BIAOAVILABILITY AND BAIEQUIVALENCE

For Class- B.Pharmacy 6th Semester

Subject- BIOPHARMACEUTICS AND PHARMACOKINETICS (BP604T)

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- “The term Bioavailability is defined as a rate & extent (amount) of absorption of unchanged drug from its dosage form.”

  \- Brahmankar & Jaiswal

THE FAMILY CIRCUS® By Bil Keane

"How will that stuff get from down there up to my sore throat?"

Objectives of Bioavailability studies :

- During primary stages of development of suitable dosage forms of new drug entity .
- Determination of influence of excipients , patient related factors & possible interaction with other drugs on the efficiency of absorption .
- Development of new formulations of existing drugs .

Significance of Bioavailability

- Drugs having low therapeutic index, e.g. cardiac glycosides, quinidine, phenytoin etc
- Narrow margin of safety (e.g. antiarrythmics, antidiabetics, adrenal steroids, theophylline)
- Drugs whose peak levels are required for the effect e.g. phenytoin, phenobarbitone, primidone, sodium valporate, anti-hypertensives,antidiabetics and antibiotics.
- Drugs that are absorbed by an active transport,e.g. amino acid analogues. Purine analogues etc.

- Drugs which are disintegrated in the alimentary canal and liver, e.g.chiorpromazine etc. or those which under go first pass metabolism.
- Formulations that give sustained release of drug.
- Any new formulation has to be tested for its bioavailability profile.
- Drugs with steep dose response relationship i.e. drugs obeying zero order kinetics / mixed order elimination kinetics (e.g. warfarin , phenytoin, digoxin, aspirin at high doses, phenylbutazone)

"I stopped taking the medicine because I prefer the original disease to the side effects."

Bioavailable fraction (F)

- It refers to the fraction of administered dose that enters the systemic circulation.

$$F = \frac{\text{Bioavailable dose}}{\text{Administered dose}}$$

Absolute Bioavailability (F)

- Def :

  "When the systemic availability of a drug administered ***orally*** is determined in comparison to its ***intravenous*** administration ,is called as Absolute Bioavailability"

$$\% \text{ Absorption} = \frac{\text{Dose (iv)} \times \text{AUC (oral)}}{\text{Dose (oral)} \times \text{AUC (iv)}} \times 100$$

Relative Bioavailability (Fr)

- Def :

  " When the systemic availability of the drug after oral administration is compared with that of oral standard of same drug (such as aqueous or non aqueous solution or a suspension) is referred as Relative Bioavailability"

  e.g. comparison between ***cap.*** Amox and ***susp.*** Amox

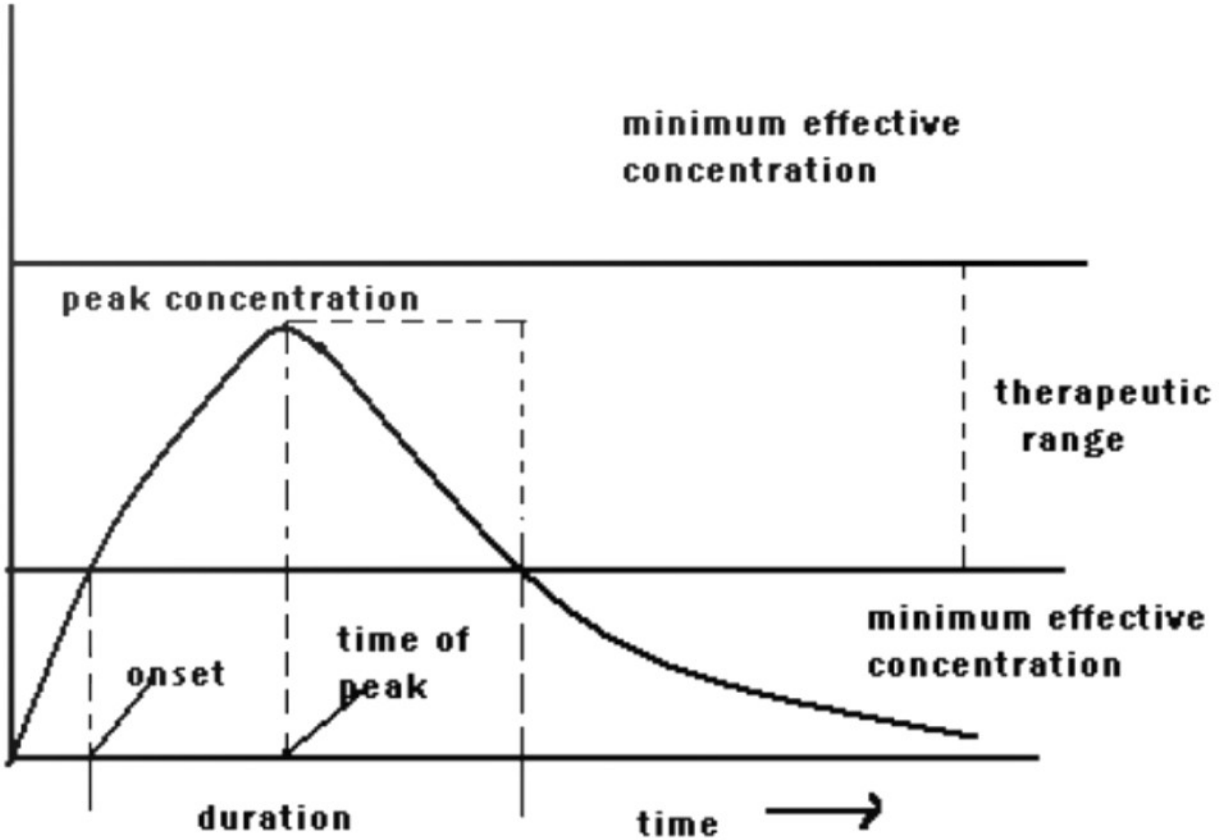
Measurement of Bioavailability

- Pharmacokinetic (Indirect)
  - 1.Plasma level time studies
  - 2.Urinary excretion studies
- Pharmacodynamic (Direct)
  - 1. Acute pharmacological response
  - 2. Therapeutic response

1) Plasma level-time studies:

- Two dosage forms that exhibit super imposable plasma level-time profiles should result in identical therapeutic response.

$$F = \frac{[AUC]_{oral} \times [D]_{iv}}{[AUC]_{iv} \times [D]_{oral}}$$



plasma concentration-time curve foll single oral dose
a-b absorption phase of curve
c-d elimination phase of curve

Based on the plasma concentration-time curve, the following measurements are important for bioavailability studies.

- *MINIMUM EFFECTIVE PLASMA CONCENTRATION-The minimum plasma concentration of the drug required to achieve a given pharmacological or therapeutic response. This value varies from drug to drug and from individual to individual as well as with the type and severity of the disease.*

- *MAXIMUM SAFE CONCENTRATION-The plasma concentration of the drug beyond which adverse effects are likely to happen.*

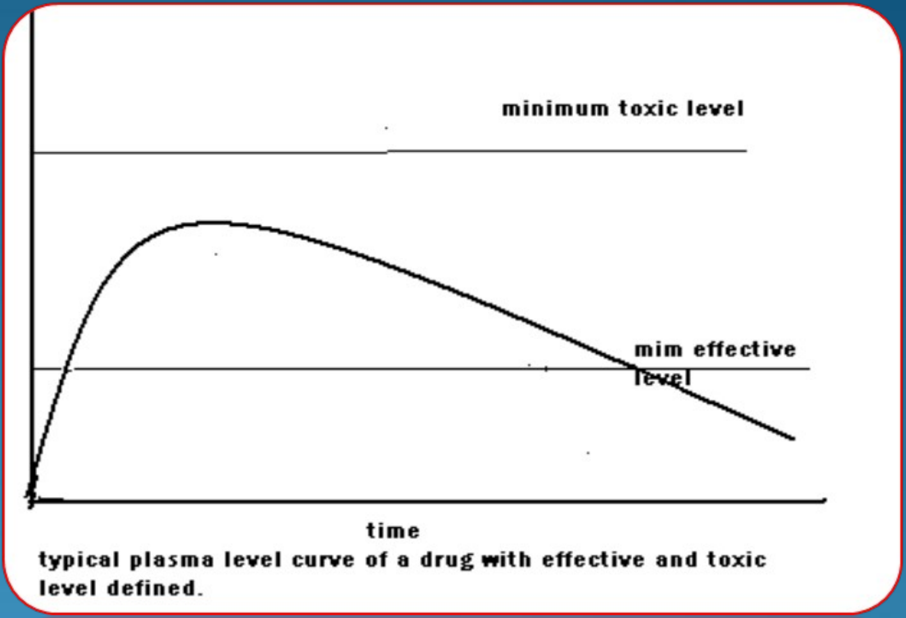
<u>THERAPEUTIC RANGE</u>-The range of plasma drug concentration in which the desired response is achieved yet avoiding adverse effect. The aim is clinical practice is to maintain plasma drug concentration within the therapeutic range.

<u>ONSET OF ACTION</u>-On set of action is the time required to achieve the minimum effective plasma concentration following administration of drug formulation.

<u>DURATION OF ACTION</u>-Duration of action of the therapeutic effect of the drug is defined as the time period during which the plasma concentration of the drug exceeds the minimum effective level.

<u>INTENSITY OF ACTION</u>-In general, the difference between the peak plasma concentration and the minimum effective plasma concentration provides a relative measure of the intensity of the therapeutic response of the drug.

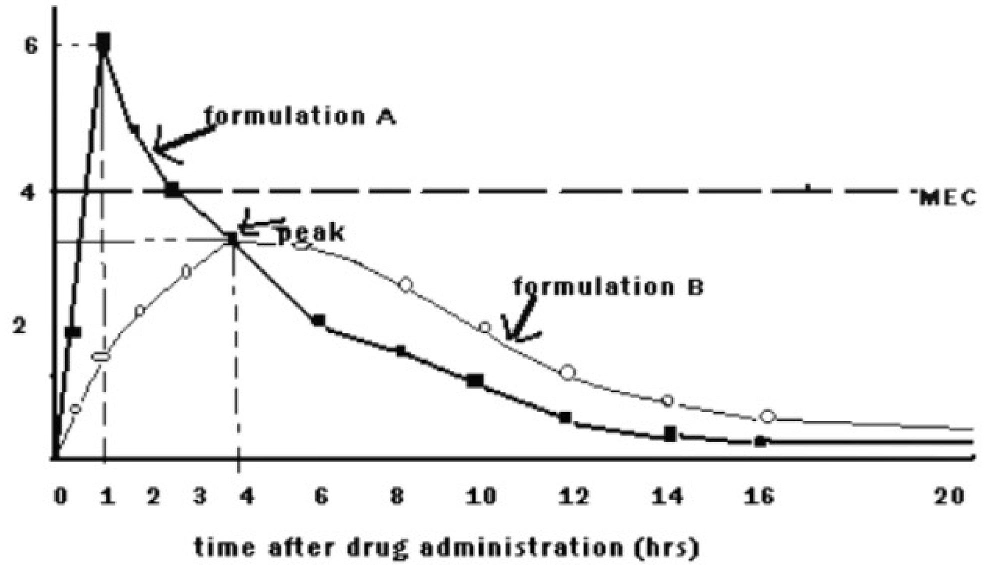
- Important parameters
  - C_{max} - peak plasma concentration



  - t_{max} - time taken to reach peak concentration
    - it indicates rate of absorption
  - AUC - Area Under the plasma level time Curve

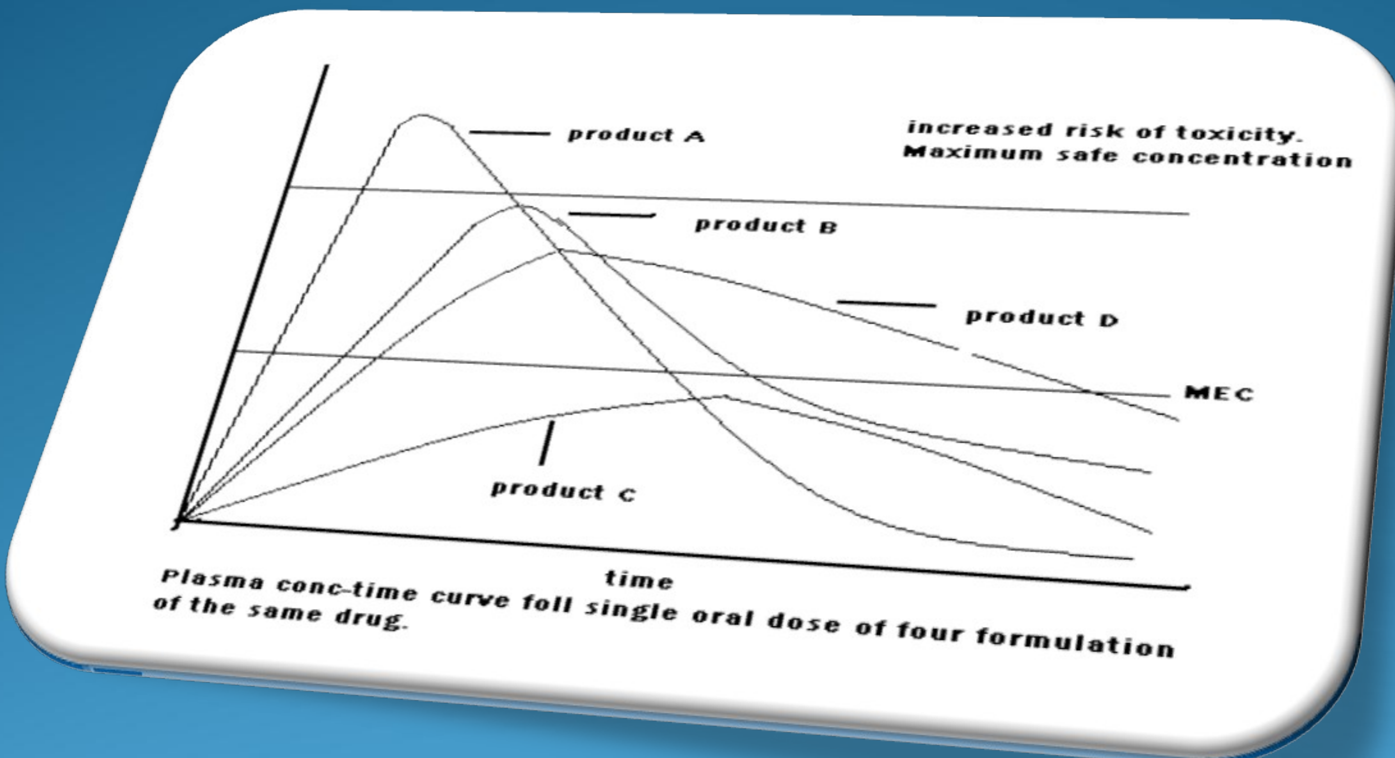
    give the measure of extent of absorption

On the other hand, if the two curves represent blood concentrations following equal doses of two different formulations of the same cardiac glycoside



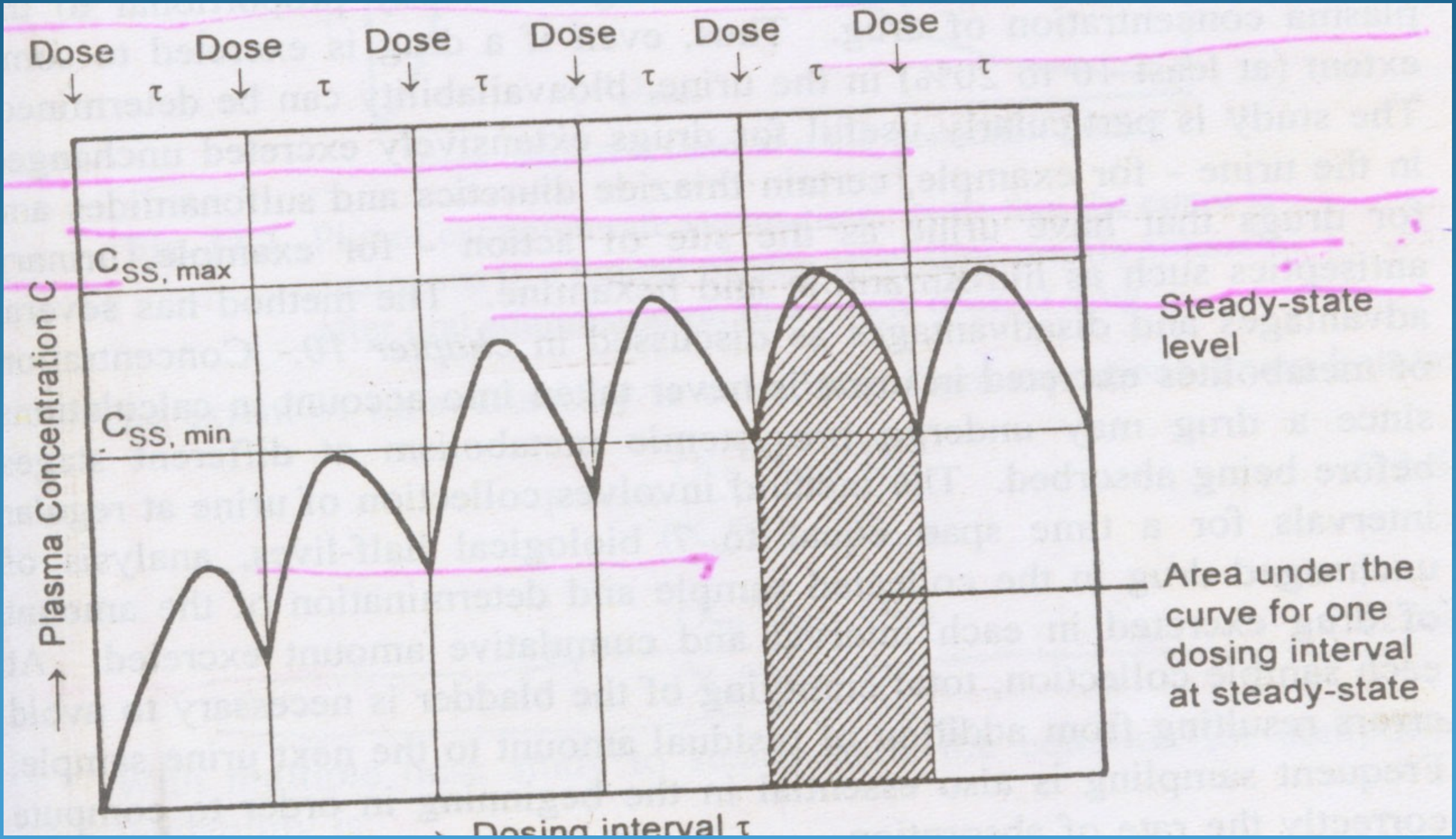
blood conc-time curves obtained for two different formulations of the same drug demonstrating relationship of the profiles to the minimum effective concentration

An example can explain how difference in bioavailability of a given drug from different formulations marketed by various firm, can result in a patient being either over, under or correctly medicated.



Product D is more desirable form of a dosage form specially for drugs with narrow safety margin and relatively shorter half life.

In multiple dose study:



b) URINARY EXCRETION-

This method can be based if urinary excretion of unchanged drug is the main mechanism of elimination of the drug

- *Bioavailability can be calculated as follows,*

$$F = \frac{(Du_\infty)}{f}$$

F = Fraction of the dose absorbed
Du_∞ = cumulative amount of drug excreted in the urine
f = fraction of unchanged drug excreted in the urine

5x the elimination ½ life = time at which the drug is "completely" (97%) eliminated from the body

1x ½ life - 50% of the original drug removed
2x ½ life - 75%
3x ½ life - 87.5%
4x ½ life - 93.75%
5x ½ life - 96.875%

- <u>**Urinary excretion**</u> α <u>**plasma concentration of drug**</u>
- Mainly used in drugs extensively excreted unchanged in urine.
  - E.g. Thiazide diuretics
    Sulfonamides
    Urinary antiseptics : nitrofurantoin , Hexamine.

$$F = \frac{[Xu_\infty]_{oral} \times D_{iv}}{[Xu_\infty]_{iv} \times D_{oral}}$$

a. $(dX_u / dt)_{max}$: Maximum urinary excretion rate

b. $(t_u)_{max}$: Time for maximum urinary excretion rate

c. X_u : Cumulative amount of drug excreted in the urine.

Biological fluids used for determination of Bioavailability

1. Plasma
2. Urine
3. Saliva
4. CSF
5. Bile

B. Pharmacodynamic methods

1) Acute Pharmacological Response :

- Used when pharmacokinetic methods are difficult , inaccurate & non reproducible.

- E.g. Change in ECG/EEG readings.
  Pupil diameter

Disadvantages :

- More variable
- Active metabolite interferes with the result.

2) Therapeutic Response :

- measurement of clinical response to a drug formulation given to patients suffering from disease for which it is intended to be used.

Disadvantages :

- Improper quantification of observed response.

Drug dissolution rate & Bioavailability :

- Correlation between Dissolution testing and bioavailability

- **In vivo determination test :**
  - Tool in the development of new dosage form.

- **In vitro dissolution test** :
  - To ensure batch to batch consistency
  - Best available tool which can quantitatively assure about bioavailability.

Drug Dissolution Apparatus

- Closed compartment apparatus
  Non sink conditions ;
- Open compartment apparatus
  Perfect sink conditions
- Dialysis system

In vitro drug dissolution rate and bioavailability

Factors to be considered:

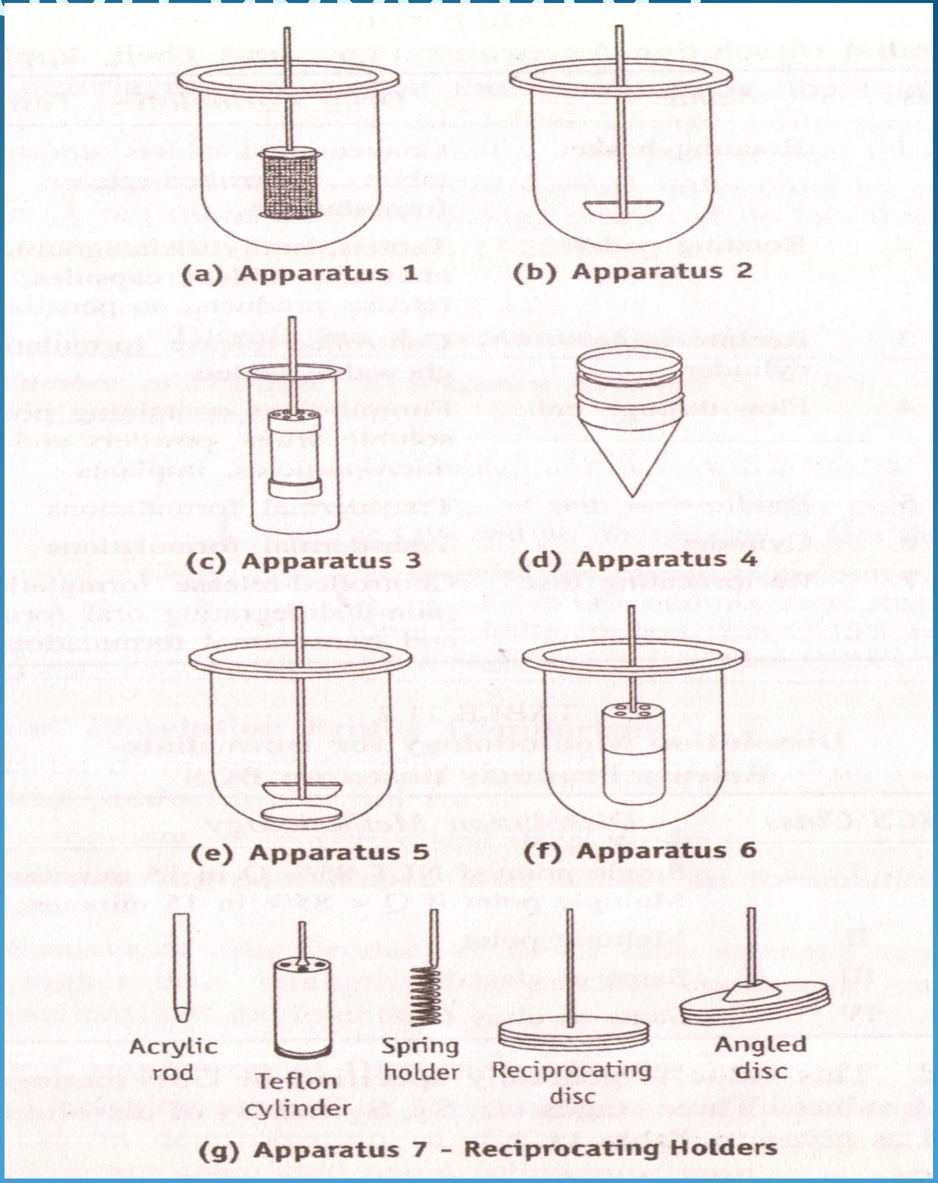
1. Factors relating to dissolution apparatus
2. Factors relating to dissolution fluid
3. Process parameters

Types of dissolution apparatus

- Closed compartment
- Open compartment

- Official compendial methods:

1. Rotating basket
2. Rotating paddle
3. Reciprocating cylinder
4. Flow-through cell
5. Paddle over disc
6. Cylinder apparatus
7. Reciprocating disc



Compendial Dissolution Apparatus Types and Their Applications

Apparatus	*Name*	*Drug Formulation Tested*
Apparatus 1	Rotating basket	Conventional tablets, chewable tablets, controlled-release formulations
Apparatus 2	Rotating paddle	Tablets, orally disintegrating tablets, chewable tablets, capsules, controlled-release products, suspensions
Apparatus 3	Reciprocating cylinder	Controlled-release formulations, chewable tablets
Apparatus 4	Flow-through cell	Formulations containing poorly soluble drugs, powders and granules, microparticles, implants
Apparatus 5	Paddle over disc	Transdermal formulations
Apparatus 6	Cylinder	Transdermal formulations
Apparatus 7	Reciprocating disc	Controlled-release formulations (non-disintegrating oral formulations and transdermal formulations)

Dissolution acceptance criteria

- Q is defined as percentage of drug content dissolved in a given time period.

Dissolution Acceptance Criteria

Stage	*Number of Dosage Units Tested*	*Acceptance Criteria*
S_1	6	No dosage unit is less than Q+5%
S_2	6	Average of the twelve dosage units ($S_1 + S_2$) ≥ Q% and no dosage unit is less than Q-15%
S_3	12	Average of the twenty four dosage units ($S_1 + S_2 + S_3$) ≥ Q% and not more than two dosage units are less than Q-15% and no dosage unit is less than Q-25%

Objectives of dissolution profile comparison

- Development of bioequivalent drug products.
- Demonstrating equivalence after change in formulation of drug product.
- Biowaiver of drug product of lower dose strength in proportion to higher dose strength product containing same active ingredient and excipients.

Method for comparison of dissolution profile

- Based on the determination of difference factor f_1 and similarity factor f_2

$$f_1 = \frac{\sum_{t=1}^{n} (R_t - T_t)}{\sum_{t=1}^{n} R_t} 100$$

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} 100 \right\}$$

where n = number of dissolution time points

R_t = dissolution value of the reference drug product at t

T_t = dissolution value of the test drug product at time t

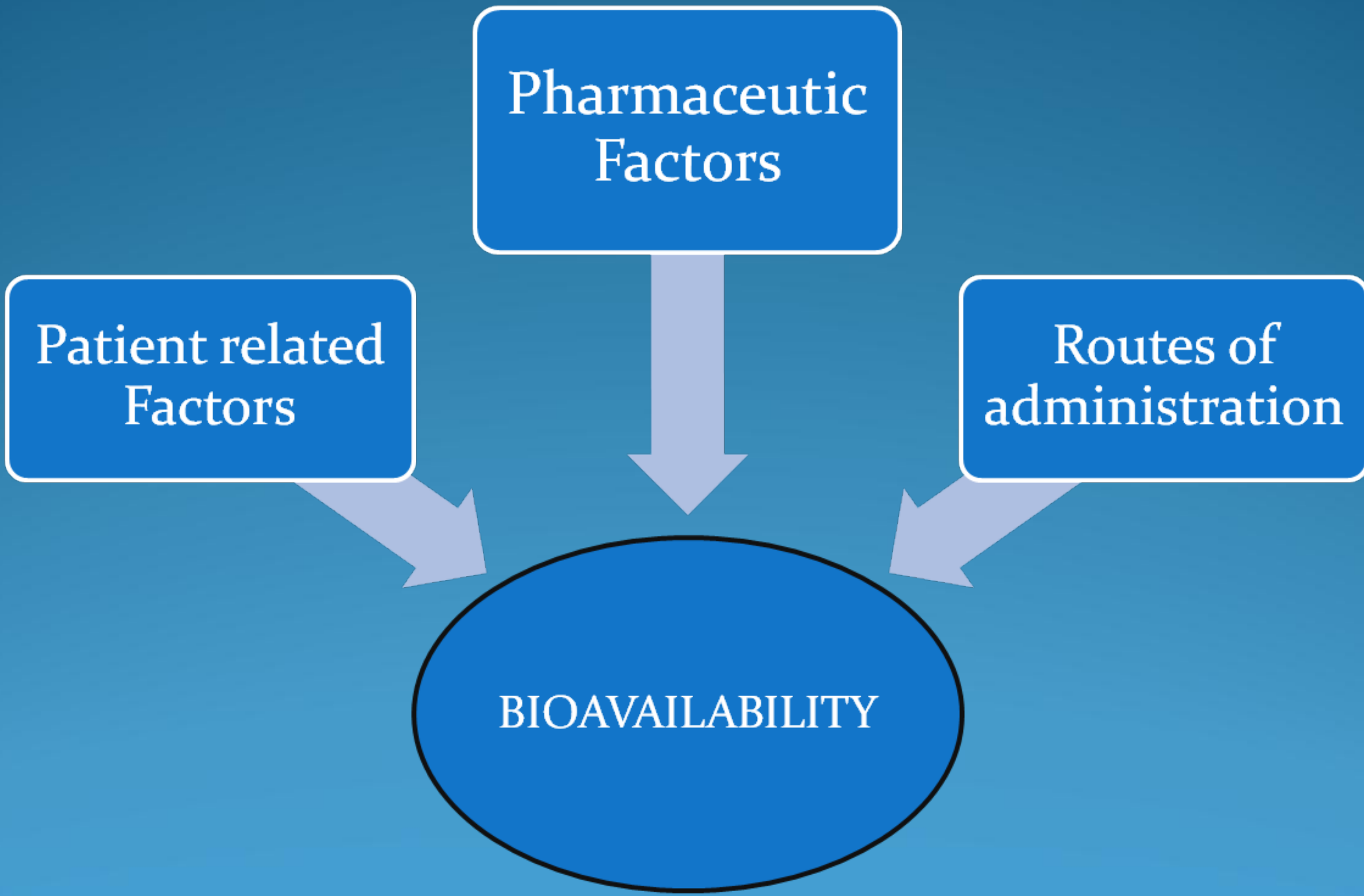
Comparison of Dissolution Profile

Difference factor f_1	*Similarity factor f_2*	*Inference*
0	100	Dissolution profiles are identical
≤ 15	≥ 50	Similarity or equivalence of two profiles

The evaluation of similarity between dissolution profiles is based on following ***conditions*** –

- Minimum of three dissolution time points are measured.
- Number of drug products tested for dissolution is 12 for both test and reference.
- Not more than one mean value of > 85% dissolved for each product.
- Standard deviation of mean of any product should not be more than 10% from second to last dissolution time point.

Factors affecting Bioavailability :



A) Pharmaceutic factors :

1) Physicochemical properties of drug :

1. Drug solubility & dissolution rate.
2. Particle size & effective surface area.
3. Polymorphism & Amorphism.
   - Amorphous > metastable > stable
4. Pseudopolymorphism (Hydrates / Solvates)
   - Anhydrates > hydrates e.g. Theophylline, Ampicillin
   - Organic solvates > non solvates e.g. fludrocortisone
5. Salt form of the drug.
   - Weakly acidic drugs – strong basic salt e.g.barbiturates , sulfonamides.
   - Weakly basic drugs – strong acid salt
6. Lipophilicity of the drug .
7. pKa of the drug & pH .
8. Drug stability.

2) Dosage form characteristics & Pharmaceutic Ingredients :

1. Disintegration time (tab/cap)
2. Dissolution time.
3. Manufacturing variables.
4. Pharmaceutic ingredients (excipients / adjuvants)
5. Nature & type of dosage form.
   - Solutions> Emulsions> Suspensions> Cap> Tab> Enteric Coated Tab > Sustained Release
6. Product age & storage conditions.

B) Patient related factors :

1. Age
2. Gastric emptying time .
3. Intestinal transit time .
4. Gastrointestinal pH .(HCL > Acetic > citric)
5. Disease States .
6. Blood flow through the gastrointestinal tract .
7. Gastrointestinal contents :
    a) Other drugs .
    b) Food .
    c) Fluids
    d) Other normal g.i. contents
8. Presystemic metabolism (First – Pass effect) by :
    a) Luminal enzymes .
    b) Gut wall enzymes .
    c) Bacterial enzymes .
    d) Hepatic enzymes .

In Vitro-in vivo correlation

- A predictive mathematical model that describes the relationship between an in-vitro property of a dosage form and an in-vivo response.

Purpose of IVIVC

- The optimization of formulations may require changes in the composition, manufacturing process, equipment, and batch sizes.
- In order to prove the validity of a new formulation, which is bioequivalent with a target formulation, a considerable amount of efforts is required to study bioequivalence (BE)/ bioavailability (BA).
- The main purpose of an IVIVC model - to utilize *in vitro* dissolution profiles as a surrogate for *in vivo* bioequivalence and to support biowaivers.

Basic approaches

- By establishing a relationship usually linear, between the in vitro dissolution and in vivo bioavailability parameters.
- By using data from previous bioavailability studies to modify the dissolution methodology.

In vitro-in vivo correlations

- Correlations based on the plasma level data
- Correlations based on the urinary excretion data
- Correlations based on the pharmacological response

IVIVC levels

- Level A:
  - Point to point correlation is developed between in vitro dissolution rate and the in vivo rate of absorption
- Level B:
  - Utilises statistical moment analysis and the mean in vitro dissolution time is compared to either the mean residence time or the mean in vivo dissolution time
- Level C:
  - single point correlation that relates one dissolution time point to one pharmacokinetic parameter

Multiple level C

S.No	*In Vitro*	*In Vivo*
	% Dissolution profile	**Plasma concentration Time profile**
1	% drug dissolved at time t	Plasma con at time t
2	Max drug dissolved at t	C_{max}
3	Time taken for max extent of drug release	T_{max}
4	Total amount of drug dissolution	AUC^{t}_{0}, AUC_{0}^{∞}
5	Time for a certain % of drug to dissolve	Time for a certain % drug reaches the circulation
	Kinetic Parameter	**Pharmacokinetic parameter**
6	Dissolution rate constant	Absorption rate constant
7	Dissolution half life	Absorption half life
8	% of drug dissolved at time t	% drug absorbed at time t
	Statistical moment analysis	
9	MDT (mean Dissolution Time)	MRT (mean residence time)

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*

Biopharmaceutics Drug Classification System for Immediate-Release Drug Products and IVIVC Expectations

Class	*Solubility*	*Permeability*	*IVIVC expectations for immediate-release product*	*Possibility of predicting IVIVC from dissolution data*
I	High	High	IVIVC expected, if dissolution rate is slower than gastric emptying rate, otherwise limited or no correlation.	Yes
II	Low	High	IVIVC expected, if *in vitro* dissolution rate is similar to *in vivo* dissolution rate, unless dose is very high.	Yes
III	High	Low	Absorption (permeability) is rate determining and limited or no IVIVC with dissolution.	No
IV	Low	Low	Limited or no IVIVC is expected.	No

Biopharmaceutics Drug Classification System for Extended-Release Drug Products and IVIVC Expectations

Class	*Solubility*	*Permeability*	*IVIVC*
Ia	High and site independent	High and site independent	IVIVC Level A expected
Ib	High and site independent	Dependent on site and narrow absorption window	IVIVC Level C expected
IIa	Low and site independent	High and site independent	IVIVC Level A expected
IIb	Low and site independent	Dependent on site and narrow absorption window	Little or no IVIVC
Va: Acidic	Variable	Variable	Little or no IVIVC
Vb: Basic	Variable	Variable	IVIVC Level A expected

BIOEQUIVALENCE

- Definition :

  " It is a relative term which denotes that the drug substance in two or more identical dosage forms , reaches the circulation at the same relative rate & to same relative extent i.e. their plasma concentration-time profiles will be identical without significant statistical differences."

- **Pharmaceutical equivalence** :
  "Drug products are considered to be pharmaceutical equivalents if they contain the same active ingredients and are identical in strength or concentration, dosage form, and route of administration."

- **Therapeutic equivalence** :
  " It indicates that two or more drug products that contain the same therapeutically active ingredient, elicit identical pharmacological effects & can control the disease to the same extent"

- **Clinical equivalence:**
  " when the same drug from two or more dosage forms gives identical in vivo effects as measured by a pharmacological response or by control of a symptom or a disease."

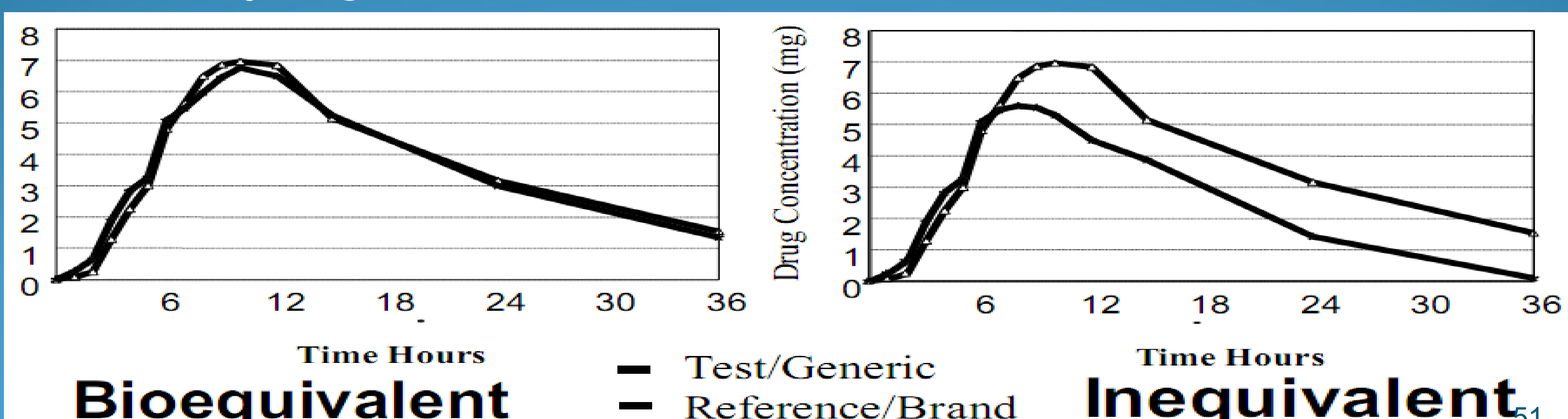
When do we do BE studies ?

- ✓ Clinical Service Form to Final Market Form
- ✓ Change of formulations (capsules to tablet)
- ✓ Generic Formulations
- ✓ Change of Process or manufacturing site (some times)
- ✓ Regulatory requirement.
- ✓ Establishment of pharmacokinetic parameters.
- ✓ Study of formulations & process variables.

What is Bioequivalence?

A generic drug is considered to be bioequivalent to the brand name drug if:

- The rate and extent of absorption do *not show a significant difference from listed drug, or*
- The extent of absorption does *not show a significant difference and any difference in rate is intentional or not medically significant*



Two kinds of drugs

- A brand name drug
  - An Innovator drug.
  - Price of new medicine
- A generic drug
  - Drug which contains the same active ingredient in the same formulation as the brand name.
  - A generic drug cannot be marketed in the US until the patent on the innovator drug has expired.
  - Same efficacy, but usually cheaper.

THE CRITICAL PATH TO MEDICAL DRUG DEVELOPMENT

New Chemical Entities (NCEs)

Conceptual chemistry

↓

Lead optimization

↓

Preclinical biology

↓

ADME

↓

Toxicology

↓

Regulatory approval for Human studies

↓

Phase I – III Clinical trials

↓

Regulatory Dossier

[Time frame : 8 -10 years; Cost : ~$1 bio]

Generics

API Process Research (GMP)

↓

Formulation Development (GMP)

↓

Bioequivalence study (GCP)

↓

Regulatory Dossier

[Time frame : 2-3 years;
Cost : $6-10 mio]

Brand Drugs vs Generic Drugs

Brand Name Drug

Patent
- Generally 10 years

Name
- Marketing Purpose
- Tylenol
- Advil
- Mylanta

Price
- Expensive

Generic Drug

Patent
- After Patent

Name
- Chemical Element
- Acetaminophen
- Ibuprofen
- Antacids

Price
- 30-84% Cheap

NDA vs. ANDA Review Process

Original Drug

NDA Requirements

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

   (Bioavailability/Bioequivalenc
   e)

Generic Drug

ANDA Requirements

1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing
6. Bioequivalence Study (In Vivo, In vitro)

Note: Generic drug applications are termed **"abbreviated"** because they are generally **not required to include preclinical (animal)** and **clinical (human) data to establish safety and effectiveness**.

Instead, generic applicants must scientifically demonstrate that their product is bioequivalent (i.e., performs in the same manner as the origina; drug).

- However bioequivalence is not straight forward for all the drugs . Many drugs shows bioinequivalence.
- In 1973 ad hoc committee on drug product selection of American Pharmaceutical Association published a list of drug that show bioinequivalence.
- Based on this list drug has been divided into 3 categories

HIGH RISK POTENTIAL	MODERATE RISK POTENTIAL	LOW RISK POTENTIAL
Aminophylline	Amphetamine	Acetaminophen
Bishydroxy coumarine	Ampicillin	Codeine
Digoxin	Chloramphenicol	Hydrochlorothiazide
phenytoin	Digitoxin	Ephedrine
prednisolone	Erythromycin	Isoniazide
prednisone	Griesofulvin	Meprobamate
quinidine	Penicillin G	Penicillin V
warfarin	Pentobarbital	Sulfixazole

BIOEQUIVALENCE PROBLEMS

Bioequivalence problem occurs due to following reason-

- Active drug ingredient has low solubility in water . (less than 5 mg/ml) .
- Dissolution rate is low.
- Certain structural forms of active drug ingredient (e.g. polymorphic forms, solvates, complexes & crystal modifications) dissolve poorly, thus altering the absorption.
- Drug product that have high ratio of excipients to active ingredients (e.g. greater than 5:1) .
- Specific ingredients such as hydrophilic & hydrophobic excipient & lubricant may interfere with absorption .
- Active ingredients absorbed in particular segment of GIT.
- Rapid metabolism in intestinal wall or in liver during absorption process.

Limitations of BA/BE studies

- Difficult for drugs with a long elimination half life.
- Highly variable drugs may require a far greater number of subjects
- Drugs that are administered by routes other than the oral route
- Drugs/dosage forms that are intended for local effects have minimal systemic bioavailability.

  E.g. ophthalmic, dermal, intranasal and inhalation drug products.
- Biotransformation of drugs make it difficult to

  evaluate the bioequivalence of such drugs :e.g. stereoisomerism

Study Protocol

1.Title

a) Principle investigator(Study director)

b) Project/protocol number & date.

2.Study objective

3. Study design

a) Design

b) Drug products

1.Test products

2. Reference Product

c) Dosage regimen

d) Sample collection schedule

e) Housing/ confinement

f) Fasting/meal schedule

g) Analytical methods

4. Study population

a) Subjects

b) Subject selection

1. Medical history
2. Physical examination.
3. Laboratory test.

c) Inclusion and exclusion criteria

d) Restriction / prohibitions

5. Clinical procedures
    A) Dosage and drug administration
    B) Biological sampling schedule
    C) Activity of subject
6. Ethical Consideration
    A) Basic principles
    B) Institutional review board
    C) Informed consent
    D) Adverse reactions
7. Facilities
8. Data analysis
    A) Analytical validation procedure
    B) Statistical treatment of data
9. Drug accountability
10. Appendix