight fasting of 10 hrs, subjects are given recommended meal 30 min before dosing---consumed over 30 min with administration of drug product immediately after meal.

- Drug product is given with 240 ml (8 fl.oz) of water.
- No food for at least 4 hrs post dose.
- Multiple-dose (steady state) study:
- In few cases, a multiple dose, steady state, randomized, two treatment, two way crossover study comparing equal doses of the test & reference products may be performed in adults, healthy subjects.

- From these three, through conc. On three consecutive days should be determined to ascertain that the subjects are at steady state.
- Last morning dose is given to the subject after an overnight fast with continual fasting for at least 2 hrs following dose administration.
- Blood sampling is performed similarly to the single dose study.

	col								
	1	2	3	4	5	6	7	8	9
	Treat - ment	Treat - ment	Treat - ment	Treat - ment	Treat - ment	Treat - ment	Treat - ment	Treat - ment	Treat - ment
row									
1	1	3	1	2	2	1	3	2	3
2	2	1	2	3	1	3	1	3	2
3	3	2	3	1	3	2	2	1	1


Subject
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Order
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C
B
C
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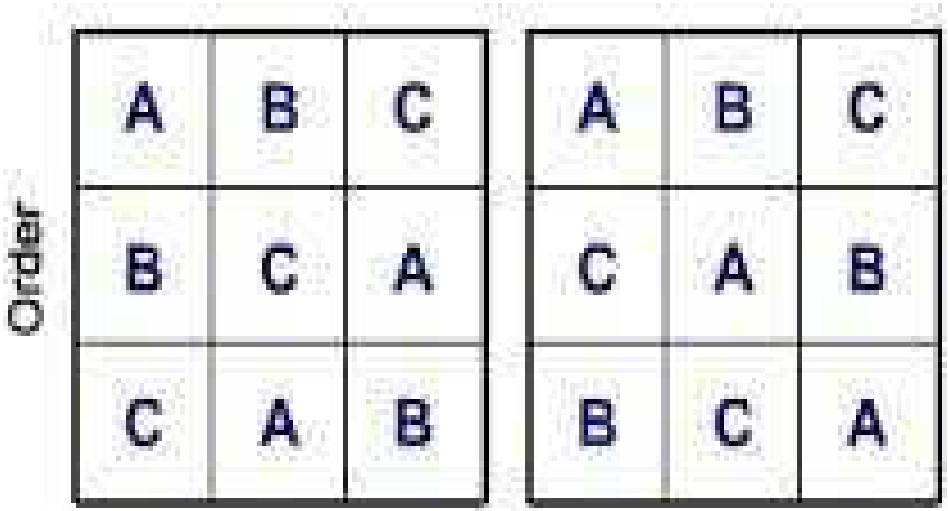
C
A
B


Order
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A

		Treatment for phase No.			
Group	Subjects/group	I	II	III	IV
1	3,8,9,14,18,22	A	B	D	C
2	5,7,12,13,20,13	B	C	A	D
3	1,4,11,16,19,23	C	D	B	A
4	2,6,10,15,17,21	D	A	C	B

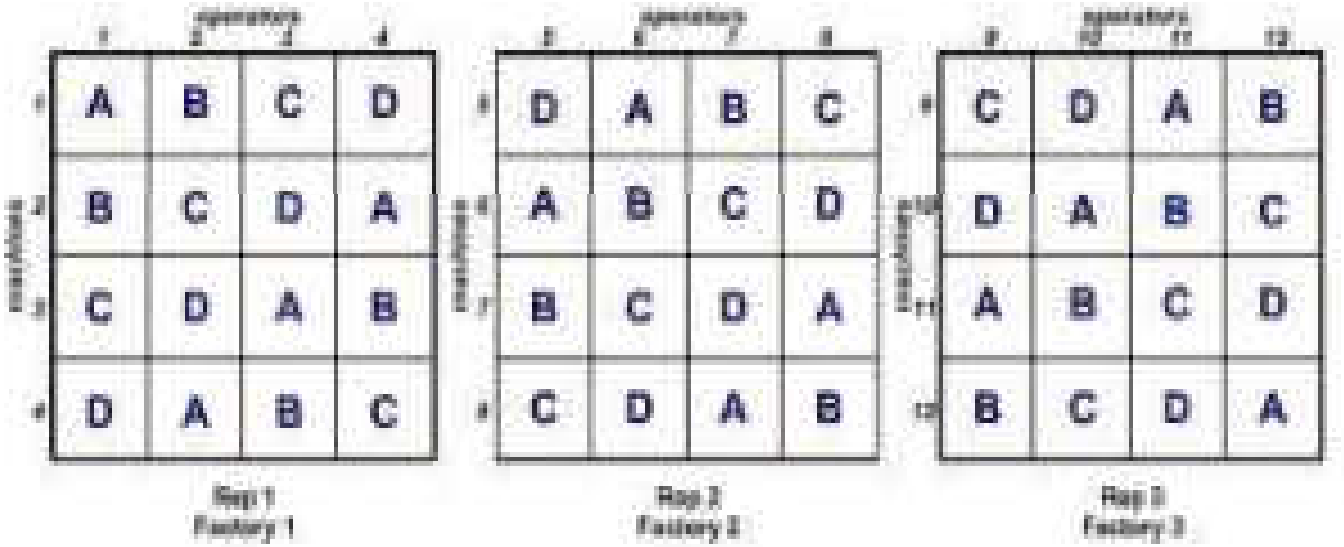
Subject	Product Study Period 1	Study Period 2	Study Period 3
1	A	B	C
2	A	C	B
3	B	A	C
4	B	C	A
5	C	A	B
6	C	B	A

A	B	C	D	E	F	G
B	C	D	E	F	G	A
C	D	E	F	G	A	B
D	E	F	G	A	B	C
E	F	G	A	B	C	D
F	G	A	B	C	D	E
G	A	B	C	D	E	F

- Period: refers the time in which study is performed
- Two period study: performed on two different days separated by washout period----10 half lives.
- Sequence: no.of different orders in the treatment groups in a study.
- Eg: two sequence, two-period study

SQ	PI	PII
Sq1	T	R
Sq2	R	T

Replicated crossover design



- Individual bioequivalence to estimate within subject variance for both the test and reference.

- A four period, two sequence, two formulation design is recommended by FDA.

SQ	PI	PII	PIII	PIV
Sq1	T	R	T	R
Sq2	R	T	R	T

Evaluation of the data

- Analytical method: accuracy, precision, sensitivity and specificity. More than one method may not be valid. Data should be presented in both tabulated and graphic form.

- Pharmaceutical evaluation of data: pharmacokinetic parameters like tmax,cmax, t1/2 , Kel, [AUC]0-t, [AUC]0-α---single dose.

- Multiple dose--- steady state area under the curve [AUC]0-t, tmax, cmax, cmin, % fluctuation [100x cmax-cmin].

- Statistical evaluation of data:

Comparison of population averages---AUC& Cmax.

90% confidence interval for the ratio of averages.

Calculated confidence interval should fall within 80-125% for the ratio of the product averages.

- Many statistical approaches assume that the data are distributed to anormal distribution or bell- shaped curve.
- It may have along right tail than observed in a normal distribution.
- Transformed to a log values resembles more closely to a normal distribution compared to the distribution of non-log transformed data. Hence log transformation of the data is performed before statistical data evaluation.

Analysis of variance

- Test the data for differences within and between treatments & control groups.
- This may evaluate variability in subjects, treatment groups, study period, formulation and other variables depending on study design.
- If the variability in the data is large, the difference in means for each parameter may be masked and investigator might erroneously conclude that the two products are bioequivalent.

- A statistical difference between the parameters obtained from two or more drug products is considered statistically significant if there is a probability of less than 1in 20 times or 0.05 ($p \leq 0.05$)----results have happened on basis of chance.

- To reduce the possibility of failing to detect small differences between the test products, a power test is performed to calculate the probability that the conclusion of the ANOVA is valid.

- Power of test depends on sample size, variability of data and desired level of significance.
- Usually power is set at 0.8 with $\beta=0.2$ and a level of significance of 0.05.
- The higher the power the more sensitive the test and greater the probability that the conclusion of ANOVA is valid.

Two one sided tests procedure

- Confidence interval approach--- used to demonstrate if the bioavailability of test formulation is too low or high in comparison to that of reference product.
- To determine the large differences (>20%) between the mean parameters.

Study submission&drug review process

- Brand name NDA requirement
- 1.Chemistry
- 2. manufacturing
- 3. controls
- 4. labeling
- 5. testing
- 6. animal studies
- 7. clinical studies
- 8. bioavailability
- Safety, efficacy by animal toxicology studies

- Generic drug ANDA requirement
- 1. chemistry
- 2.manufacturing
- 3.controls
- 4.labeling
- 5. testing
- 6. bioequivalence
- ANDA replaces animal and pharmacokinetic studies.

Biowaivers

- In some cases in vitro dissolution testing may be used in lieu of in vivo bioequivalence studies.
- If the drug product is in the same dosage form but in different strengths and is proportionally similar in active and inactive ingredients. An in vivo study of one or more lower strengths can be waived based on the dissolution tests and an in vivo bioequivalence study on the highest strength.

- IR tablet is available in 200 mg,100 mg and 50 mg. 100,50 mg---- invitro studies, 200 mg---human bioequivalence study.
- Manufacturer does not need to perform additional in vivo bioequivalence studies on the lower strength products if the products meet all invitro criteria.

Study Designs

- Sample size determination
  - significant level ($\alpha = 0.05$)
  - 20% deviation from the reference product
  - power > 80%
- Sample time determination
  - adequate data points around t_{max}
  - 3 or more time of $t_{1/2}$ to around AUC_{0-t} = at least 80% AUC_{0-inf}

Study Designs

- Subjects? (Inclusion/exclusion criteria)

LABEL

(such as...)
Healthy subjects (male and female)
18-55 years old, BMI = 18 - 25 kg/m2
Non-smokers/without a history of alcohol or drug abuse
Medical history/Clinical Lab test values must be within normal ranges
Contraindication
Refrain from the concomitants use of any medications or food interact with GI, renal, liver function from 28 days prior study Day1 through the safety follow up-visit.

Statistical Analysis
(Two one-sided Tests Procedure)

- AUC (Extent) and C_{max} (Rate) – Log transformation

- 90% Confidence Intervals (CI) of the difference in Log (AUC_t) –Log (AUC_R) must fit between 80%-125%

Statistical Analysis 80%-125%

- What does this mean?
- Can there be a 46% difference?
- What is a point estimate?
- What is a confidence interval?

Problems of 2×2 Crossover Design

- Overparameterization

Carry-over effect is confounded

- If carryover effect exists, the drug effect cannot be estimated correctly