Bioavailability and Bioequivalence Studies A Review
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ABSTRACT

Essential to ensure uniformity in standards of quality, efficacy & safety of Pharmaceutical products. Reasonable assurance is to be provided that various products containing same active ingredient, marketed by different licensees are clinically equivalent & interchangeable, Release of an active substance should be known & reproducible, Both Bioavailability & Bioequivalence focus on release of drug substance from its dosage form & subsequent absorption in circulation, Similar approaches to measure Bioavailability should be followed in demonstrating Bioequivalence. 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. Bioavailability, Measurement of the relative amount & rate at which, the drug from administered dosage form, reaches the systemic circulation & becomes available at the site of action. Bioavailable fraction (F), refers to the fraction of administered dose that enters the systemic circulation.

Keywords: Bioavailability, BA & BE Studies, Generic Drug, Therapeutic equivalence

I. INTRODUCTION

• Essential to ensure uniformity in standards of quality, efficacy & safety of Pharmaceutical products
• Reasonable assurance is to be provided that various products containing same active ingredient, marketed by different licensees are clinically equivalent & interchangeable
• Release of an active substance should be known & reproducible
• Both Bioavailability & Bioequivalence focus on release of drug substance from its dosage form & subsequent absorption in circulation
• Similar approaches to measure Bioavailability should be followed in demonstrating Bioequivalence

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Bioavailability

Measurement of the relative amount & rate at which, the drug from administered dosage form, reaches the systemic circulation & becomes available at the site of action Bioavailable fraction (F), refers to the fraction of administered dose that enters the systemic circulation

\[ F = \frac{\text{Bioavailable dose}}{\text{Administered dose}} \]

Factors affecting Bioavailability of a Drug

Physical properties of a drug

Physical state:
- Liquids > Solids
  - Solution > Suspension > Capsule > Tablet > Coated tablet
- Crystalloids > Colloids

Lipid or water solubility:
- Aqueous phase at absorption site
- Passage across Cell surface

Dosage forms

Particle size:
- Important for sparingly soluble drugs
- ↓ the size, ↑ the absorption, ↓ the dose
- Nano-crystalline formulations of Saquinavir
- If ↓ absorption needed (local action on GIT), ↑ the size

Physiological factors

Ionization:
- Unionized form penetrates the GI mucosal lining quickly

pH of the fluid:
- Weakly acidic drugs: Aspirin, Barbiturates→ Stomach, duodenum
- Weakly basic drugs: Pethidine, Ephedrine→ Small intestine
- Strongly acidic / basic drugs: highly ionized & poorly absorbed

GI transit time

Prolonged gastric emptying:
- Delays absorption due to stasis (e.g. with anticholinergics / Diabetic neuropathy)

Increased peristaltic activity: (e.g. Metoclopramide→ speeds up the absorption of analgesics)

Excessive peristaltic activity (as in Diarrhoea) impairs absorption

Fed state:
- impairs progress of drug to intestine→ ↓ absorption (Indinavir) • ↑ splanchnic blood flow→ ↑ absorption (Propranolol)

First pass metabolism:
- Gut wall (e.g. Isoprenaline)
- Liver (e.g. Opioids, β-blockers, Nitrates)

Presence of other agents:
- Vitamin C ↑ Iron absorption, Phytates retard it
- Calcium ↓ absorption of Tetracyclines

Disease states:
- Malabsorption, Achlorhydria, Cirrhosis, Biliary obstruction can hamper absorption

Entero-hepatic cycling:
- Increases bioavailability (e.g. Morphine, OC pills)

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

Amount of drug released from the dosage form
Amount of drug absorbed from the dosage form

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

Amount of drug released from the dosage form
Amount of drug absorbed from the dosage form

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- Concentration of drug in the central compartment
- Concentration of drug at site of action RESPONSE
- Strength of dosage form
- Excipients
- Other pharmaceutical factors
- Patient related factors
- Administration related factors PD studies/ Clinical Trials

**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

**May have different:**
- Inactive ingredients
- Colour
- Shape
Almost half of drugs in market have Generics

**Reference Drug**

- Expensive
- 5/5000 new drug candidates tested in humans & 1 approved
- Takes 12-15 yrs
- Costs around 1 billion $
- Drug Patents of 20yrs, applied before clinical trials begin
- Effectively 7-12 yrs

**Generic Drug**

- 30-80% cheaper
• Since already tested & approved, cost of simply manufacturing
• Fraction of the cost of testing & development
• Approved for sale after drug patent protection expires Price difference between Reference

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 (IIInd 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) Optic/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

<table>
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<th>ANDA Review Process</th>
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<td>ANDA Requirements</td>
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<tr>
<td>1. Chemistry</td>
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<tr>
<td>3. Controls</td>
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<td>4. Labelling</td>
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<td>5. Testing</td>
<td>5. Testing</td>
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<td>7. Clinical Studies</td>
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<td>8. Bioavailability</td>
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Orange Book

- All FDA approved drugs listed (NDA’s, ANDA’s & OTC’s)
- Expiration of patent dates
- FDA required to publish Approved Drug Products with Therapeutic Equivalence & Evaluations

Methods used to assess Equivalence

1. Pharmacokinetic Studies
2. Pharmacodynamic Studies
3. Comparative Clinical Studies
4. Dissolution Studies

Pharmacokinetic Studies

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
- For highly variable drugs: Replicate design

- Any drug whose rate and extent of absorption shows large dose-to-dose variability within the same patient

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

After a wash period (5 half-lives), in second period, each member of the respective groups will receive an alternative formulation & experiment will be repeated. Subjects Period 1 Period 2 1-8 T S 9-16 S T

1. Latin Square Design
- More than two formulations
- A group of volunteers will receive formulations in the sequence shown

<table>
<thead>
<tr>
<th>VOL.NO</th>
<th>PERIOD.1</th>
<th>PERIOD.2</th>
<th>PERIOD.3</th>
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<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>C</td>
<td>A</td>
</tr>
<tr>
<td>3</td>
<td>C</td>
<td>A</td>
<td>B</td>
</tr>
</tbody>
</table>

2. 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

3. Parallel-Group Design
- Even number of subjects in two groups
- Each receive a different formulation
- No washout necessary
- For drugs with long half life

<table>
<thead>
<tr>
<th>Treatment A</th>
<th>Treatment B</th>
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<tbody>
<tr>
<td>1</td>
<td>2</td>
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<tr>
<td>3</td>
<td>4</td>
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<tr>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>
4. 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

<table>
<thead>
<tr>
<th>Period</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<tr>
<td>Group 1</td>
<td>T</td>
<td>R</td>
<td>T</td>
<td>R</td>
</tr>
<tr>
<td>Group 2</td>
<td>R</td>
<td>T</td>
<td>R</td>
<td>T</td>
</tr>
</tbody>
</table>

5. 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

Subject selection

- Healthy adult volunteers
- Age: 18-45 yrs.
- Age/Sex representation corresponding to therapeutic & safety profile
- Weight within normal limits → BMI
- Women: Pregnancy test prior to 1st & last dose of study; OC pills C/I
- Drug use intended in Elders (Age >60yrs)
- Teratogenic Drugs → Male volunteers High toxic drugs: Patients with concern disease (stable) eg. Cancer

Exclusion Criteria

- H/o allergy to test drug
- H/o liver or kidney dysfunction
- H/o jaundice in past 6 months
- Chronic diseases eg. Asthma, arthritis
- Psychiatric illness
- Chronic smoker, alcohol addiction, drug abuse
- Intake of enzyme modifying drug in past 3 months
- Intake of OTC/Prescription drugs past 2 weeks
- HIV positive
- BA & BE studies in past 3 months
- H/o bleeding disorder

Selection of Number of Subjects

Sample size is estimated by:
- Pilot experiment
- Previous studies
- Published data
- Significance level desired, usually 0.05
- Power of the study, normally 80% or more
- Expected deviation (Δ) from the reference product, as compatible with BE
- If no data available, reference ratio of 0.95 (Δ = 5%) used
• Minimum 16 subjects, unless ethical justification
• Allow for drop-outs
• Replace drop-outs→ substitute follow same protocol; similar environment
• Sequential/ Add-on Studies→ large no. of subjects required, results of study do not convey adequate significance

Genetic Phenotyping
• Drug is known to be subject to genetic polymorphism
• Cross-over design→ Safety & Pharmacokinetic reasons
• All Parallel group design
• Indian population:
  • Captures genetic diversity of the world
  • Forms continuum of genetic spectrum
  • >1000 medically relevant genes
• Diverse patient/ volunteer pool for conducting BA & BE studies

Characteristics to be measured
• Accessible biological fluids like blood, plasma &/or serum to indicate release of the drug substance from the drug product into the systemic circulation
• Mostly: Active drug substance

Active / Inactive metabolite maybe measured in cases of:
• Concentration of drug too low
• Limitation of analytical method
• Unstable drug
• Drug with very short half-life
• Pro-drugs
Excretion of drug & its metabolites in urine→ Non-linear kinetics

Measure individual enantiomers when they exhibit:
• Different pharmacokinetic/ pharmacodynamic properties
• Non-linear absorption
• Safety/Efficacy purposes

Surrogate marker

<table>
<thead>
<tr>
<th>Drug product</th>
<th>Drug</th>
<th>Possible surrogate marker for bioequivalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDI</td>
<td>Albuterol</td>
<td>FEV1</td>
</tr>
<tr>
<td>Topical</td>
<td>Hydrocortisone</td>
<td>Skin blanching</td>
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<tr>
<td>steroid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anion</td>
<td>Cholestyamine</td>
<td>Binding to bile acids</td>
</tr>
<tr>
<td>exchange</td>
<td></td>
<td></td>
</tr>
<tr>
<td>resin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antacids</td>
<td>Mg &amp; Al</td>
<td>Neutralization of acid</td>
</tr>
<tr>
<td>hydroxide gel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical</td>
<td>Ketoconazole</td>
<td>Drug uptake into stratum corneum</td>
</tr>
<tr>
<td>antifungal</td>
<td></td>
<td>Surrogate Markers</td>
</tr>
</tbody>
</table>

Blood Sampling points/ Schedule

Single-dose study of an immediate release product
• For at least three elimination half-lives (cover >80% of AUC)
• Absorption phase : 3-4 points
• Around Tmax : 3-4 points
• During elimination : 4 points
• Intervals not longer than the half-life of the drug
• If urine tested, collect it for at least 7 half-lives

Method Validation
• Accuracy/ Relative Recovery
• Closeness of determined value to the true Value
• Precision

Closeness of agreement obtained from the multiple sampling of the same homogeneous samples under certain prescribed conditions

Repeatability
Precision under same conditions
same analyst, same apparatus, same interval of time, identical reagents

Reproducibility Precision under
different conditions different analysts, apparatus from different manufacturers, different days, reagents from different sources

Sensitivity
Capacity of the test procedure to record small variations in concentration

Limit of detection (LOD):
Lowest concentration of drug that will yield an assay response significantly different from that of a sample blank

Limit of quantitation (LOQ/ sensitivity limit):
Lowest concentration of drug that can be determined with acceptable precision & accuracy under the stated experimental conditions

Selectivity/ Specificity
Ability of the method to measure only what it is intended to measure

Calibration of Instruments
• Should be done regularly & as per standard procedures in USP/BP/IP
• Done before starting the analysis at the development phase & during the study phase
• Predetermined SOPs
• Accreditation of analysing laboratory

Parameters to be measured
Pharmacokinetic Parameters measured are:
• Cmax
• Tmax
• AUC0-t
• AUC0–∞

For steady state studies:
• AUC0-t
• Cmax

• Cmin
• Degree of fluctuation
  AUC 0–∞ = AUC 0-t + Clast /k

Fasting & Fed State Conditions
Fasting Conditions:

Single dose study:
Overnight fast (10 hrs) and subsequent fast of 4 hrs

Multiple dose study:
Two hours fasting before and after the dose

Fed State Studies
Required when:
• Drug recommended with food
• Modified release product

Assessment of Cmax and Tmax 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

Disadvantages:
• Difficult to conduct
• Costly
• Longer monitoring
• Longer exposure to drug
Parameters in Multiple dosing studies

Reporting for products likely to accumulate: Steady State studies

- Acetaminophen accumulation in pediatric patients after repeated therapeutic doses
- 10 patients studied at steady-state after repeated doses

**Total AUCss for Acetaminophen was as:**
0.181 (ml/min/kg)–1 after the first dose 0.202 (ml/min/kg)–1 at steady-state ( p < 0.05)

- There was no evidence of hepatotoxicity
- These data suggest that acetaminophen may accumulate after repeated therapeutic doses in children with fever

Statistical Evaluation

- Primary concern of bioequivalence is to limit Consumer’s & Manufacturer’s risk
- Cmax & AUC analysed using ANOVA
- Tmax analysed by non-parametric methods
- Use natural log transformation of Cmax and AUC
- Calculate Geometric means of Cmax of Test [Cmax’t]
- Calculate Geometric means of Cmax of Reference [Cmax’r]
- Calculate Geometric Mean Ratio= [Cmax’t] / [Cmax’r]
- Calculate 90% confidence interval for this GMR for Cmax
- Similarly calculate GMR for AUC

To establish BE

- The calculated 90% CI for Cmax & AUC, should fall within range: 80-125% (Range of Bioequivalence)
- Non-parametric data 90% CI for Tmax should lie within clinical acceptable range

II. BE RESULTS

- 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

Modified-release drug products

- Drug release characteristics of time course &/or release location
- Chosen to achieve therapeutic &/or convenience objectives not offered by immediate release forms
Includes:
✓ Delayed release
✓ Sustained release
✓ Mixed immediate & sustained release
✓ Mixed delayed & sustained release
✓ Mixed immediate & delayed release

Should meet following criteria:
Meet the label claims
Preclude any dose-dumping
Provide therapeutic equivalence with:
Multiple doses of reference product
OR
Reference modified release formulation
Produce plasma levels within therapeutic range

Study Design for Modified Release formulation
Unlikely to accumulate:
First market entry
Comparison between Single dose of Modified release preparation & Immediate release formulation as per established dose regimen

Subsequent market entry
Comparison with Reference Modified release product

Likely to accumulate:
Both single & steady state doses of Modified Release formulation compared with immediate release formulation as per established dose regimen

Effect of food:
Not known/ Known that food affects absorption:
Two way cross over studies both in Fasting & Fed state

Known that it not affected by food:
Three way cross over study done with

• Reference product in Fasting state
• Test product in Fasting state
• Test product in Fed state

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]
• Administration of the study medication is supervised by the investigator
• Same time of dosing (multiple dosing)
• Sampling time with deviation of 2 mins allowed
• Uniform & identical meals at identical times in all periods
• Restriction of xanthines, grapefruit, citrus fruits, smoking, alcohol
• Physical activity & posture standardized → limit effects on GI flow & motility
• All activities recorded in CRFs with time & date

**End of Study**

• Post-study examination for safety assessment
• Compensation to subjects as per agreed terms
• Clinical part of study completed

**Documentation**

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

**Pharmacodynamic Studies**

• Measurement of effect on a Patho-physiological process as a function of time, after administration of 2 different products

**Necessity**

1. Quantitative analysis in plasma or urine not possible with sufficient accuracy & sensitivity
2. Drug concentrations are not surrogate endpoints e.g. Topical formulations without systemic absorption
3. In situations of ‘Superiority Claims’
   • In case only Pharmacodynamic data is collected → other methods tried & why they were unsuitable

**Special considerations while conducting this study:**

**Response measured** → Pharmacological/ Therapeutic effect → relevant to Efficacy/ Safety of drug

**Methodology validated** → Precision, accuracy, reproducibility, specificity

• Neither should produce a maximal response → not possible to distinguish differences between formulations given in those doses
• Response measured “quantitatively” under double-blind conditions, on repetitive basis, to record pharmacodynamic events → Pharmacodynamic effect curve
• Eg: Heart rate, pupil diameter, BP

**Parameters studied:**
- Area under the curve
- Maximum response
- Time for maximum response

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• Non Responders excluded by prior screening
• If Placebo effect can occur → 3rd Stage with Placebo treatment in study design
• In Patients → Underlying Pathology & Natural-history considered
• Conventional acceptance range → defined in protocol, case to case basis

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