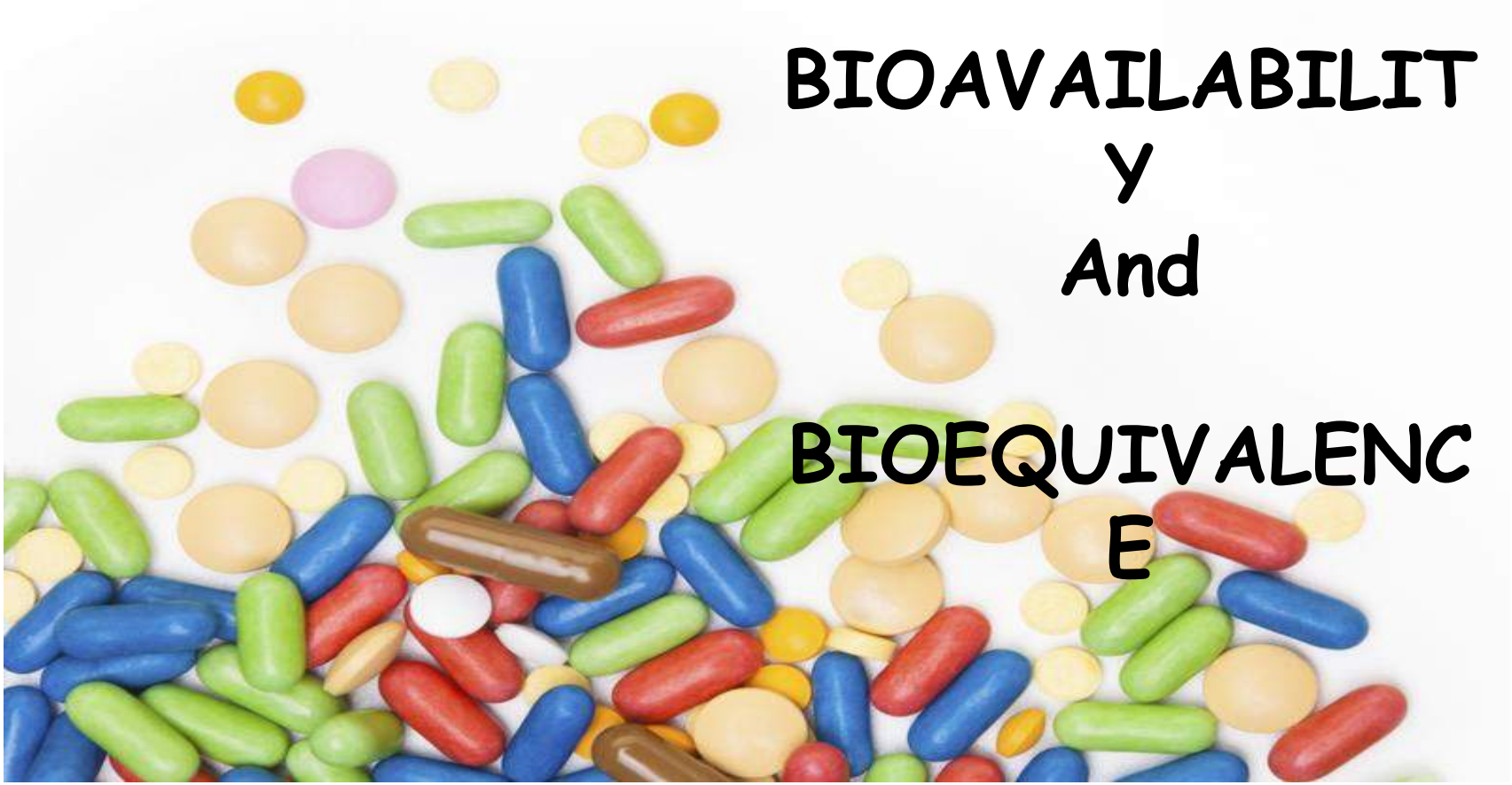
Concept of



Good morning

Perception !

Process for Generics (ANDA) development

Abbreviated New Drug Application (ANDA)

ANDA contains data for the review and ultimate approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative.

A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics and intended use.

Generic Drug

- Same active ingredient (s)
- Same dosage form drug (RLD)
- Same route of administration
- Same indications
- Same strength

Generic Drug Advantage

- Life expectancy of patients has increased globally due to increased new drug discovery (brand-name) & generic drugs.
- Most health care interventions occur through medications leading to high cost of medications.
- To lower cost of medication, generic equivalents of brand-name drugs (innovator drugs) are introduced.
- Generic drugs have captured more than 65% of global market.
- Because of importance of generic drugs in health care, pharmaceutical quality, safety and efficacy of generics should be reliably compared with the innovator drugs.

History & Inclusion of Hatch Waxman Act

- Before 1984, generic formulations were allowed primary for innovator products that were approved for sale before 1962
- Inclusion of Hatch Waxman in 1984
- Drug Price Competition and Patent Term Restoration Act (1984) allows marketing of any off patent drug. Provided specific ANDA criteria are met.
- ANDA applicant can submit four types of patent certifications :
  - Paragraph I – Patent information was not submitted to FDA by RLD company
  - Paragraph II – Patent has expired
  - Paragraph III – Patent will expire on specific date
  - Paragraph IV – Patent challenge - Generic drug company can challenge validity of patents issued to innovator drug companies.

Generic Drug ANDA Requirement

- Abbreviated New Drug Application
  - For a product already approved for marketing
  - Must demonstrate bioequivalence
  - Safety and efficacy are not necessary as they are already proved
- Since last two decades. bioequivalence studies serving as an established tool to substitute or interchangeability of formulations

ANDA Application Process

- Generic drugs (ANDA application) are subjected to four major reviews & inspections:
  - Bioequivalence review
  - Chemistry/micro review
  - Labeling review
  - Plant inspection

Bioavailability

The concentration of active component or their modified active metabolites present in the blood indicate the concentration at the site of action

A valid measurement of bioavailability

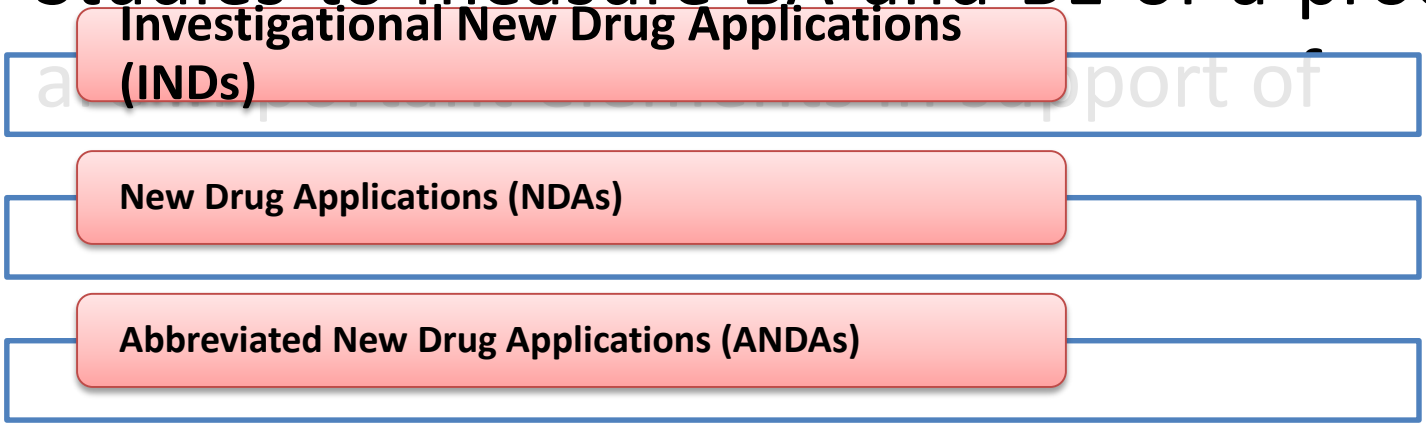
Bioequivalance (BE)

- The absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study
- If two medicines are bioequivalent, there is no clinically significant difference in their bioavailability.

Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations

BA/BE

- Studies to measure BA and BE of a product



Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations

BA/BE

- The systemic exposure profile determined during clinical trials in the IND period can serve as a benchmark for subsequent BE studies.
- Studies to establish BE between two products are important for certain changes before approval for a pioneer product in NDA and ANDA submissions, and in the presence of certain post approval changes in NDAs and ANDAs.

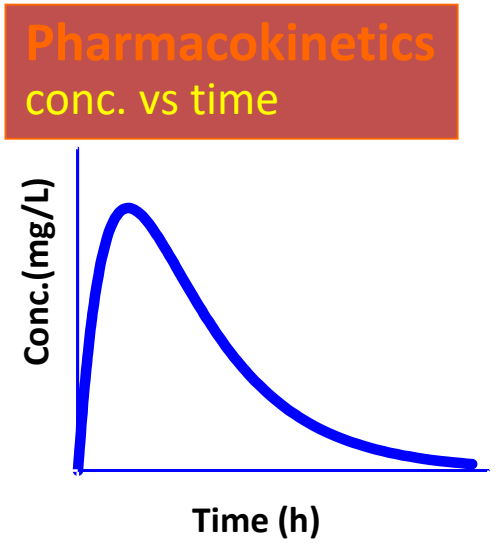
Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations

Bioavailability

- Bioavailability is defined as the rate and extent (amount) of absorption of unchanged drug from its dosage form.

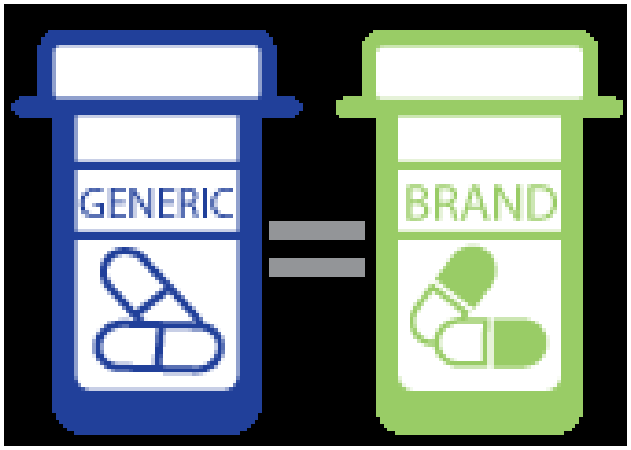
<u>Why bioavailability studies?</u>

- To evaluate pK parameters after single & multiple dose administration
- For new formulations of active drug which have full NDA approval and are approved for marketing, bioavailability study should be carried out and pharmacokinetics parameters of new formulation should be established
- To determine safety and efficacy of the drug product



Bioequivalence

- "Bioequivalence" is a comparison of the bioavailability of two or more drug products.
- Two products or formulations containing the same active ingredient are bioequivalent if their rates and extents of absorption are the same



Why BE studies?

- Bioequivalence studies are a surrogate marker for clinical effectiveness and safety data as it would not normally be practical to repeat clinical studies for generic products.

Pharmaceutical Equivalents

- Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), have the same dosage form and route of administration, and are identical in strength or concentration
- Equivalent products contain the same amount of ingredient in the same dosage form but may differ in characteristics, such as shape, release mechanisms, and packaging

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. Accessed September 29, 2003.

Pharmaceutical Alternatives

- Drug products are considered pharmaceutical alternatives if they contain the same therapeutic moiety, are different salts, esters, or complexes of the same moiety, are different dosage forms, or are different strengths
- Other pharmaceutical alternatives
  - Different dosage forms and strengths within a single product line by a single manufacturer
  - Extended-release formulations when compared with immediate- or standard-release formulations

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.

Therapeutic Equivalents

- Drug products are considered therapeutic equivalents if they are all of the following
  - Pharmaceutical equivalents
  - Bioequivalent
  - Approved as safe and effective
  - Adequately labeled
  - Manufactured in compliance with current Good Manufacturing Practice regulations
- Therapeutic equivalents are expected to have the same clinical effect and safety profile

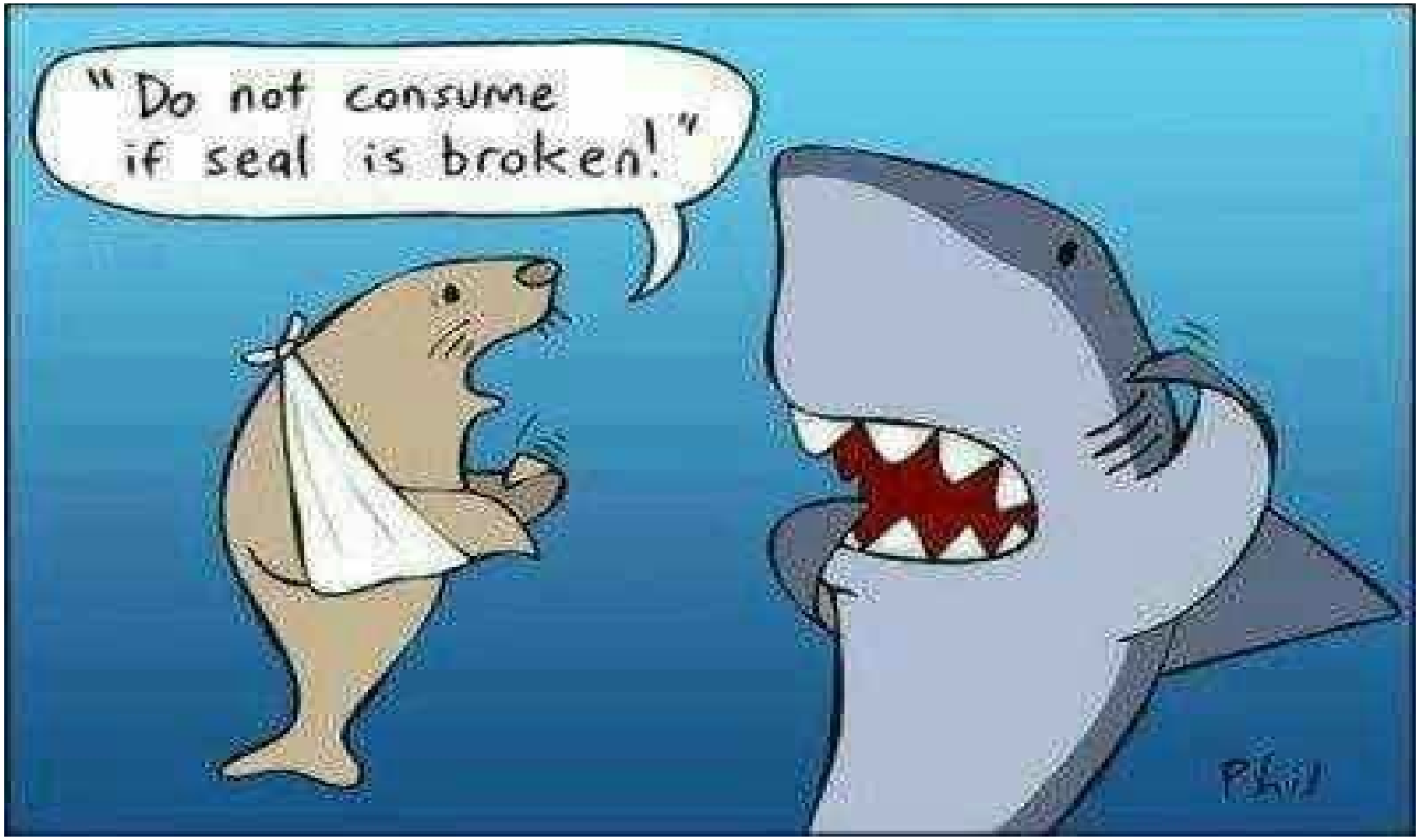
Approved Drug Products With Therapeutic Equivalence Evaluations. 23rd ed. 2003. FDA/CDER Web site. Available at: http://www.fda.gov/cder/ob/docs/preface/ecpreface.htm#Therapeutic Equivalence-Related Terms. Accessed September 29, 2003.

THE CONCEPT OF BIOAVAILABILITY

- Absorption is only one of the steps separating drug administration from its delivery to the site of action.
- From a mechanistic point of view, it can be helpful to distinguish the two concepts in order to explain the origin of low bioavailability
  - A drug can be 100% absorbed from a given formulation (therefore no possible improvement) but have nevertheless a low bioavailability due to breakdown after absorption.
- This is the case for prostaglandin (PgF2a), which undergoes a 90% lung first-pass effect and for many drugs undergoing variable hepatic first pass effect after oral or intra-peritoneal administration.

P. L. Toutain et AL.Bioavailability and its assessment

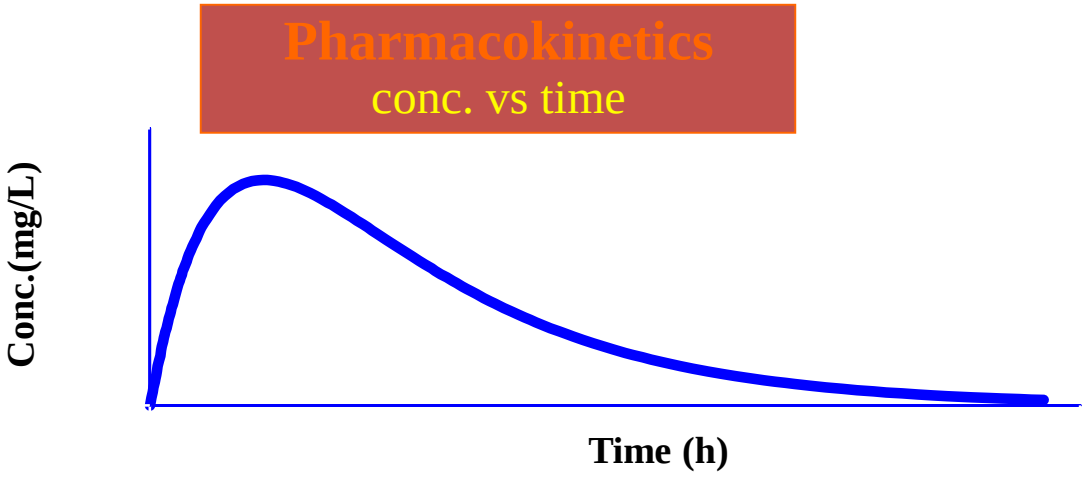
Warning !!



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



Why do we care about BIOAVAILABILITY ?

The “true dose” is not the drug swallowed; BUT is the drug available to exert its effect which depends on

- 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)

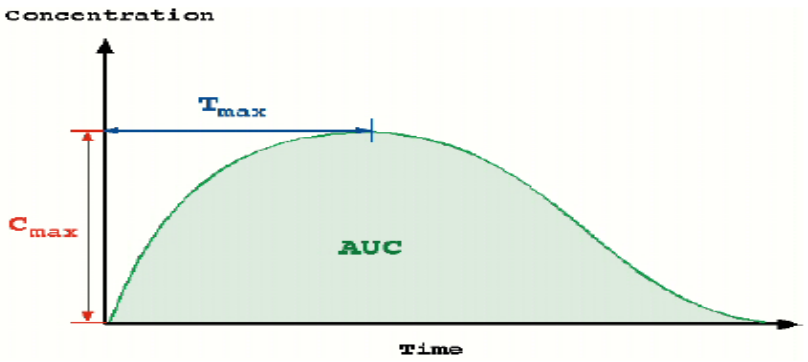
Important component of overall variability

- Variable bioavailability may produce variable exposure

BA STUDY CRITERIA

Bioavailability is assessed using three main pharmacokinetic variables.

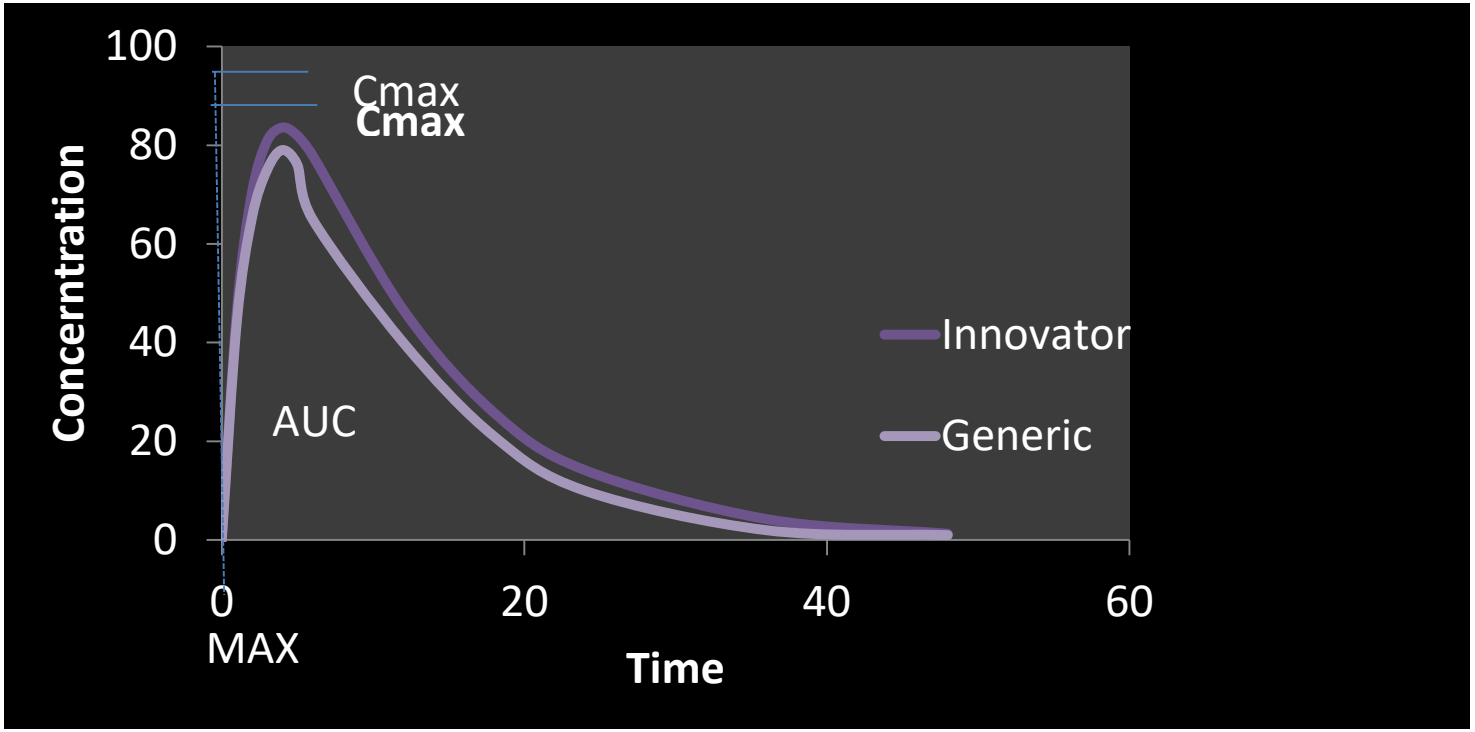
- The area under the blood drug concentration versus time curve (AUC)
- The maximum blood concentration (C_{max})
- The time to reach maximum concentration (T_{max})



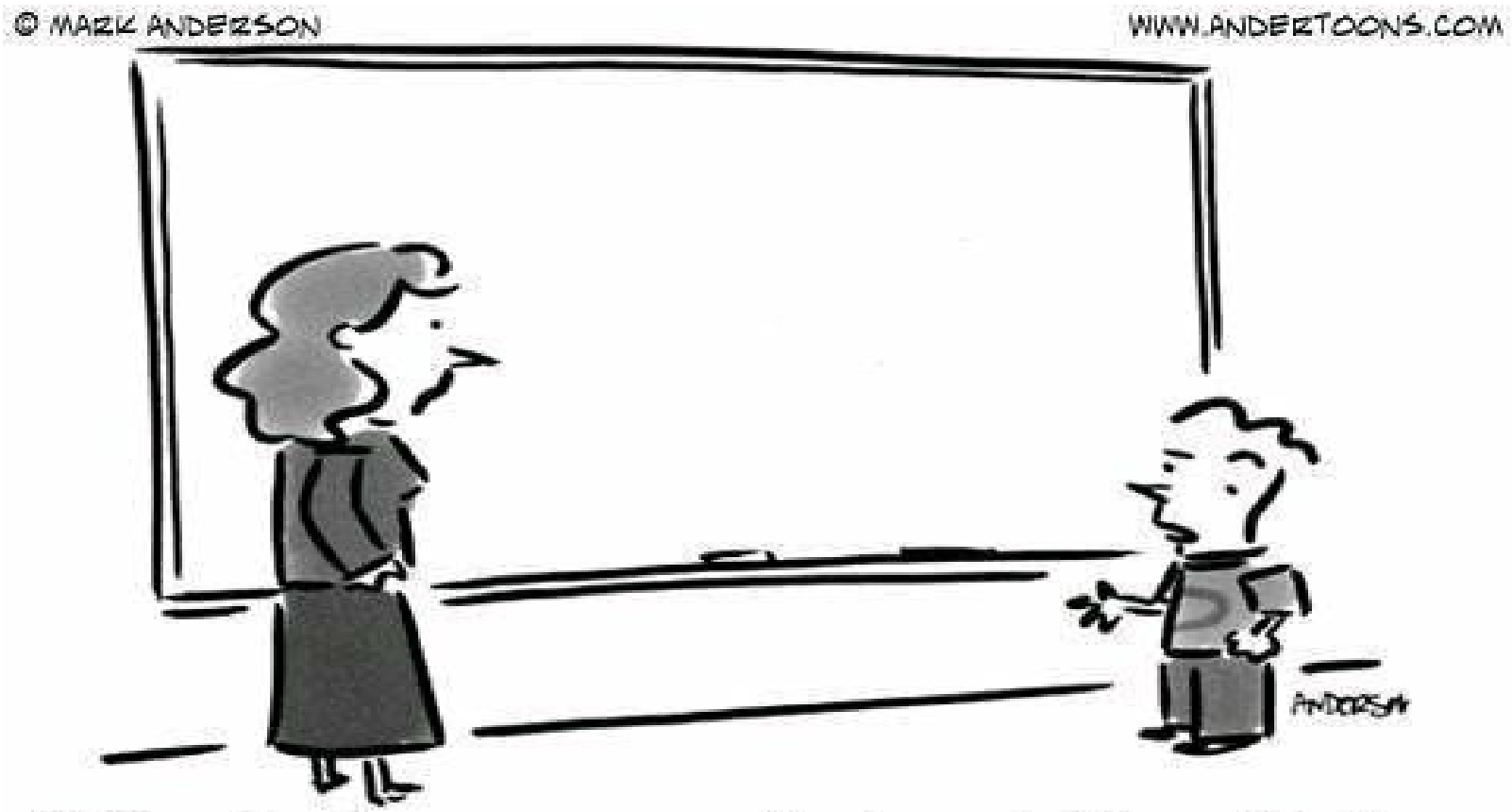
ROUTE OF ADMINISTRATION	BIOAVAILABILITY(%)
INTRAVENOUS	100%
INTRAMUSCULAR/ SUBCUTANEOUS	75-100%
ORAL	5 – 100%
RECTAL	30 – 100%

Bioavailability of Drugs – howMed

Comparison of innovator drug with generic drug



Data Integrity



"Before I write my name on the board, I'll need to know how you're planning to use that data."

AMOUNT OF DRUG RELEASD FROM 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

Other Bioequivalence Requirement

- During IND/NDA stage, establishes link between early and late Clinical Trial formulation used in Clinical Trial and stability studies, if different

  - In each comparison, the new formulation or new method of manufacturing is the test product and the prior formulation or method of manufacturing reference product

How Is BE Determined?

- For systemically available drugs: Based on pharmacokinetic measures of Cmax and AUC , Test (T) and Reference (R) products are considered bioequivalent when the 90% CI of the geometric mean ratios (T/R) of Cmax and AUC are within 80% to 125%
- Typically, a group of subjects (n=18 - 36) are administered test and reference drug products sequentially in two dosing periods, which are separated by a washout period
- Serial samples of biologic fluid (eg., plasma, serum, urine) are collected at pre-dose and at various time points after dosing and are analyzed for determination of drug and/or active metabolite concentrations

Types Of Studies Determining Bioequivalence

Bioequivalence of any product is determined by conducting any of the following studies:

- Pharmacokinetic endpoint studies
- Pharmacodynamic endpoint studies
- Clinical endpoint studies
- In vitro endpoint studies

Addressed by most regulators

Pharmacokinetic endpoint studies

Purpose

- To know rate & extent of absorption of active moiety to site of action

PK endpoint studies are carried out when

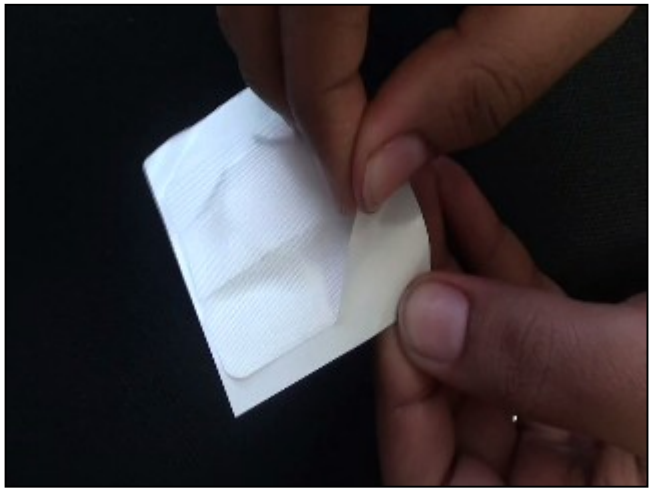
- Drug level can be determined in easily accessible biological fluid like plasma, blood, urine.
- Drug level can be correlated with clinical effect

Limitations

- PK studies measure systemic exposure but are generally inappropriate to know the BA & BE at local site.

Pharmacodynamic Endpoint Studies

- Measurement of effect on a pathophysiological process after administration of two different products to serve as basis for BE assessment.
- Required in case of
  - If drug &/or metabolite in plasma or urine cannot be analyzed quantitatively with sufficient accuracy and sensitivity
  - If drug concentration measurement cannot be used as surrogate endpoints for demonstration of safety & efficacy
- Examples
- Dermatological or topical products.



Clinical End Point Studies

- Requirement :
- Clinical endpoint studies are done when pharmacokinetic & pharmacodynamic studies not feasible.
- Clinical endpoint refers to occurrence of
  - Disease
  - Symptom
  - Sign or lab abnormality

Outcome of trial & if it happens then individual withdrawn from study

- For example,
- Acne study

In-Vitro End Point Studies

- Biopharmaceutics Classification System (BCS)
    - drug substances - either high or low solubility & permeability & exhibiting rapid dissolution.
- Helps in establishing in-vitro in-vivo correlation.
- Purpose of such classification is to assess the need for in-vivo BE studies for such products.
- E.g.
- Highly permeable, highly soluble drug substance formulated into rapidly dissolving drug product may need only in vitro dissolution studies to establish BE.

BIOEQUIVALENCE STUDY DESIGN
HOW TO CHOOSE BETWEEN PILOT AND PIVOTAL BE STUDIES

- PILOT STUDIES
  - Carried out on small number of subjects, usually on 12 subjects
  - Carried out before pivotal BE studies. »
  - To validate analytical methodology
  - Optimize sample collection intervals
  - Assess variability in formulation

- PIVOTAL BIQSTUDIES
  - For regulatory filing, part of ANDA filing
  - On larger number of subjects, usually 24 and above
  - Comply with regulatory, GLP, GCP requirements
  - Undergo regulatory agency's audit

Factors influencing BA/BE assessment

- Science
- Ethics

Regulatory Aspects

Regulatory Guidance for BA/BE

South Africa (mcc)

USA (FDA)

India (CDSCO)

Brazil (ANVISA)

Europe (EMEA)

Australia (TGA)

Japan (NIHS)

Canada (TPD)

GUIDELINES BY VARIOUS COUNTRIES

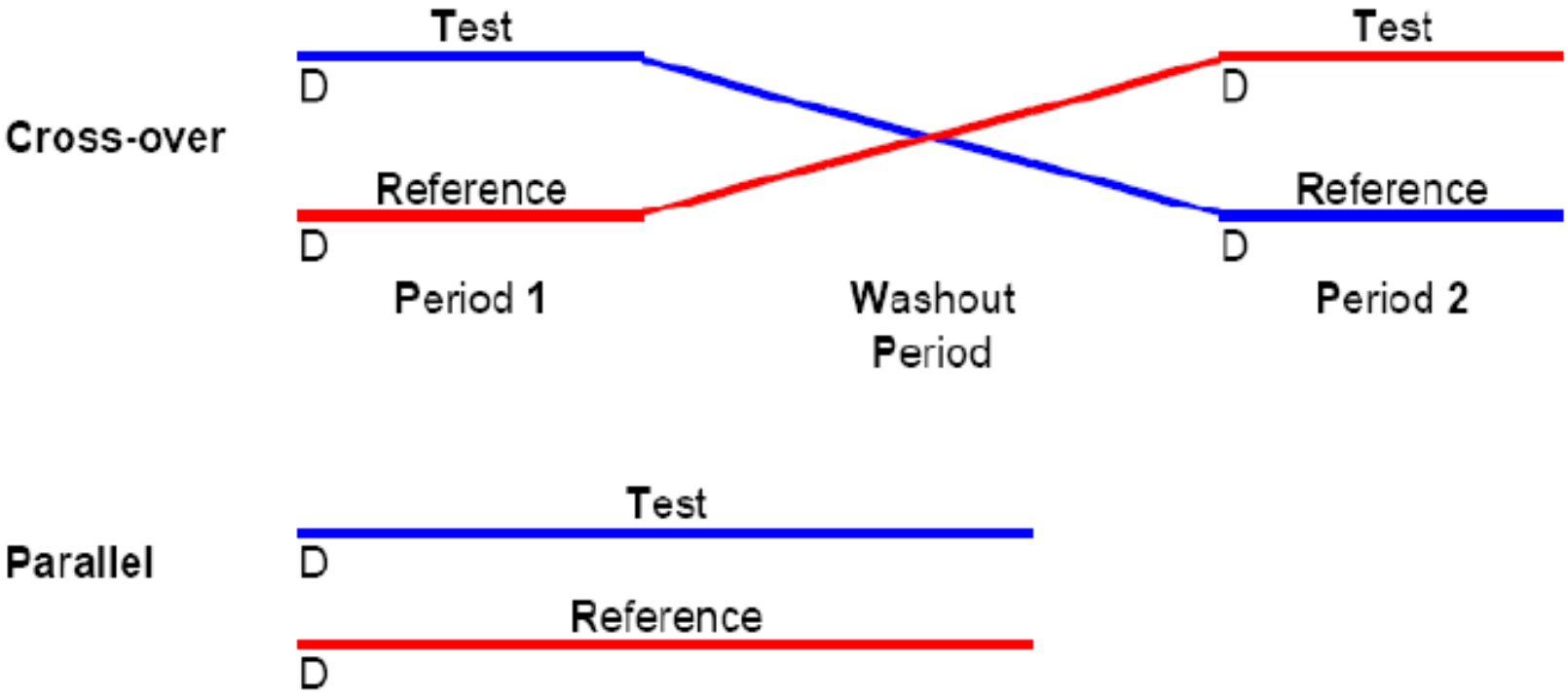
NAME OF COUNTRY	TITLE
USA	Guidance For Industry Bioavailability And Bioequivalence Study For Orally Administered Products – General Consideration
CANADA	1) GUIDANCE DOCUMENT Conduct and Analysis of Comparative Bioavailability Studies 2) GUIDANCE DOCUMENT Comparative Bioavailability Standards: Formulations Used for Systemic Effects
EUROPEAN UNION	Guideline On The Investigation Of Bioequivalence
INDIA	Guideline On The Investigation Of Bioequivalence
AUSTRALIA	Note of Guidance on the Investigation
MEXICAN	NOM-177-SSA1-1998

Study design

- Includes Description of the type or design of trial
  - Fasting study
  - Fed study
  - Food effect study
  - Single dose study
  - Multiple dose or repeat dose study
  - Crossover study
  - Parallel study
  - Replicate study

CROSSOVER BE STUDIES

- Widely used study design
- Each subject receives all treatments
- Physiological factors have less inter-occasion variability compared to variability due to formulation
- Each subject acts as his / her own control. It eliminates intersubject variability.
- Only intra-subject variability
- Can be fasting or fed steady


Cross-over
Test
D
Reference
D
Test
D
Reference
D
Period 1
Washout Period
Period 2
Parallel
Test
D
Reference
D

PARALLEL BE STUDIES

- Rarely used design
- Suitable for molecules having very long half life
- Can be fasting or fed study
- Each subject receives only one treatment
- Gives only inter-subject variability
- Period

  T / R

REPLICATE BE STUDIES

- Suitable for highly variable molecules
- Each subject receives all treatments twice
- Can be fasting or fed study
- Allows comparisons of within subject variances for test and reference
- More information about intrinsic factors underlying formulation performance
- Less number of subjects

Steady State BE STUDY

- Steady-state BE study
- Can be fasting or fed study
- Repeated administration of drug product till steady state concentrations achieved
- Gives indication of drug accumulation after repeated administration
- Small intra subject variability and few subjects required

BIOEQUIVALENCE STUDY DESIGN
FASTING BE STUDIES

- When focus is on the release of drug substance from drug product into systemic circulation, single dose fasting study is performed
- If formulation to be administered under fasting conditions, only fasting study is required
- For US ANDA filing, in many cases both fasting and fed biostudies required to meet regulatory requirement
- For European filings, mostly fasting biostudy is enough
- Both test and reference products to be administered with overnight fast (at least 10 hours) and continued fasting 4 hours post dose
- Water not allowed one hour before and one hour after dosing

BIOEQUIVALENCE STUDY DESIGN
FED BE STUDIES

- **FED BE STUDIES NOT REQUIRED WHEN**
  - Drug substance belongs BCS class I
  - Label states that product to be taken on only empty stomach
  - When label does not make any statements about effect of food on the absorption or administration

- **FOOD EFFECT STUDIES**
  - Usually conducted for new molecules or formulations
  - To assess the effect of food on the rate and extent of absorption of drug administered after a meal as compared to drug administered under fasting conditions
  - Effect of various variables like different types of meals, different timings of meals can be tested on drug absorption

HOW TO CHOOSE PRODUCTS FOR BE EVALUATION

- Generally highest marketed strength, in case of linear pharmacokinetics
- If pharmacokinetics are not linear, studies to be done on highest and lowest strength
- Where volunteer safety is concern can go for lower strengths
- Remaining strengths eligible for bio-waiver, if complies with following conditions

  - Drug product is in same dosage form but different strength
  - Remaining strengths meets appropriate dissolution test
  - Remaining strength is proportionately similar

HOW TO CHOOSE DOSE

- The molar equivalent dose of test and reference product to be used
- Generally highest marketed strength as a single unit
- For analytical reasons, multiple units of highest strength can be administered, provided the total dose remains within the labeled dose range
- In this case pharmacokinetics should be linear
- For safety reasons, lower strength can be dosed

HOW TO CHOOSE SAMPLING TIMEPOINTS

- Blood samples to be drawn at appropriate times to describe the absorption, distribution and elimination phases of drug
- For most drugs around 18 sampling time points would be required
- Sampling to be continued till at least three or more half lives of the drug
- Sampling collection to be spaced for proper characterization of maximum concentration of drug (Cmax) and terminal elimination rate constant (Kel)
- At least three to four samples to be obtained during terminal phase to obtain accurate estimate of Kel > Tmax and T1/2 values of the molecule required to choose sampling time points

HOW TO CHOOSE WASHOUT PERIOD

- The time interval between any two treatment periods
- It should be uniform between all study periods
- Should be enough to 'washout' previously administer treatment
- Each period to be separated by at least 7 to 10 ha1f lives of active moiety to be measured
- If more than one analytes measured in the study, analyte having highest half life to be considered

HOW TO CHOOSE BIOLOGICAL MATRIX

- Usually plasma or serum
- Sometimes whole blood is used
- Urine can be collected when
  - The concentrations in the blood are too minute to be detected
  - A substantial amount (>40%) of the drug is eliminated unchanged in the urine
  - When collecting urine, volume of each sample to be measured
  - Urine should be collected over three times of terminal elimination half-life

HOW TO CHOOSE MATRIX VOLUME

- Volume based on following points
  - Number of analytes
  - Analytical method available
  - Ethical issues

HOW TO CHOOSE SAMPLE SIZE

- Sample size estimation is made prior to the commencement of any pivotal bioequivalence study.
- A correct sample size is needed to establish the desired results(i.e. bioequivalence between the test and the innovator product).
- It is based on -data of previously conducted similar trials, pilot studies or from published literature of similar trials.

HOW TO CHOOSE STUDY POPULATION

- Should be 18 years and be capable of giving Informed consent Form (JCF)
- Should be representative of general population taking into account age, sex and race
- If the product to be used predominantly in elderly. Should attempt to include as many subjects of 60 years of age or more
- If the product is intended to use in both sexes, should be attempted to include similar proportions of male and females in the study
- Total subjects in the study should provide adequate power for BE demonstration
- Statistical analysis of subgroups Is not recommended
- Restriction on admission into the study generally be based on safety considerations
- If patients admit in BE study. their disease process should be stable during BE study

HOW TO CHOOSE RANDOMIZATION SCHEDULE

- Randomization schedule always based on study design specified in the protocol
- The order of receiving treatments for each subject is determined by SAS generated randomization schedule
- Decrease the effect of bias
- Randomization schedule should be balanced
- Generated by bio-statistician, distributed to investigator and pharmacy custodian
- Dispensing of test and reference products by pharmacy custodian as per randomization schedule

HOW TO CHOOSE ANALYTES TO BE QUANTIFIED

- Parent drug versus Metabolites
- Only the parent drug released from the dosage form, rather than metabolite is generally recommended
- The concentration profile of the parent compound is more sensitive to changes in formulation performance than a metabolite which is more reflective of metabolite formation, distribution and elimination.
- Measurement of metabolite is recommended when parent drug levels are too low to allow reliable analytical measurement in blood, serum or plasma

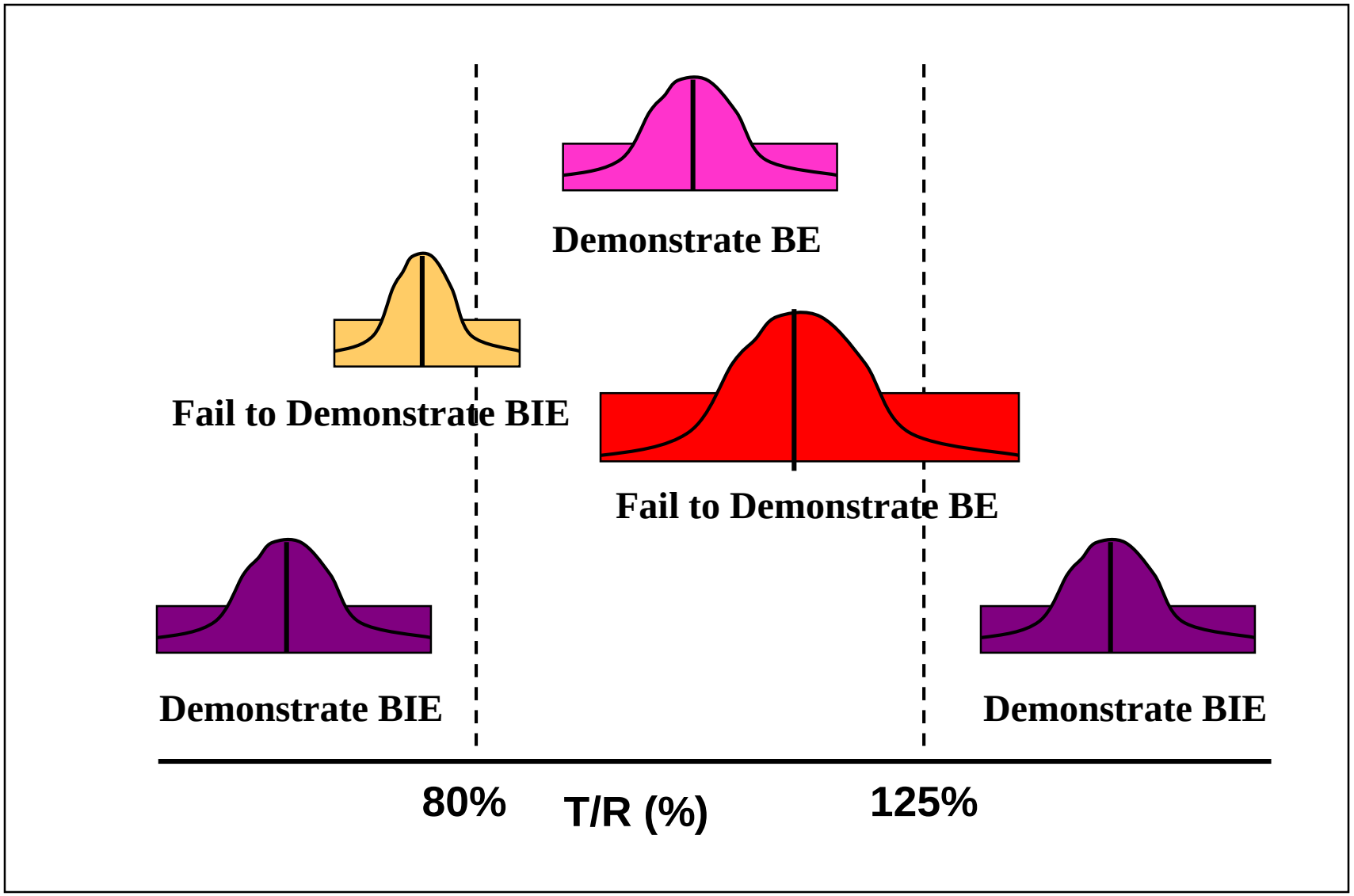
HOW TO CHOOSE PHARMACOKINETIC PARAMETERS

- Single Dose Study
  AUC0~t, AUCO-i, Cmax, Tmax, T1/2 and Kel
- Multiple Dose Study
  Tmax, Cmax~ss. AUC-ss and Flux (Flux1 and Flux 2), T1/2 and Kel
- Replicate Design Study
  AUC0-t, AUCO-co, Cmax, Tmax, T1/2 and Kel
- Long Half Life Drugs
  AUC0-72, Cmax, Tmax, T1/2 and Kel

HOW TO CHOOSE STATISTICAL ACCEPTANCE CRITERIA

- Bioequivalence criteria based on three pharmacokinetic parameters Cmax, AUC (0-t) and AUC (0-inf)
- 90% Confidence Intervals (CIs) between 80 -125%
- For highly variable drugs, 90% CIs for Cmax - 75-133% and for AUC 0-t and AUC 0-i 80 -125%
- For other molecules 90% CIs 80 – 125% for all three parameters

BE Results (90% CI)



TYPES OF FORMULATIONS - BE REQUIREMENTS

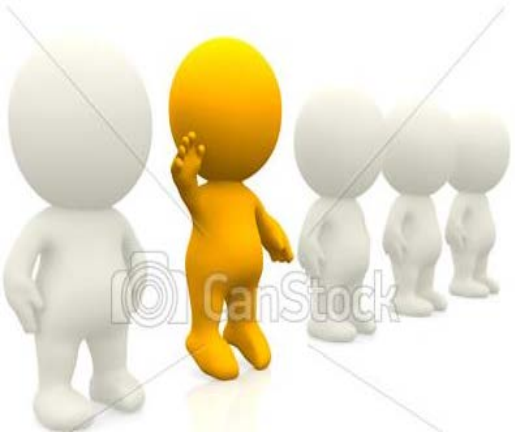
- In vivo study is recommended for all solid dosage forms approved after 1962 and for bio-problem drugs approved before 1962
- Waiver of in vivo studies for different strengths of a drug product can be granted under certain conditions
- For oral solution. elixirs, syrups. tinctures or other soluble forms in-vivo BE can be waived
- For solutions usually in-vivo BE studies are waived since the release of drug substance from drug product is self evident
- For suspensions BE studies are recommended
- For modified release products, both fasting and fed studies required to prove BE

Blinding

- Avoid study bias
- Subjects not aware of treatment
- Persons checking for AE and those conducting bioanalysis of samples should not know the treatment sequence

Outliers

Protocol should specify methods for identifying biologically implausible outliers. Post-hoc (after experiment over) exclusion of outliers is not recommended.



Sample Retention

Retention period of 3 years after conduct of study or 1 year after expiry of drug whichever is earlier.

Quantity to carry out twice all in-vitro & in-vivo tests required in BA/BE study

Study Design

- Frequent sampling in the area of Cmax
- Spread samples evenly between t=0 and tmax
- Sampling schedule adjusted according to clinical practicability!

Study Design

- Simulations help in setting the working range of the analytical method. Ideal:

  LLOQ ~ Clast

  ULOQ ~ Cmax

- Rule of thumb in BE-GL: LLOQ ~ 5% of Cmax
- Cooling prior to centrifugation
- Prevent sample mix-up at plasma separation (barcode system)
- Adsorption to surfaces (PP, glass stoppers)
- Stabilize unstable compounds

Study Design-Light sensitive drug

- Light sensitive compound – check first! Example nifedipine (clinical phase)
- Glass vials (vacutainers) shield almost perfectly against UV-radiation.
- The entry-depth of light into whole blood is in the range of a few millimeters only.
- Similar absorption wavelength as compared to albumin; the compound is well protected after centrifugation in plasma / plastic tubes.
- Working in the clinical phase under light protection (e.g., sodium vapour lamps) may lead to difficulties in venipuncture, sampling errors, etc.

Study Design

- Light sensitive compound – check first! Example nifedipine (analytical phase)
- Stock solutions and sample extracts are much more susceptible to light-degradation than plasma samples.
- Validate all sample preparation steps under varying light conditions (daylight through – closed windows, fluorescent light, dimmed light, sodium vapor light) and different light protection measures (glass vials, brown glass vials, PP vials, etc).
- Don’t forget to close the lid of the autosampler...

Ethical Issues in Study Design

- EC permission - MUST
- Cross-over design not always feasible
- Long half live drugs
- Patients: change in disease state
- Safety considerations
- Paediatrics : Bioequivalence studies in children not acceptable!
- PK studies for NDAs: Population PK with sparse sampling preferred

Ethical Issues in Study Design

Healthy subjects *vs.* patients

Healthy subjects generally preferred, except if main effect and/or adverse reactions unacceptable (anti-psychotics, chemotherapeutic agents)

Hormones in postmenopausal women (driven by analytical requirements)

Ethical Issues

The subject population for bioequivalence studies should be selected with the aim of permitting detection of differences between pharmaceutical products.

In order to reduce variability not related to differences between products, the studies should normally be performed in healthy volunteers unless the drug carries safety concerns that make this unethical.

Bioanalysis

Describe the quantitative measurement of drug or its metabolite in biological fluids like

- plasma
- blood
- serum
- urine or tissue extracts.

Consists of two important considerations

Sample preparation

Detection of desired compound using a validated method

Subsequent step after clinical operations of study & executed with strict adherence to GLP, SOPs & specific regulatory requirements.

Pharmacokinetic & Statistical Analysis

A description of the statistical methods to be employed, including timing of any planned interim analysis (ses).

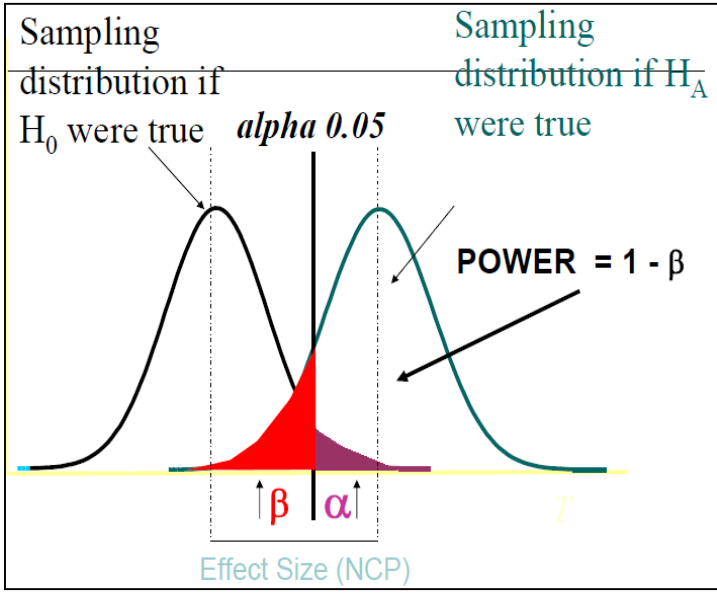
- The number of subjects planned to be enrolled.

- For multi centric trials → specify the number of enrolled subjects projected for each trial site.

-Reason for choice of sample size, including reasons on (or calculations of) the power of the trial its clinical justification.

- The level of significance to be used.

- Criteria for the termination of the trial.



Acceptance Criteria

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Europe & Australia	80-125	80-125	Not Applicable
Canada	Ratio must be between 80-125 Need to pass also on potency corrected data. Add-on studies may be allowed if intra- CV greater than expected	80-125	Not Applicable
South Africa	75-133	80-125	Not Applicable
Saudi Arabia	80-125	80-125	80-125
ASEAN	80-125	80-125	80-125
South Korea	80-125	80-125	80-125
Mexico	80-125	80-125	Not Applicable

When equivalence studies are NOT necessary (Biowaivers)

- Aqueous parenteral solutions
- Solutions for oral use (syrups, elixirs, tinctures & other soluble forms but not suspensions)
- Ophthalmic aqueous solutions
- Topical aqueous solutions
- Aqueous nebulizing inhalations or nasal sprays

- For some products bioequivalence may be demonstrated by evidence obtained in vitro instead of in vivo data:
  - The drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to another product by the same manufacturer that was found to be bioequivalent.

- For high potency drug substances, the same inactive ingredients are used for all strengths, and the change in any strength is obtained by altering the amount of the active ingredients and one or more of the inactive ingredients are within the limits defined by the SUPAC guidances (up to level II)

Waiver of Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (B.C.S)

BCS Classifications

According to the BCS, drug substances are classified as follows:

- Class I - High Permeability, High Solubility
- Class II - High Permeability, Low Solubility
- Class III - Low Permeability, High Solubility
- Class IV - Low Permeability, Low Solubility

Solubility

- A drug substance is considered *highly soluble* when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1 - 7.5 (WHO , pH: 1.2 – 6.8)

Permeability

- A drug substance is considered to be *highly permeable* when the extent of absorption in humans is determined to be 90% or more of an administered dose (WHO, 85%).

Conditions for BCS Bio-waivers

- Firms can request waivers of in vivo testing for Class 1 drug substances
- Drug products must meet these criteria:
  - Immediate-release solid oral dosage forms
  - Highly soluble, highly permeable drug substance
  - Rapid in vitro dissolution

- Note: Waivers not applicable for narrow therapeutic range (Digoxin, Lithium, phenytoin, warfarin) drugs

Documentation of methods, procedures and test results

- **Methods used and procedures set up to control the various processes within the service, should be well documented.**
- **This is important for inspection of the service by official authorities as part of an approval system.**

Documentation of methods, procedures and test results

- **Quality Handbook**
  - **covers all aspects of the quality system in a concise and practical way.**
  - **uses other documents as references as needed.**
- **Appropriate parts of the documentation should be made available to staff members**
- **It may even be useful to display operational instructions "on the spot".**

Perception !

Conclusion

- Bioavailability and Bioequivalence plays major role in Oharma industry
- Should be conducted as per the regulatory guidelines
- Strict adherence to GCP, GLP, GDP Guidelines
- Subjects safety – utmost importance.
- Reduces the cost of Healthcare of patients.
- Healthy subjects participation- Social cause.

See your tomorrow

Two islands

In Bering straits

- 2.4 km apart
- International Date line bet 2
- Big Diomede -29km2, Russian/Siberia.
- No inhabitants

- Little Diomede- 7.3km2,
- 170 inhabitants, USA part of Alaska
- See Tomorrow from small to Big island

Future !!!!

Thank you


I AM DROPPING OFF PRESCRIPTIONS FOR BOTH MY DOG AND HUSBAND . GIVE BRAND DRUG ONLY FOR MY DOG. GENERIC IS OK FOR MY HUSBAND !
PHARMACY
SUMANTA BARUAH
©pharmainfo.net

Drug Accountability

- **All records** of in vivo or in vitro tests shall be maintained by the manufacturer for **at least 2 years after the expiration date of the batch** and submitted to the Food and Drug Administration on request.

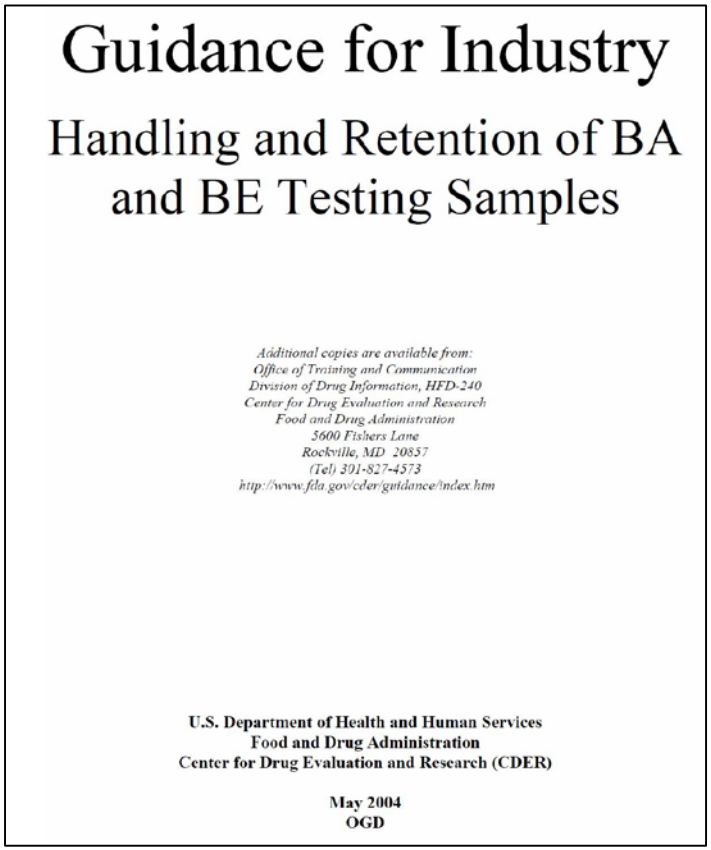
Drug Accountability

- Each reserve sample shall be stored under conditions consistent with product labeling and in an area segregated from the area where testing is conducted and with access limited to authorized personnel.

- Each reserve sample shall be retained for a period of at least 5 years following the date on which the application or supplemental application is approved, or, if such application or supplemental 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.

Drug Accountability

- The guidance highlights
  - how the test article and reference standard for BA and BE studies should be distributed to the testing facilities
  - how testing facilities should randomly select samples for testing and material to maintain as reserve samples
  - how the reserve samples should be retained.



Guidance for Industry

Handling and Retention of BA and BE Testing Samples

Additional copies are available from:
Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2004
OGD

Drug Accountability

- A frequent finding from these inspections is the **absence of reserve samples at the testing facilities** where the studies are conducted:
  - In many cases, FDA finds that testing facilities **return** reserve samples to the study sponsors and/or drug manufacturers,
  - In other cases, study sponsors and/or drug manufacturers, SMOs, or contract packaging facilities **designate** the study test article and reference standard **for each subject**, and preclude the testing facilities from randomly selecting representative reserve samples from the supplies.

- The study sponsor and/or drug manufacturer should send to the testing facility batches of the test article and reference standard packaged in such a way that the testing facility can **randomly select samples** for bioequivalence testing and samples to maintain as reserve samples.

Drug Accountability

- Quantity of Reserve Samples
  - Sufficient to perform five times all of the release tests required in the application or supplemental application
  - For solid oral dosage forms (e.g., tablets, capsules), an upper limit of 300 units each for the test article and reference standard
- Each site is asked to retain a reasonable amount of test article and reference standard
  - a minimum limit (e.g., 5 dose units) for each of the test articles and reference standards
- In-House Studies Conducted by a Study Sponsor and/or Drug Manufacturer
  - If a study sponsor and/or drug manufacturer conducts such a study, manufacturing reserve samples (21 CFR 211.170) and BE study reserve samples (21 CFR 320.38 and 320.63) should be separated.

ABSOLUTE BIOAVAILABILITY

- Absolute bioavailability compares the bioavailability of the active drug in systemic circulation for
  - Oral
  - Ocular
  - Transdermal
  - Sublingual

Conti….

- Compared with the bioavailability of the same drug following intravenous administration
- Fraction of drug absorbed through non-IV administration compared with IV administration of same drug
- Comparison must be dose normalized
  - i.e., account for different doses or varying weights of the subjects
  - consequently, the amount absorbed is corrected by dividing the corresponding dose administered

Conti….

- A PK study is required for
  - Plasma drug concentration vs time plot for drug after both **intravenous (iv) and extravascular (ex) for oral** administration
- Absolute bioavailability is the dose-corrected AUC non-intravenous divided by AUC intravenous
- For example, the formula for calculating F for a drug administered by the oral route (po) is given below. (D is dose)

$$F_{abs} = 100 \times \frac{AUCpo \times Div}{AUCiv \times Dpo}$$

Conti….

- AMS methods can be used For IV – AUC
- Standard LCMS/MS methods for oral - AUC
- Bioavailability is calculated by normalizing the IV AUC to the oral dose size and calculating the ratio obtained from the oral AUC and the normalized IV AUC

RELATIVE BIOAVAILABILITY

- Measures bioavailability of a formulation (A) of a certain drug when compared with another formulation (B) of the same drug
  - Usually an established standard, or through administration via a different route. When the standard consists of intravenously administered drug,

$$F_{rel} = 100 \times \frac{AUCA \times DB}{AUCB \times DA}$$

Absolute/ Relative Bioavailability - Pharma Mirror Magazine

Conti….

- If, IV bolus injection is not feasible, then
  - Relative (or comparative) BA is determined rather than the absolute BA
  - BA of a drug from a ‘test’ dosage form is compared to same drug administered in a ‘standard’ dosage form
    - i.e., either an orally administered solution (from which the drug is known to be well absorbed) or an established commercial preparation of proven clinical effectiveness

Absolute/ Relative Bioavailability - Pharma Mirror Magazine

Conti….

- “Relative BA is a measure of the fraction (or percentage) of a given drug that is absorbed intact into the systemic circulation from a dosage form relative to a recognized (i.e. clinically proven) standard dosage form of that drug.”

Absolute/ Relative Bioavailability - Pharma Mirror Magazine

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