PHARMACEUTICAL QUALITY ASSURANCE

UNIT 3 NOTES

QUALITY CONTROL

- QC FOR CONTAINERS
- RUBBER CLOSURES
- 2o PACKAGING MATERIALS

GOOD LAB PRACTICES

- GENERAL PROVISIONS
- ORGANIZATION & PERSONNEL
- FACILITIES & EQUIPMENTS
- TEST & CONTROL ARTICLES
- NON CLINICAL LAB STUDIES
- DISQUALIFICATION

IMPERFECT PHARMACY

CONNECT WITH US ON :

IMPERFECT PHARMACY APP

@IMPERFECTPHARMACY

Quality Control Test

- Quality Control Test is a procedure used to check & ensure that a product meets specified standards of quality, safety & performance.
- Quality control tests for containers, rubber closers & packaging materials are performed to ensure that they do not interact with the drug & maintain its quality, stability & safety throughout storage & use.

Packaging Materials

- Packaging materials in pharmaceuticals are used to protect the drug from environmental factors like light, moisture & contamination, and to ensure safe storage, transport & proper identification of the product.

Types Of Packaging Materials

Packaging Materials can be classified in 3 categories:

1. Primary packaging
2. Secondary packaging
3. Tertiary packaging

① Primary Packaging

- Directly in contact with the drug.
- Provides main protection
- Examples:
  - Tablets → blister packs
  - Syrups → bottles
  - Injections → vials, ampoules

② Secondary Packaging

- Outer covering of primary package
- Provides additional protection & labeling
- Examples:
  - Carton boxes
  - Leaflets

③ Tertiary Packaging

- Used for bulk handling & transportation
- Protects during shipping
- Examples:
  - Corrugated boxes
  - Containers

CONTAINERS

- A container is device that holds a p'ceutical product & protects it, from external factors like moisture, light & contamination.
- Most common types of materials used for containers are:

① Glass
② Plastic
③ Metal

GLASS

- Glass is most commonly used packaging material in p'ceuticals because it is chemically inert, impermeable & transparent, making it suitable for storing many drug product safely.

Properties of Glass

- It is non-reactive & does not interact with most drugs.
- It is impermeable to gases & moisture.
- Provides good protection & stability.
- Can be transparent or amber (light-resistant).
- Easily sterilized & can be reused.

TYPES OF GLASS

There are mainly 4 types of Glass containers used in p'ceutical packaging:

① Type I
② Type II
③ Type III
④ Type IV

① Type I (Borosilicate Glass)

- Contains silica + boron oxide
- Very high chemical & thermal resistance
- Doest not release alkali into solution
- Used for parenterals, injections, sensitive drugs

② Type II (Treated Soda-Lime Glass)

- Surface treated with sulphur dioxide to reduce alkalinity
- Good chemical resistance (less than Type II)
- Suitable for acidic & neutral aqueous preparations
- Commonly used for IV fluids & injections

③ Type III (Soda-Lime Glass)

- Contains sodium & calcium
- Moderate chemical resistance
- Can release small amount of alkali
- Used for oral preparations like syrups & tablets.

④ Type IV (General Purpose Glass)

- Lowest chemical resistance
- Not suitable for parenteral use
- Used for non-pharmaceutical or external preparations.

Quality Control Test For Glass

- Following quality control tests are performed to check quality, safety & stability of glass.

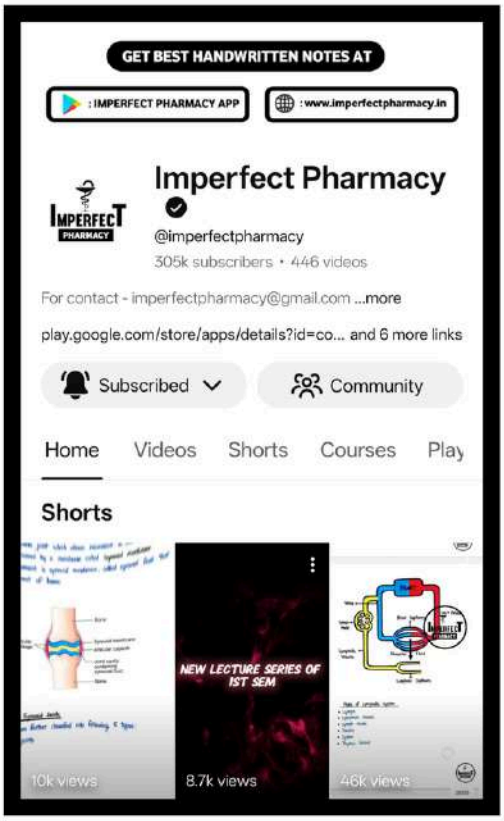
1. Chemical Resistance Test
2. Powder glass
3. Water Attack
4. Hydrolic Resistance Test
5. Light Transmission Test
6. Thermal Shock Test
7. Internal Bursting Pressure Test
8. Leakage Test

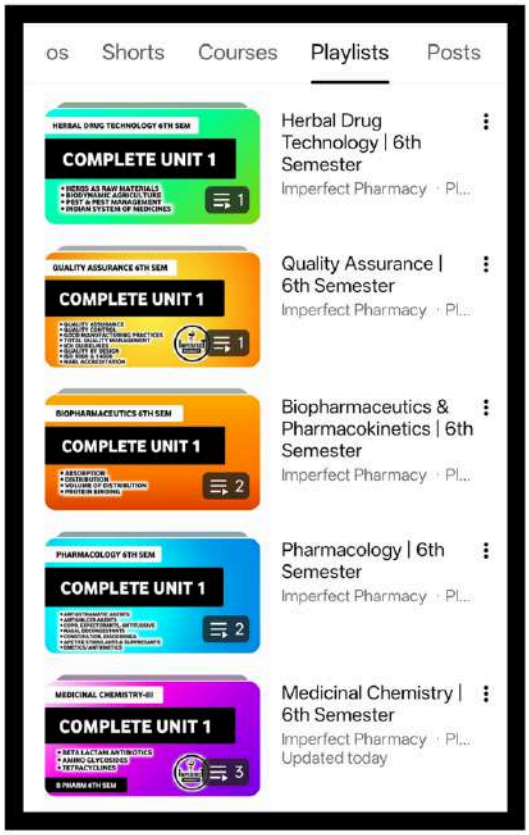
1. Chemical Resistance Test

- It determines the ability of glass to resist chemical attack (i.e., amount of alkali released).
- It is of two types:

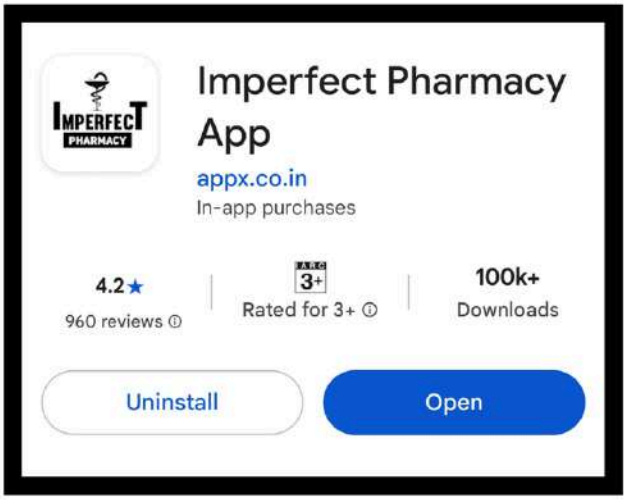
a. Powdered Glass Test
b. Water Attack Test

FOR LECTURE VIDEOS VISIT OUR CHANNEL





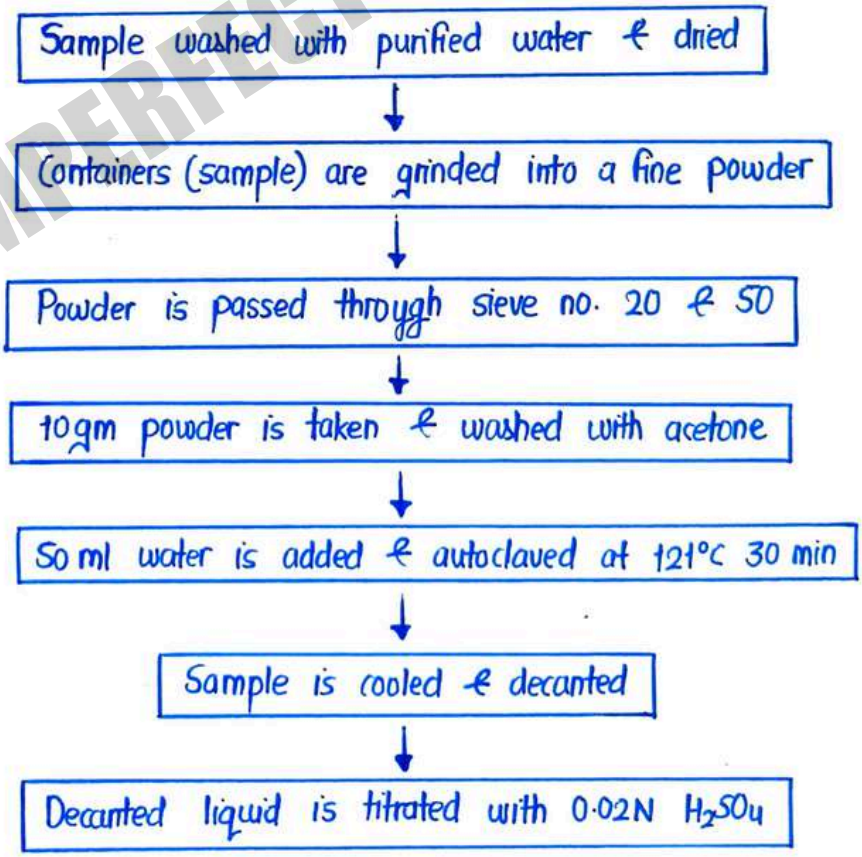
FOR MORE CONTENT : VISIT OUR APP



ⓐ Powdered Glass Test

- Glass containers are washed with purified water.
- Containers are crushed using mortar & pestle and converted into fine powder.
- Powder is passed through sieve no. 20 & 50 to obtain uniform particle size.
- About 10g powder is taken.
- Washed with acetone to remove impurities
- Add 50 ml purified water to powder & Autoclave at 121°C for 30 minutes.
- Sample is cooled, liquid is separated (decanted)
- Separated liquid is titrated with 0.02 N H_2SO_4.

Note : Alternatively you can explain it as a flowchart as follows:



LIMITS

Test	Container	Vol. of 0.02N H_2SO_4
Powdered Glass Test	Type I (borosilicate glass)	1.0
	Type II (soda-lime glass)	8.5
	Type N.P. (general purpose soda-lime glass)	15.0

ⓑ Water Attack Test

- It is mainly used for type II glass.
- Whole (unbroken) container is filled with distilled water upto 90% of its capacity.
- It is then autoclaved at 121°C for 30 min.
- Sample is cooled & liquid is separated
- Separated liquid is titrated using 0.2N H_2SO_4.
- Volume of H_2SO_4 consumed is recorded & compared with limits.

LIMITS

Test	Container	Vol of 0.02N H_2SO_4 (ml)
Water Attack Test	Type II	
	Size - 100 ml	0.7
	Less than 100 ml	0.2

② Hydrolic Resistant Test

- It measure amount of alkali releases when in contact with water.

Procedure

- Rinse containers with CO_2 - free water (3 times).
- Fill with same water & autoclave:
  - 100°C for 10 min
  - Then raise temperature to 121°C over 20 min
  - Maintain 121°C for 60 min
  - The lower the temperature from 121°C to 100°C over 40 min.
- Titrate with 0.01M HCl (methyl red)
- Perform a blank test.
- Volume of HCl used is directly related to amount of alkali released.

③ Light Transmisson Test

- This test measures the amount of light passing through glass, especially UV light.
- It ensures that glass can protect light-sensitive drugs.

Procedure

- Glass container is placed in a spectrophotometer.
- Light is passed through the glass.
- % transmittance is measured at specific wavelengths.
- Low light transmission (especially UV) → Good protection.

④ Thermal Shock Test

- It determines the ability of glass containers to withstand sudden temperature changes without breaking.

Procedure

- Glass containers are first heated to a high temperature
- They're suddenly cooled (usually by cold water)
- The containers are observed for cracks or breakage.
- No cracks → Pass (good quality).

⑤ Internal Bursting Pressure Test

- It determines the ability of glass containers to withstand internal pressure without bursting.

Procedure

- The glass container is filled with liquid (usually water)
- It is connected with as device named American Glass. Research Increment Pressure Te

Research Increment Pressure Tester

- Internal pressure is gradually increased.
- Process continues until the container bursts or fails.
- High pressure tolerance → Strong containers.

⑥ LEAKAGE TEST

- Leakage test is used check whether a glass container is properly sealed & free from leakage.

Procedure

- Containers are filled with water.
- Filled bottles are sealed, inverted & observed for 24 hours at room temperature for any signs of liquid leakage.
- No leakage → Pass

PLASTIC CONTAINERS

- Plastic containers are packaging systems made from polymeric materials (such as polyethylene, polypropylene or PVC) used to store, protect & deliver pharmaceutical products.
- They're designed to ensure stability, safety & compatability of the drug during storage, transportation & use.

QUALITY CONTROL TEST FOR PLASTIC CONTAINERS

1. Leakage Test
2. Collapsibility Test
3. Clarity of Aqueous Extract
4. Transparency Test
5. Eye Irritation Test

1. LEAKAGE TEST

- A properly sealed plastic container should not allow any liquid to leak under pressure or vaccum.

Procedure

- Fill the container with coloured water.
- Close it tightly with its cap.
- Place the container in a vaccum chamber or keep them inverted at room temperature for 24 hours.
- Observe for leakage or formation of bubbles.
- No leakage or bubbles should be observed.

② Collapsibility Test

- The container should collapse uniformly when pressure is applied so that the contents can be easily dispensed.

Procedure

- Fill the container with water or product.
- Apply pressure manually or mechanically.
- The container should collapse smoothly & yeild (release) 90% of its content at required rate or flow.

③ Clarity Of Aqueous Extract

- Plastic materials should not release insoluble particles into aqueous solutions.

Procedure

- Cut the plastic container into strips with area less than 20 cm^2.
- Wash the sample with distilled water to remove any extraneous matter (impurity).
- Transfer the sample to flask (previously washed with chromic acid).
- Add 250 ml distilled water to the flask & autoclave at 121°C for 30 min.
- Cool & filter the solution.
- The solution should be clear & free from turbidity.

④ Transparency Test

- Transparent plastic containers should allow clear visibility of contents.

Procedure

- Take an empty container.
- Place a standard object or printed text behind it.
- Observe through the container under proper light.
- The object / text should be clearly visible without distortion.

⑤ Eye Irritation Test

- This test is used to check whether the extract of a plastic container causes irritation in the eye.

Procedure

- Healthy albino rabbits are selected (usually 3)
- 100 µL of sterile water (blank) is instilled into one eye.
- 100 µL of the sample extract in instilled into the other eye.
- The eyes are observed at 24, 48 & 72 hours.
- Signs of irritation like redness & swelling are noted.
- Sample extract should be not shows any significant irritation compared to the blank.

METAL CONTAINERS

- Metal Containers are packaging containers made of metals such as aluminium or tin-plated steel, used for storing & protecting pharmaceutical products like ointments, creams & aerosols.

QUALITY CONTROL TEST FOR METALS

- The tests checks the presence of metal particles in metal collapsible tubes used for eye ointments.

Procedure

- Take 50 tubes & clean them properly.
- Fill tubes with molten ointment base & seal them.
- Allow them to cool overnight (15-20°C).
- Ointment is removed & A metal filter assembly is heated to melt the ointment base.
- Melted ointment filtered using a filter paper.
- Remove & dry the filter paper and observe under magnifying glass.
- Count metal particles of different sizes :
  - ≥ 1 mm
  - 0.5 - 1 mm
  - 0.2 - 0.5 mm

Each metal particle detected on the filter paper is given a score as follows:

- Particles 1 mm & above — 50
- Particles 0.5 mm but less than 1 mm — 10
- Particles 0.2 mm but less than 0.5 mm — 2
- Particles less than 0.2 mm — nil

LIMIT

- If total score is <100 = Pass
- If total score is >150 = fail
- If score is 100 - 150 = repeat

Closures

- Closures are devices used to seal a container in order to protect the contents from contamination, leakage & loss.
- Following Materials are used in closure:
  - Rubber closures
  - Plastic closures
  - Metal closures

NOTE: In our syllabus, we only need to study about "Rubber closures".

Rubber Closures

- Rubber closures are flexible sealing devices made of natural or synthatic rubber, used to close pceutical containers like vials & bottles to prevent contamination & leakage.
- They provide good sealing & flexibility.

Quality Control Test For Rubber Closures

1. Residue on Evaporation
2. pH of Aqueous Extract
3. Sterility Test
4. Fragmentation Test
5. Self - sealability Test
6. Penetrability Test

① Residue On Evaporation

- This test checks how much non- volatile (solid) impurity is left after evaporating the sample sol^{n}.

Procedure

- Closures are washed with 0·2% w/v anionic surfactant for 5 minutes.
- Rinsed with distilled water for 5 minutes & transferred in 200 ml solvent
- Autoclaved at 119 -123°C for 20-30 minutes (covered with alluminium foil)
- Cooled & the sol^{n} is separated → this is the sample solution.
- Take 50 ml of the prepared sample sol^{n}.
- Evaporate at 105°C until dry
- Measure the residue left
- Residue should be not more than 4 mg.

② pH Of Aqueous Extract

- It is the measurement of acidity or alkalinity of the aqueous extract obtained from packaging material (closures) to ensure it does not alter the pH of the p'ceutical product.

Procedure

- First sample sol^{n} is prepared same as mentioned in residue of evaporation.
- 20 ml of sample is taken & 0·1 ml of bromomethyl blue is added to it.
- Sample sol^{n} is titrated with 0·01M NaOH till colour changes from yellow to blue.
- Volume of NaOH consumed should not be more than 0·3 ml.

③ Sterility Test

- This test checks whether the closure is free from micro-organisms & can maintain sterility.

Procedure

- Closures are first sterilized (usually by autoclaving)
- Then they are placed in sterile culture media
- The media is incubated for a specific time (usually a few days)
- Observe for any microbial growth (turbidity / cloudiness)
- No turbidity → Test pass

④ Fragmentation Test

- This test checks whether rubber closures release small particles (fragments) when pierced by a needle.

Procedure

- Take 12 vials with about 4ml water & close them with closures.
- Keep them for 16 hours.
- Pierce each closure using a hypodermic needle.
- Inject 1 mL water & remove 1 ml air.
- Repeat this 4 times (using a new needle each time).
- Filter the water using a 0.5 µm filter.
- Count the rubber fragments on the filter.

Limits

- Not more than 10 fragments (for butyl rubber)
- Not more than 5 fragments (others)

⑤ Self-Sealability Test

- It is a test used to check whether a closure can reseal itself after repeated needle punctures without leakage.

Procedure

- Take 10 vials & fill them with water (nominal volume).
- Close them with the closures.
- Pierce each closure 10 time at different sites using a hypodermic needle.
- Immerse the vials in 0.1 % w/v methylene blue soln under pressure
- Keep them immersed for 30 minutes
- Remove & wash the vials, then check for entry of dye inside.
- No blue colour inside the vials → Test pass.

⑥ Penetrability Test

- It is a test used to measure the force required for a hypodermic needle to penetrate (pierce) a closure.

Procedure

- Fix the closure on a vial & place it in a piercing machine.
- A hypodermic needle is positioned above the closure.
- The machine pushes the needle through the closure at a constant speed.
- The force required to pierce the closure is measured & recorded.
- The force should be within specified limits otherwise needle can get damaged.

SECONDARY PACKAGING

- Secondary packaging is the outer packaging that holds one or more primary containers (like bottles, blister packs, vials)
- It is not directly in contact of the drug product.

FUNCTIONS

- Provides additional protection from physical damage
- Helps in grouping & handling of products.
- Provides labeling & information (branding, instructions, batch no, expiry)
- Improves transportation & storage.

MATERIALS FOR SECONDARY PACKAGING

The most commonly used materials for secondary packagings are :

1. Paper & Boards
2. Cartons
3. Corrugated Fiberboard

Quality Control Test For Secondary Packaging

1. Grammage
2. Thickness
3. Moistue Content
4. Folding Endurance
5. Bursting Strength
6. Water Absorption / Cobb's Test
7. Tear Resistant Test
8. Puncture Resistant Test
9. Box compression Test
10. Drop test

1 Grammage

- It measures the weight of paper per unit area (GSM).
- Indicates strength & quality of paper.
- High GSM → strong paper ; Low GSM → Weak paper
- Calculated by weighing a known area sample.

2 Thickness

- It measures the thickness of paper or board.
- Affects strength, stiffness & printing quality.
- Uniform thickness ensures good packaging.
- Measured using a micrometer. screw gauge.

③ Moisture Content

- It determines the amount of water present in paper.
- High moisture weakens paper & cause damage.
- Low moisture makes paper brittle.
- Calculated by drying & weighing difference.

④ Folding Endurance

- It shows how many times paper can be folded without breaking.
- Indicates flexibility & durability.
- Important for cartons & labels.
- Measured using folding endurance tester.

⑤ Bursting Strength

- It measures resistance of paper to bursting under pressure.
- High value means strong paper.
- Important for packaging safety.
- Measured using bursting strength tester.

⑥ Water Absorption Test

- It measures how much water is absorbed by paper.
- High absorption reduces strength.
- Low absorption gives better protection.
- Determined by weight difference after water exposure.

⑦ Tear Resistance Test

- It measures force required to tear the paper.
- High resistance means strong material.
- Important for handling & transport.
- Measured using tear testers.

⑧ Puncture Resistance Test

- It checks resistant against sharp object penetration.
- Prevent damage during transport.
- High value means better protection.
- Measured by applying force with a probe.

⑨ Box Compression Test

- It measures how much load a box can withstand before collapsing.
- Important for stacking during storage.
- High strength prevents damage.
- Measured using compression machine.

⑩ Drop Test

- It evaluates package safety when dropped from height.
- Simulates real handling conditions.
- Checks damage at corners, edges & surfaces.
- Used to ensure product protection.

Good Laboratory Practices

- Good Laboratory Practices (GLP) are set of rules & guidelines that ensure the quality, reliability & integrity of Non-clinical Laboratory studies.
- GLP helps in maintaining proper documentation, safety & standard procedures during experiments.
- It is especially important for studies related to drug safety, toxicity testing & regulatory submissions during Non-clinical trials.

Objectives Of GLP

- To ensure high-quality & reliable data from laboratory studies.
- To maintain consistency & reproductibility of experimental results.
- To provide proper documentation & traceability of all activities.
- To ensure safety of personnel & environment.
- To avoid, errors, fraud & data manipulation.
- To meet regulatory requirements for approval of drugs.
- To increase Global acceptance.

General Provisions

1. Organization & Management
2. Personnel
3. Facilities
4. Equipments
5. Test & Control Articles

① Organization & Management

- The laboratory should have a clear organizational structure with defined roles & responsebilities.
- It includes:

a) Study Director

- Study director is the main person responsible for the whole study.
- He/She ensures that the study is done according to GLP rules.
- Approves the study plan & final repoot.
- Responsible for accuracy & reliability of data.

b) Management

- Management provides resources, staff & facilities.
- They ensure that the lab follow GLP guidelines.
- Appoints qualified personnel & Study Director.
- Responsible for maintaining proper working environment.

c) QA Unit

- QA unit checks that all work is done according to GLP.
- It is an independent team.
- Performs inspection & audits regularly.

② PERSONNEL

- All staff should be qualified, trained & experienced.
- Personnel must have clear roles & responsibilities.
- Regular training programs should be conducted.
- Staff must follow SOPs, Proper hygiene & safety measures.
- Records of training & work must be maintained.

③ FACILITIES

- A good laboratory must have following facilities:

a) GENERAL FACILITIES

- Lab should be clean, well organized & properly designed.
- Enough space should be available to avoid mix-ups.
- Proper lighting, ventilation & cleanliness must be maintained.

b) TESTING FACILITIES

- There must be separate areas for different types of testing.
- Prevent contamination & errors
- Temperature & humidity should be controlled.

c) WASTE DISPOSAL

- There must be proper system for safe disposal of waste
- Hazardous waste should be handled carefully.
- Follow environmental & safety rules.

d) Animal Care Facilities

- Animals should be kept in clean & safe environment.
- Proper food, water & care should be given.
- Conditions like temperature & hygiene should be maintained.
- Ethical rules for animal handling must be followed.

④ Equipments

- Equipment should be suitable for its use.
- Regular calibration & validation must be done.
- Equipment should be cleaned & maintained properly.
- SOPs should be available for operation of each equipment.
- Faulty equipment should be labeled & not used.
- Records of use, storage & disposal must be maintained.

⑤ Test & Control Articles

- Test & Control Articles should be labelled properly.
- Laboratory should maintain records of name, batch, & purity information.
- Facility must store articles under process conditions.
- Personnel should handle substances according to SOPs.
- Staff should check stability & uniformity of articles.
- Record of uses, storage & disposal must be maintained.

Non-Clinical Laboratory Studies

- Non-clinical laboratory studies are laboratory exprimental in which scientist evaluates the safety & effectiveness of new drug substances by testing it on animals, cells or tissues before using it on humans.
- It is done before Clinical trials.
- It is simply known as 'Non-Clinical Trials'.

Protocol For Non Clinical Studies

- A protocol is a written & approved plan that describes how we'll conduct a non-clinical laboratory studies.
- It helps ensure accuracy, safety & GLP compliance.

Contents Of Protocol

- Identification
- Title & Purpose
- Names & Address
- Name of study director & personnel
- Proposed dates
- Justification for selection of the test system
- Description of the test system
- Experimental design

① Identification

- Each study is assigned a unique protocol number or code.
- It helps in tracking, documentation & record keeping.

② Title & Purpose

- Title clearly defines the study (e.g., acute toxicity of drug X).
- Purpose explains why the study is conducted.
- Example: To evaluate safety or toxic effects of drugs.

③ Name & Address

- Name & Address of sponser and test site must be recorded for accountability & traceability.

- Sponsor: Organization funding the study
- Test site: Where the study is conducted.

④ Name of Study Director & Personnel

- Study director is overall responsible for the study.
- Personnel includes other staff such as Technicians, scientists
- Their roles & responsibilities must be defined clearly.

⑤ Proposed Dates

- Start date & expected completion date must be mentioned.
- It helps in planning & monitoring process.

⑥ Justification For Selection Of Test System

- Explains why a particular animal species, organ or cell line is selected.
- Example: Rats choosen due to similarity in metabolism with humans.

⑦ Description Of Test System

- It contains detailed information about:
  - Species/strain
  - Age
  - Weight
  - Sex
  - Health condition
- It ensures uniformity & reproductibility of results.

⑧ Experimental Design

- This is the most important part of the protocol.
- It includes:
  - Number of groups (control & treated)
  - Dose levels & frequency
  - Routes of administration (oral, IV, etc)
  - Duration of study
  - Parameters to be observed (toxicity, behaviour, biochemical tests)
- It ensures systematic & scientific execution of the study.

RECORDS & REPORTS

RECORDS

- Records refer to all original data & documentation generated during the conduct of a non-clinical laboratory study.
- These include the study protocol, raw data, observations, test results & intrument outputs.
- All records must be accurate, complete & signed by responsible personnel.
- Any correction made in the records should not erase original data & properly justified.

STORAGE & RETRIEVAL

- All records must be securely stored & archived after the completion of the study.
- Proper storage condition should be maintained to prevent loss, damage or unauthorized access.
- Record must be retained for a specified period as per regulatory requirements.

REPORTS

- A final study report must be prepared at the end of each non-clinical laboratory study.
- The report should provide a complete & accurate description of study.
- It generally includes:
  - Title & objective of the study
  - Details of test substances
  - Description of methods & procedures
  - Results & their interpretation
  - Conclusion of the study.

- The report must be signed by the Study Director, confirming the validity & integrity of the study.

Disqualification Of Testing Facilities

- Disqualification means a testing facility is not allowed to conduct non-clinical studies due to non-compliance with GLP.
- Reasons for Disqualification includes:
  - Failure to follow GLP principles
  - Submission of false or manipulated data
  - Poor record keeping
  - Lack of proper facilities or trained staff
  - Repeated non-compliance during inspections

Procedure Of Disqualification

- The regulatory authority conducts inspections to evaluate compliance.
- If significant deficiencies are identified:
  - The facility is issued a notice describing the non-compliance.
  - An opportunity is provided to take corrective actions.
  - If the facility fails to address the issues satisfactory, it may be formally disqualified.

REINSTATEMENT

- A disqualified facility may be reinstated only after:
  - Rectifying all deficiencies
  - Demonstrating full compliance with GLP standards.
  - Successful re-inspection by the regulatory authority.

THANK YOU

FOR CHOOSING IMPERFECT PHARMACY AS YOUR STUDY PARTNER

IMPERFECT PHARMACY

JOIN US ON :


IMPERFECT PHARMACY


IMPERFECT PHARMACY


@IMPERFECTPHARMA


IMPERFECT PHARMACY


@IMPERFECTPHARMACY


IMPERFECT PHARMACY


IMPERFECTPHARMACY@GMAIL.COM