BIOEQUIVALENCE STUDIES

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CONCEPT OF EQUIVALENTS

➢ Pharmaceutical equivalents

✓ equal amounts of the identical active drug ingredient,
(i.e. the same salt or ester of the therapeutic moiety)
✓ identical dosage forms
✓ not necessarily containing the same inactive ingredients

➢ Pharmaceutical alternatives

✓ identical therapeutic moiety, or its precursor
✓ not necessarily the same:

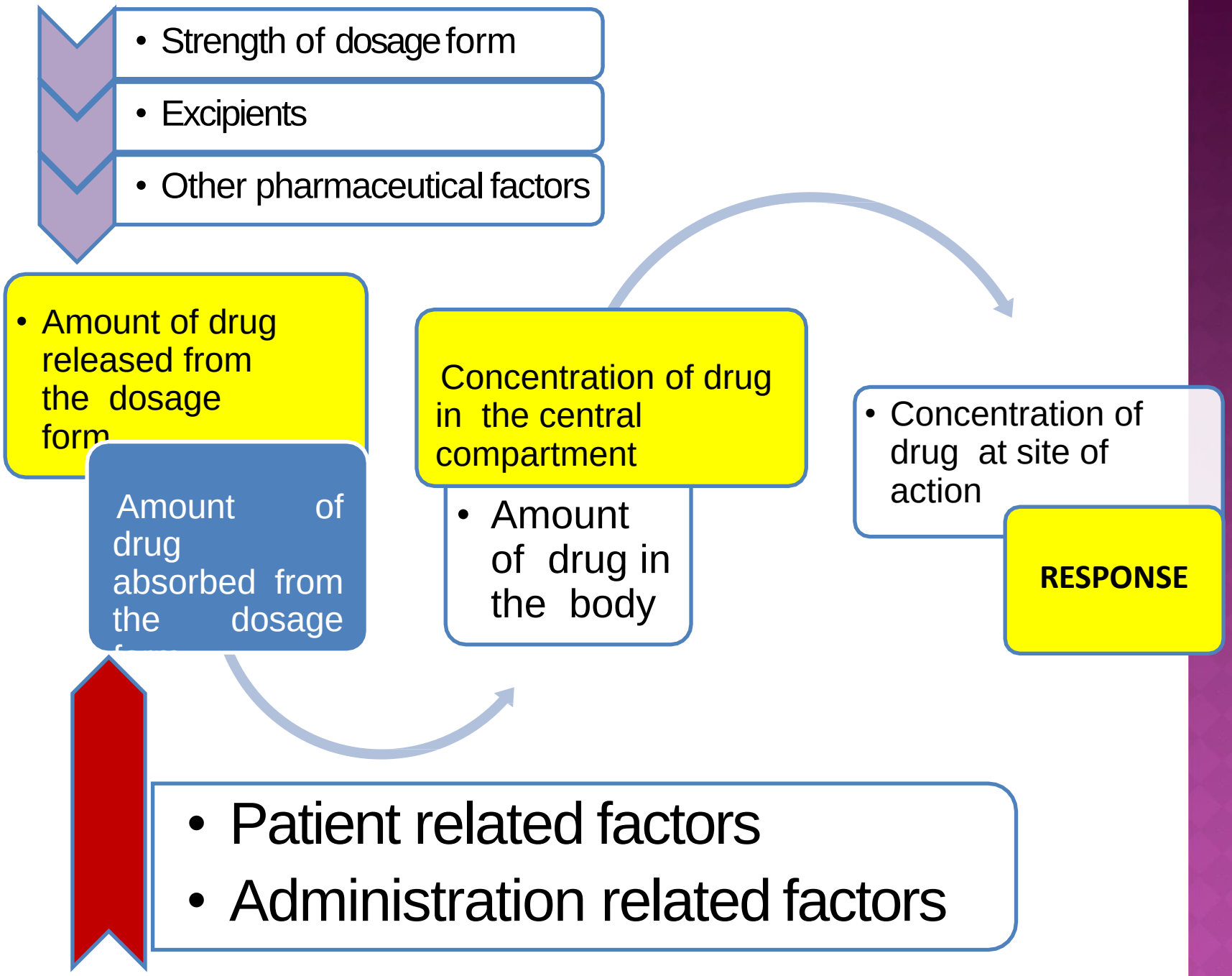
- salt or ester of the therapeutic moiety
- amount
- dosage form

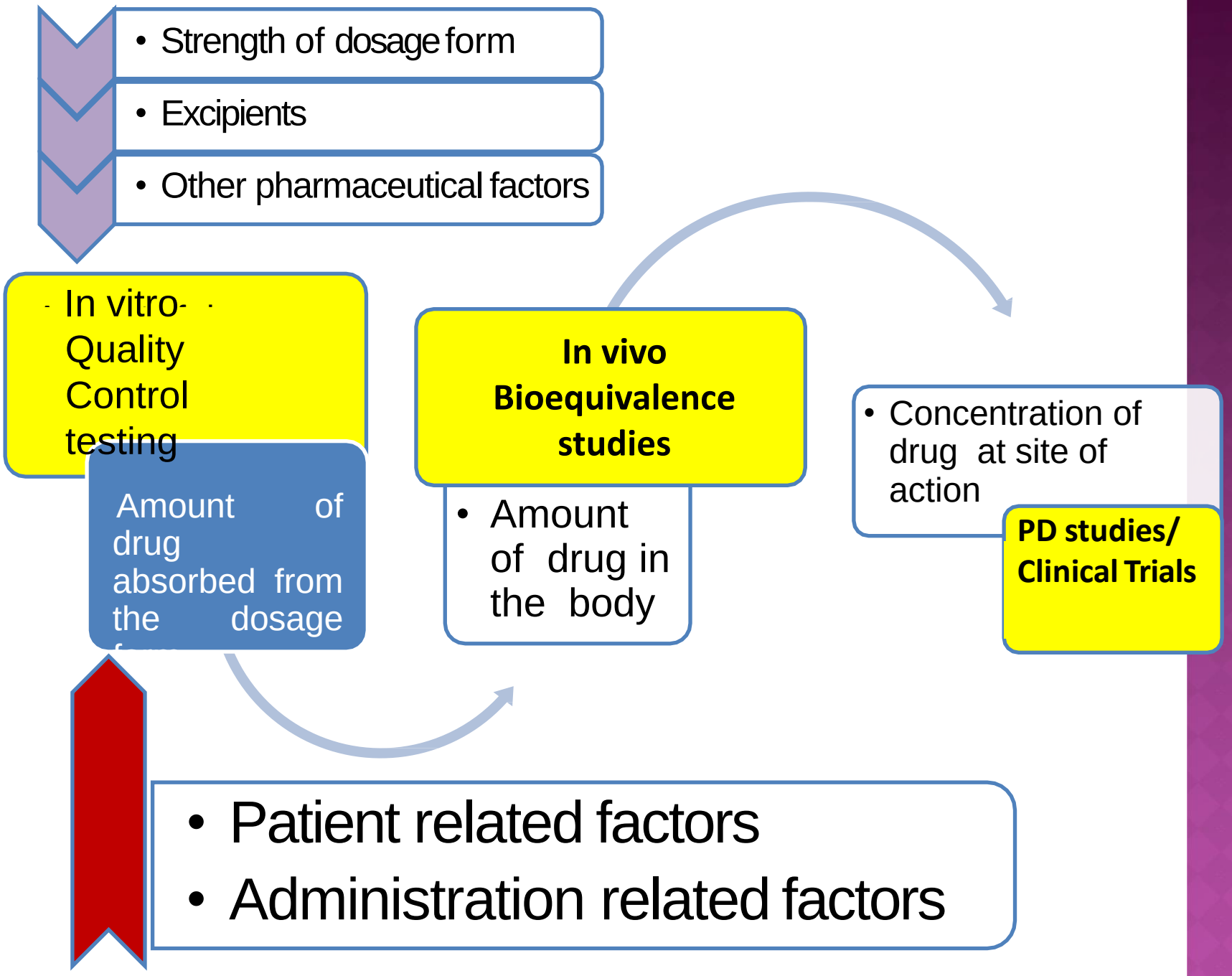
➢ Bioequivalence

- ✓ Pharmaceutical equivalent / alternative of the test product,
- ✓ when administered at the same molar dose,
- ✓ has the rate and extent of absorption
- ✓ not statistically significantly different from that of the reference product

➢ Therapeutic equivalence

- ✓ Same active substance or therapeutic moiety
- ✓ Clinically show the same efficacy & safety profile


• Strength of dosage form
• Excipients
• Other pharmaceutical factors
• Amount of drug released from the dosage form
Amount of drug absorbed from the dosage
Concentration of drug in the central compartment
• Amount of drug in the body
• Concentration of drug at site of action
RESPONSE
• Patient related factors
• Administration related factors


• Strength of dosage form
• Excipients
• Other pharmaceutical factors
In vitro- Quality Control testing
Amount of drug absorbed from the dosage
In vivo Bioequivalence studies
• Amount of drug in the body
• Concentration of drug at site of action
PD studies/ Clinical Trials
• Patient related factors
• Administration related factors

REFERENCE PRODUCT

- ✓ Identified by the Regulatory Authorities as "Designated Reference Product"
- ✓ Usually the Global Innovator's Product
- ✓ Protected by a patent
- ✓ Marketed under manufacturers brand name
- ✓ Clinical efficacy & safety profile is well documented in extensive trials
- ✓ All generics must be Bioequivalent to it
- ✓ In India, CDSCO may approve another product as Reference product

GENERIC DRUG

✓Drug product which is identical or bioequivalent to Brand/ Reference drug in:

- Active ingredient (s)
- Route of administration
- Dosage form
- Strength
- Indications
- Safety

✓<u>May have different</u>:

- Inactive ingredients
- Colour
- Shape

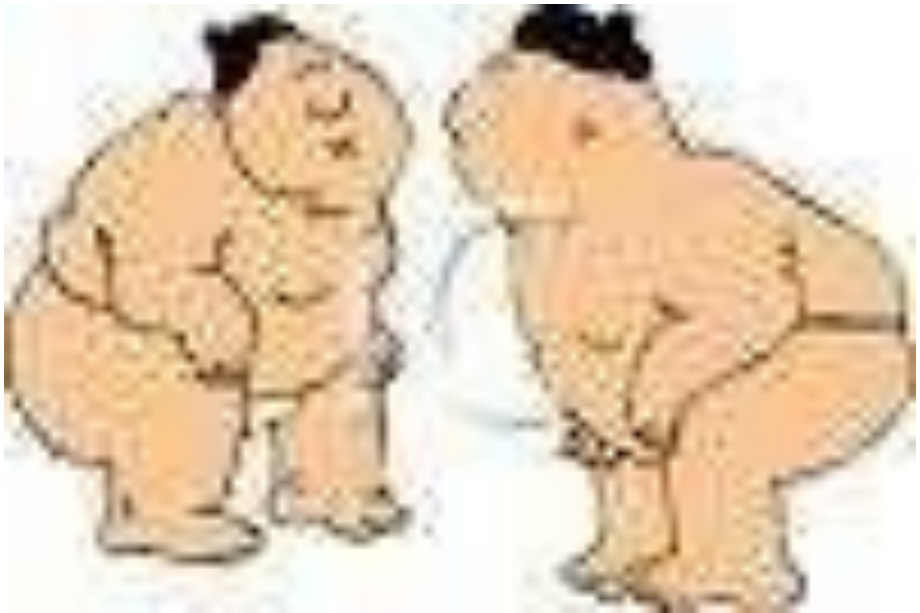
✓Almost half of drugs in market have Generics

PRICE DIFFERENCE BETWEEN REFERENCE & GENERIC DRUGS

Reference Drug	Generic Drug
• Expensive	• 30-80% cheaper
• 5/5000 new drug candidates tested in humans & 1 approved • Takes 12-15 yrs • Costs around 1 billion $	• Since already tested & approved, cost of simply manufacturing • Fraction of the cost of testing & development
• Drug Patents of 20yrs, applied before clinical trials begin • Effectively 7-12 yrs	• Approved for sale after drug patent protection expires

FUNDAMENTAL BIOEQUIVALENCE ASSUMPTION

When a generic drug is claimed **bioequivalent** to a Reference drug, it is assumed that they are **therapeutically equivalent**



BIOEQUIVALENCE BACKGROUND

✓Using bioequivalence as the basis for approving generic copies in US "Drug Price Competition and Patent Term Restoration Act of 1984," also known as the Waxman-Hatch Act

✓Created Generic Industry & ↑ their availability

✓Most successful legislation

✓Benefited Brand & Generic firms

•Generic firms→ Rely on findings of safety & efficacy of Innovator drug after Patent expiration

•Innovator firms→ Patent extensions of 5yrs to make up for time lost while their products were going through FDA's approval process

INDIAN LEGISLATION

✓ In India, CDSCO provides "**Guidelines for Bioavailability & Bioequivalence Studies**" mentioned in Schedule Y

✓ As per the Drugs & Cosmetic Rules (IInd Amendment) 2005, all bioavailability and bioequivalence studies should be conducted in accordance to these Guidelines

REQUIREMENT OF BA & BE STUDIES

✓ For IND/NDAs:

To establish equivalence between:

- *Early & late* clinical trial formulations
- Formulations used in clinical trial & stability studies
- *Clinical trial formulations & to-be-marketed* drug product
- Any *other comparisons*, if appropriate

✓ ANDA for a generic drug product

✓ Change in components, composition, &/or manufacturing process

✓ Change in dosage form (capsules to tablet)

OBJECTIVES OF BA & BE STUDIES

- ✓ Development of suitable dosage form for a New Drug Entity
- ✓ Determination of influence of excipients, patient related factors & possible interactions with other drugs
- ✓ Development of new drug formulations of existing drugs
- ✓ Control of quality of drug products, influence of → processing factors, storage & stability
- ✓ Comparison of availability of a drug substance from different form or same dosage form produced by different manufacturers

WHEN IS BIOEQUIVALENCE NOT NECESSARY (BIOWAIVERS)

a) Parental Solution; same active substance with same concentration, same excipient

b) Oral Solution; same active substance with same concentration, excipient not affecting GI transit or absorption

c) Gas

d) Powder for reconstitution as solution; meets criterion (a) or (b)

e) Otic/Ophthalmic/Topical Solution; same active substance with same concentration, same excipient

f) Inhalational Product/ Nasal Spray; administered with or w/o same device as reference product ; prepared as aqueous solution ; same active substance with same concentration, same excipient

NDA VS ANDA REVIEW PROCESS

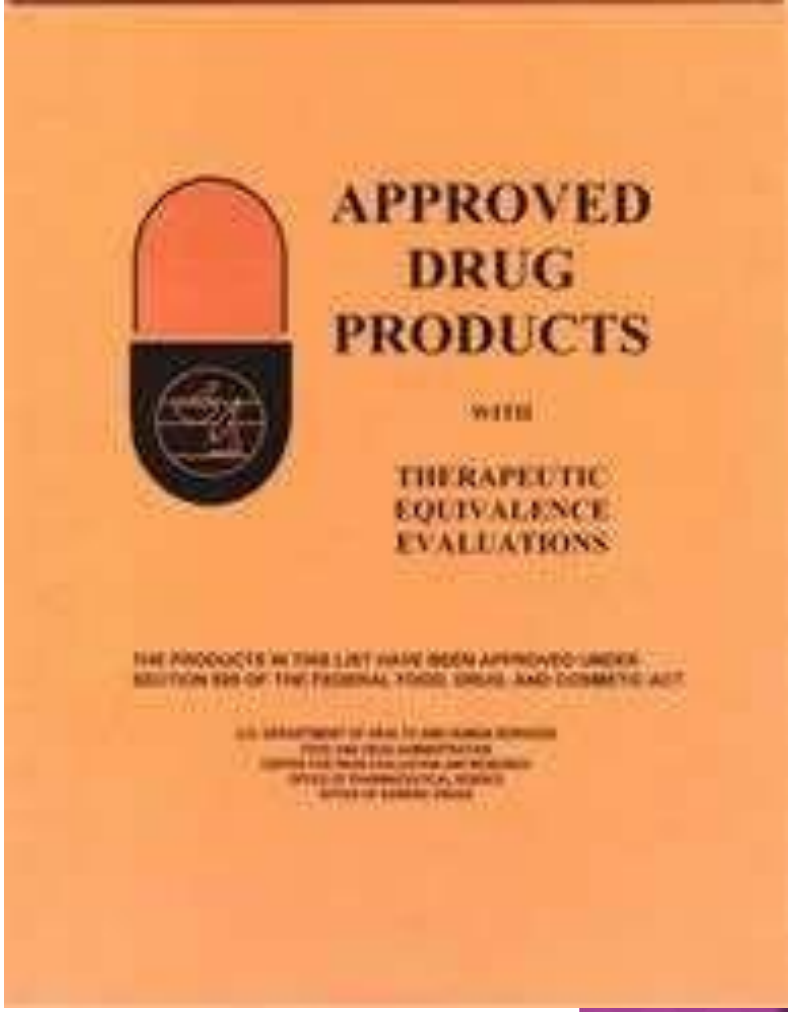
NDA Requirements

1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing
6. Animal Studies
7. Clinical Studies
8. Bioavailability

ANDA Requirements

1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing
6. Bioequivalence

ORANGE BOOK



- ✓All FDA approved drugs listed (NDA's, ANDA's & OTC's)
- ✓Expiration of patent dates
- ✓<u>Drug, Price and Competition Act (1984)</u>

FDA required to publish Approved Drug Products with Therapeutic Equivalence & Evaluations

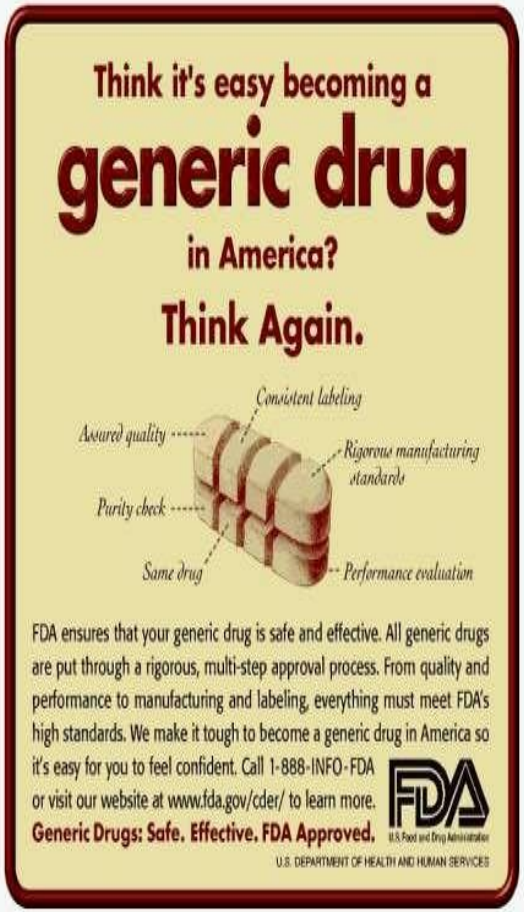
METHODS USED TO ASSESS EQUIVALENCE

I. Pharmacokinetic Studies

II. Pharmacodynamic Studies

III. Comparative Clinical Studies

IV. Dissolution Studies



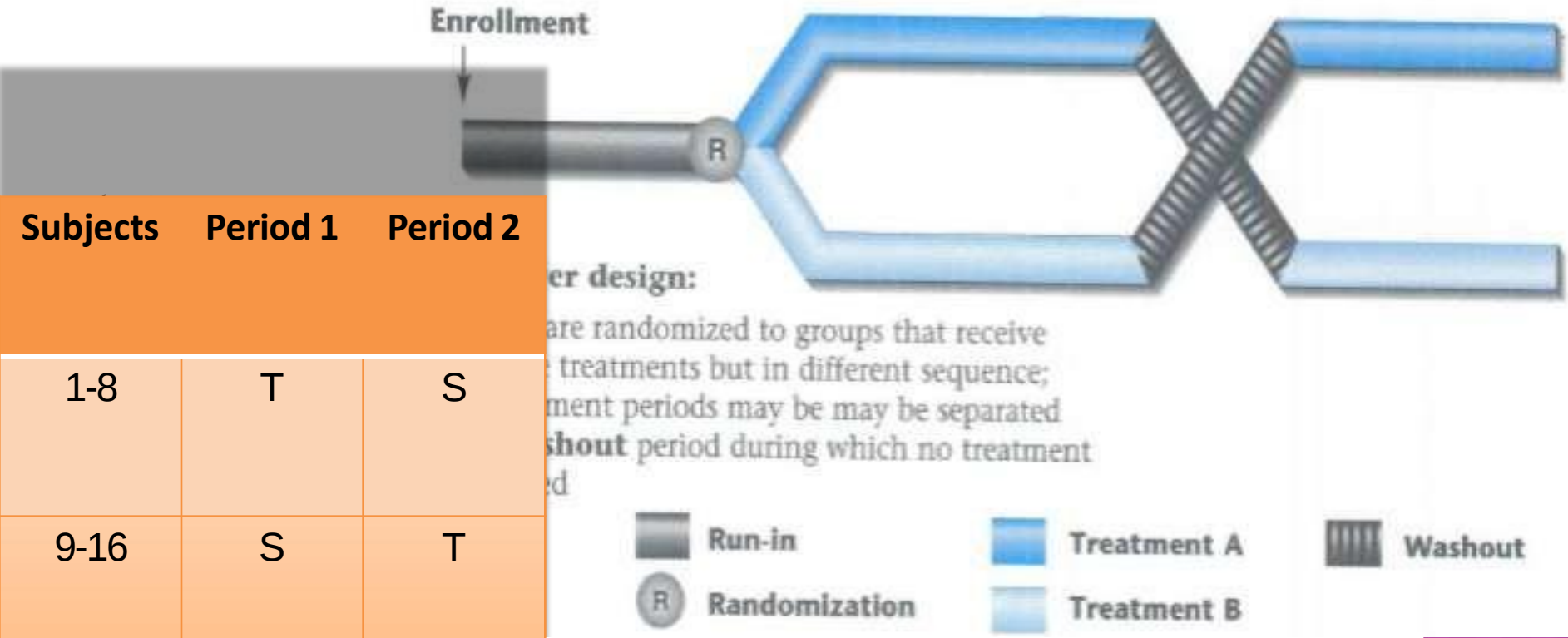
PHARMACOKINETIC STUDY DESIGN

- ✓Good experimental design, enhances the power of the study
- ✓Depends on: question to be answered, nature of reference drug/ dosage form, benefit-risk ratio
- ✓As far as possible, the study should be of crossover design & suitably randomized
- ✓Ideal design: Randomized two-period, two-sequence, Crossover design with adequate washout period
- ✓If the half-life is long: Parallel design
- ◉Any drug whose rate and extent of absorption shows large dose-to-dose variability
- ◉For highly variable drugs : Replicate design within the same patient

I. TWO-PERIOD CROSSOVER DESIGN

- ✓2 formulations, even number of subjects, randomly divided into 2 equal groups
- ✓First period , each member of one group receive a single dose of the test formulation; each member of the other group receive the standard formulation

Subjects	Period 1	Period 2
1-8	T	S
9-16	S	T



II. LATIN SQUARE DESIGN

- ✓ More than two formulations
- ✓ A group of volunteers will receive formulations in the sequence shown

Vol.No.	Period 1	Period 2	Period 3
1	A	B	C
2	B	C	A
3	C	A	B

III. BALANCE INCOMPLETE BLOCK DESIGN (BIBD)

- ✓ More than 3 formulations, Latin square design will not be ethically advisable

- ✓ Because each volunteer may require drawing of too many blood samples

- ✓ If each volunteer expected to receive at least two formulation, then such a study can be carried out using BIBD

Vol. No.	Period 1	Period 2
1	A	B
2	A	C
3	A	D
4	B	C
5	B	D
6	C	D
7	B	A
8	C	A
9	D	A
10	C	B
11	D	B
12	D	C

IV. PARALLEL-GROUP DESIGN

- ✓ Even number of subjects in two groups
- ✓ Each receive a different formulation
- ✓ No washout necessary
- ✓ For drugs with long half life

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

V. REPLICATE CROSSOVER-STUDY DESIGN

✓For **highly variable drugs**

✓Allows comparisons of within-subject variances

✓Reduce the number of subjects needed

➢Four-period, two-sequence, two-formulation design (recommended)

OR

➢Three-sequence, three-period, single-dose, partially replicated

Period	1	2	3	4
Group 1	T	R	T	R
Group 2	R	T	R	T

VI. PILOT STUDY

✓ If the sponsor chooses, in a small number of subjects

✓ To assess variability, optimize sample collection time intervals & provide other information

✓ Example:

- Immediate-release products: careful timing of initial samples→ avoid a subsequent finding that the first sample collection, occurred after the plasma concentration peak

- Modified-release products: determine the sampling schedule → assess *lag time* & *dose dumping*

✓ Can be appropriate, provided its design & execution are suitable & sufficient number of subjects have completed the study

PARAMETERS TO BE MEASURED

✓ Pharmacokinetic Parameters measured are:

- C_{max}
- T_{max}
- AUC_{0-t}
- $AUC_{0-\infty}$

$$AUC_{0-\infty} = AUC_{0-t} + C_{last}/k$$

For steady state studies:

- AUC_{0-t}
- C_{max}
- C_{min}
- Degree of fluctuation

FASTING & FED STATE CONDITIONS

➢ Fasting Conditions:

✓ Single dose study:

- Overnight fast (10 hrs) and subsequent fast of 4hrs

✓ Multiple dose study:

- Two hours fasting before and after the dose

➢ Fed State Studies

✓ <u>Required when:</u>

- Drug recommended with food
- Modified release product
- Assessment of C_{max} and T_{max} difficult with fasting state study

✓ Requires consumption of a high fat food, 15 minutes before dosing

✓ Provide 950-1000 kcals

✓ Fat- 50%, Proteins 15-20%, Carbohydrate- 30-35%

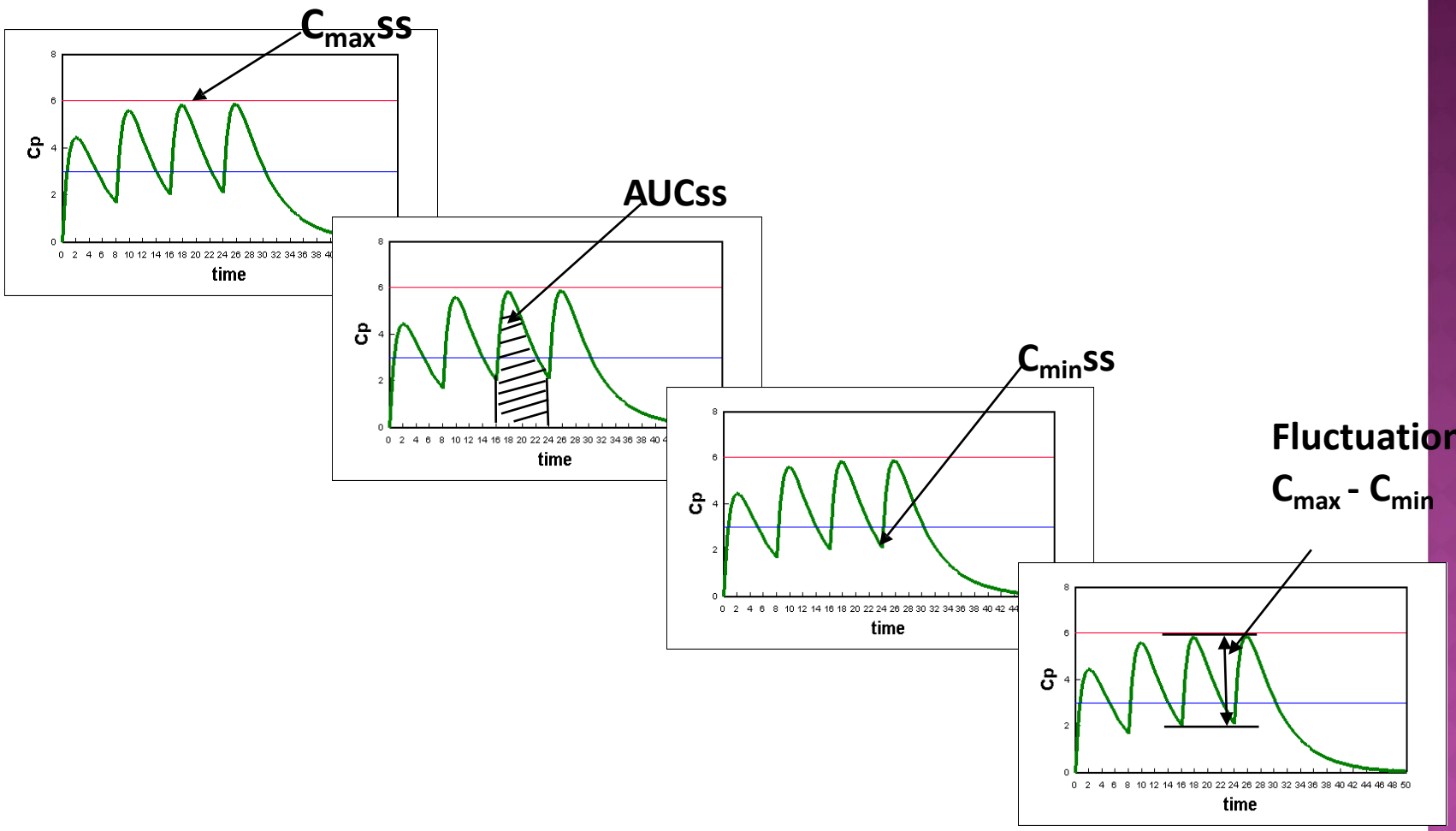
✓ Ethnic & cultural variation considered

✓ Specified in protocol

STEADY STATE/ MULTIPLE DOSE STUDIES

- ✓ Long elimination half life→ Accumulation in the body
- ✓ Toxic drugs requiring multiple dose therapy
- ✓ Some Modified-release drugs
- ✓ Combination products
- ✓ Drugs inducing own metabolism
- ✓ Drugs showing non-linear pharmacokinetics

PARAMETERS IN MULTIPLE DOSING STUDIES



Fluctuation:

$C_{max} - C_{min}$

STATISTICAL EVALUATION

- ✓ Primary concern of bioequivalence is to limit Consumer's & Manufacturer's risk

- C_{max} & AUC analysed using ANOVA
- T_{max} analysed by non-parametric methods

- ✓ Use *natural log transformation* of C_{max} and AUC

- Calculate Geometric means of C_{max} of Test [C_{max}'t]
- Calculate Geometric means of C_{max} of Reference [C_{max}'r]
- Calculate **Geometric Mean Ratio**= [C_{max}'t] / [C_{max}'r]

- ✓ Calculate 90% confidence interval for this GMR for C_{max}

- ✓ Similarly calculate GMR for AUC

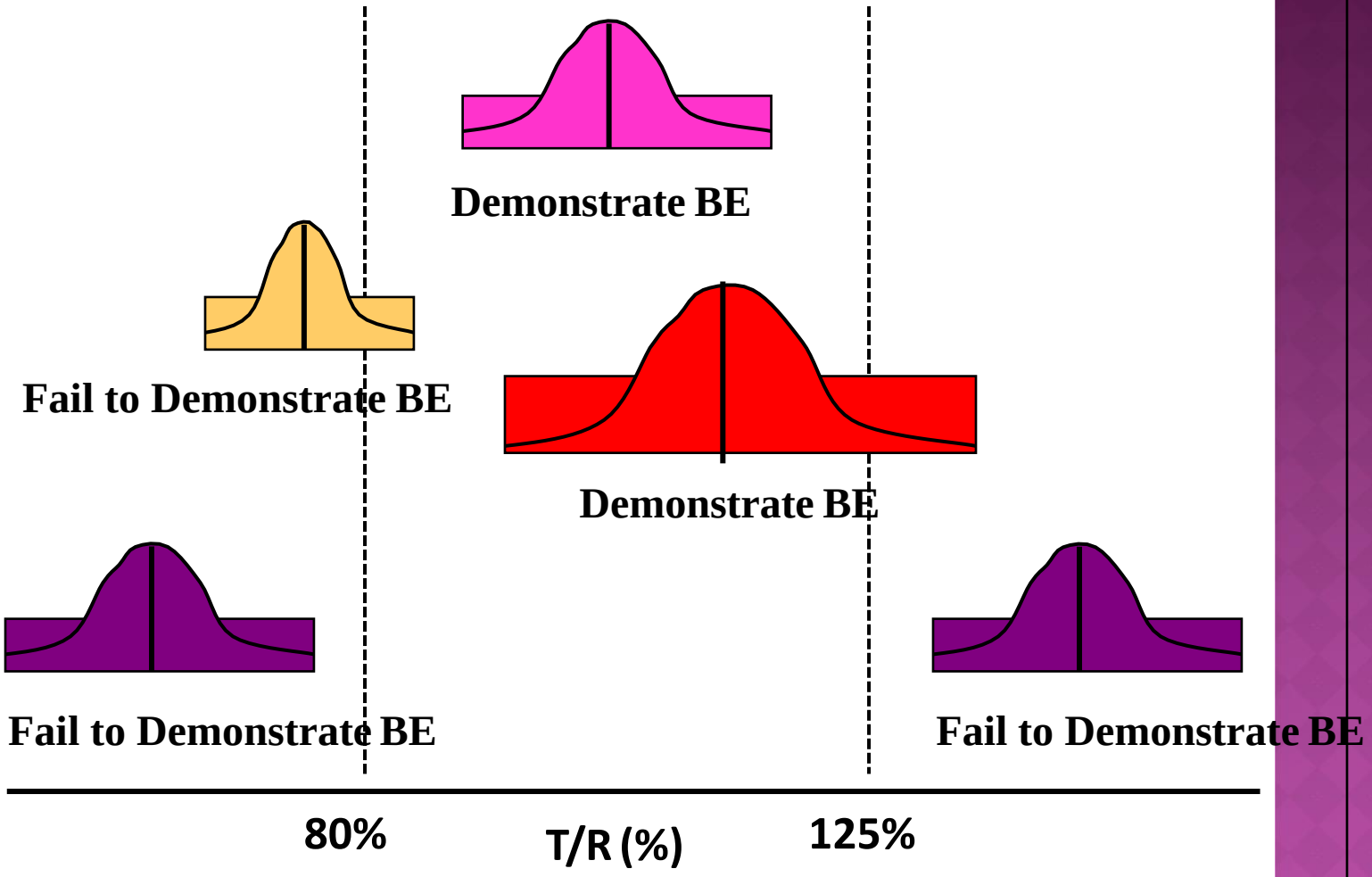
TO ESTABLISH BE:

- ✓ The calculated 90% Confidence Interval for **C_{max} & AUC**, should fall within range:

80-125% (Range of Bioequivalence)

- ✓ Non-parametric data - 90% Confidence Interval for **T_{max}** should lie within clinical acceptable range

BE RESULTS


Demonstrate BE
Fail to Demonstrate BE
Demonstrate BE
Fail to Demonstrate BE
Fail to Demonstrate BE
80%
T/R (%)
125%

✓ Tighter limits may be required for drugs which have:

- A narrow therapeutic index
- A serious dose-related toxicity
- A steep dose-response curve
- Non-linear pharmacokinetics within therapeutic range

✓ Wider range maybe acceptable, based on sound clinical justification

✓ Suprabioavailability

- New product displays an extent of absorption, larger than approved product
- Reformulation to lower dosage f/b fresh BA & BE study
- Otherwise, clinical data required

BIOEQUIVALENCE ASSESSMENT OF TWO FORMULATIONS OF IBUPROFEN

Table 5 Pharmacokinetic parameters over eight hours with two formulations, Brufen® (reference) and Dolaraz® (test) after a single oral dose of 100 mg formulation in 24 healthy adult male volunteers

Parameter	Reference mean (±SD)	Test (Mean ± SD)
$AUC_{0-\infty}$ µg/mL/hour	31.79 (10.60)	29.69 (9.79)
AUC_{0-t} µg/mL/hour	28.17 (8.12)	27.21 (9.01)
C_{max} µg/mL	9.92 (2.13)	10.05 (1.84)
T_{max}, hours	0.80 (0.42)	0.90 (0.58)
K_e	0.31 (0.22)	0.36 (0.23)
$T_{1/2}$, hours	2.98 (1.37)	2.44 (1.19)

Table 6 Statistical results and ratios of means of test and reference products and 90% confidence intervals

Pharmacokinetic parameters	Doloraz® mean	Brufen® mean	Ratio of means	90% CI
$LnAUC_{0-\infty}$	3.34	3.41	0.981	0.807–1.092
$LnAUC_{0-t}$	3.26	3.30	0.987	0.838–1.098
LnC_{max}	2.29	2.27	1.009	0.914–1.138

CONDUCT OF STUDY

➢ Pre-study Requirements

- ✓ IEC approved protocol
- ✓ Written procedure (SOPs) for all the study related activities
- ✓ In accordance with ICH-GCP Guidelines
- ✓ Adequate infrastructure- Clinical facility
- ✓ Trained Study personnel
- ✓ Healthy Volunteers

➢ Screening of Healthy volunteers

- ✓ Recruitment through advertisements
- ✓ Written consent for Screening & Consent for HIV testing
- ✓ Height & weight
- ✓ Medical History
- ✓ Physical examination, ECG& vital signs examination
- ✓ Blood & Urine sample

(Lab testing,; tests for HIV, Hepatitis A, B & C; UPT→females)

➢ Volunteer Selection & Recruitment

- ✓ Volunteers called 1 day before study & admitted
- ✓ Written ICF taken

➢ During the Study

- ✓ Standardized study environment
- ✓ Vital signs examination at scheduled times
- ✓ Standardised amount of water [~240ml]
- ✓ No concomitant medications [including herbal remedies]

DOCUMENTATION

- Signed detailed protocol
- Approval by Ethics Committee
- Volunteer Information sheet
- Informed Consent Form (ICF)
- Case Record Form (CRF)
- Undertaking by investigator
- CVof investigator
- Randomization chart
- Laboratory certification
- Analytical method validation details
- Chromatograms of all volunteers including any aberrant ones
- Tabulated Raw Data of volunteers

MAINTENANCE OF RECORDS & RETENTION OF STUDY SAMPLES

- ✓ All **Records** of in vivo tests on any marketed batch of a drug product should be maintained by the Sponsor for at least 2 years after expiry date of the batch

- ✓ All **Drug samples** to be retained for a period of at least 3 years after conduct of the study

OR

- ◉ 1year after expiry of the batch

  [Stored in conditions consistent with the product labeling]

COMPARATIVE CLINICAL STUDIES

✓ Necessity:

- Both pharmacokinetic & pharmacodynamic parameters
  - *not properly measurable or not feasible*
- Mention which methods were tried & found unsuitable

✓ Statistical principles to be considered:

- *No. of patients* → *Variability* of assessed parameters & *acceptance range*
- Much higher than BE studies

FOLLOWING CRITICAL POINTS NEED TO BE DEFINED IN ADVANCE, ON CASE TO CASE BASIS:

- ✓ Clinical end points (Target parameters)→ intensity & onset of response
- ✓ Size of equivalence range→ case-to-case basis
  - ◉ (dependins on natural course of disease, efficacy of available treatments, target parameter)
- ✓ Statistical confidence interval approach:
  - ◉ *one-sided interval*→ rule out inferiority
- ✓ Placebo included when appropriate
- ✓ Safety end-points in some cases

CONCLUSION

✓Concept of BE has been adopted by the pharmaceutical industry & national regulatory authorities throughout the world for over 20 years

✓There is a continuing attempt to understand & develop more efficient & scientifically valid approaches to assess bioequivalence of various dosage forms including some of the tough complex special dosage forms

✓Bioequivalence industry always existed in India→ become more matured now

✓Changes in patent laws has added tremendous fuel to this growth

✓Many BA/BE CROs in India

- ✓ Generics help patients by making drugs available at affordable price while retaining their quality

- ✓ Balance public interests especially in diseases like Cancer & AIDs which have high prevalence in developing countries & patented drugs are steeply priced

- ✓ Value of drugs going off-patent in the regulated market is estimated very high in next 5 years

- ✓ Translated into increased opportunities for Indian Pharmaceutical Industry → Export of generics to the regulated markets