UNIT-III

QUALITY CONTROL

Points to be covered in this topic

- ❖ Quality control test for containers
- ❖ Rubber closures
- ❖ Secondary packing materials

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QUALITY CONTROL

❖ INTRODUCTION

- Along with **safety and efficacy, quality** is one of the most important criteria to assess the fitness of a medicinal product for use by the patient.

❖ DEFINITION

- **The World Health Organization (WHO)** defines the term quality control as, **"The sum of all procedures undertaken to ensure the identity and purity of a particular pharmaceutical. Such procedures may range from the performance of simple chemical experiments which determine the identity and screening for the presence of particular pharmaceutical substance (thin layer chromatography, infrared spectroscopy etc.), to more complicated requirements of pharmacopoeial monographs."**

❖ SCHEDULE M

- Schedule M of the Indian Drugs and Cosmetics Act and Rules defines a QC system as follows:
- "Quality Control shall be concerned with **sampling, specifications, testing, documentation, release procedures which ensure that the necessary and relevant tests are actually carried** and that the materials are not released for use, **nor products released for sale or supply** until their quality has been judged to be satisfactory.
- It is not confined to laboratory operations but shall be involved in all decisions concerning the quality of the product. It shall be ensured that all quality control arrangements are effectively and reliably carried out the department as a whole shall have other duties such as to establish evaluate, validate and implement all Quality Control Procedures and methods."

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❖ PARAMETERS TESTED

- Packaging materials are tested for their **appearance, dimensions, compatibility, chemical composition and customer usability.** Tests are performed to check suitability of:
  - **(a) Material of primary packaging** – chemical tests, mechanical tests and environmental tests.
  - **(b) Final pack in secondary packaging** – mechanical tests and environmental tests.

❑ Some Important Chemical Tests:

✓ **Tests for glass containers:**

- Water attack test
- Hydrolytic resistance test
- Powdered glass test
- Light transmission test
- Arsenic test
- Internal bursting pressure test
- Thermal shock test
- Annealing test
- Vertical load test
- Autoclaving

✓ **Ampoule sealing tests:**

- Appearance
- Quality of seal
- Sealed ampoule length
- Head space oxygen

✓ **Plastic containers testing:**

- Physicochemical tests on aqueous extracts
- Heavy metals test
- Non-volatile residue
- Biological in-vivo test
- Haemolytic effect of aqueous extracts

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- Acute systemic toxicity

✓ **Rubber closure testing:**

- Self sealability test
- Fragmentation test

✓ **Collapsible tubes testing:**

- Leakage test
- Lacquer compatibility test
- Lacquer curing test

✓ **Strip and blister packs testing:**

- Leakage test

✓ **Paper and board tests:**

- Paper and board density
- Moisture content
- Air permeability
- Folding endurance
- Grammage
- Tear strength
- Tensile strength
- Burst strength
- Puncture resistance
- Cobb test for water absorbance
- Creasability
- Stiffness
- Rub resistance
- Ink absorbency
- Brightness
- Roughness/smoothness

✓ **Tests on cartons:**

- Compression
- Coefficient of friction
- Carton opening force

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- Crease stiffness
- Joint shear strength

❖ TYPES OF GLASS CONTAINERS USED IN PHARMACEUTICAL INDUSTRY

TYPE OF GLASS	GENERAL DESCRIPTION	TYPES OF TEST	GENERAL USE
I	Highly resistant borosilicate glass	Powdered glass	Buffered and Unbuffered aqueous solutions
II	Treated soda - lime glass	Water Attack	Buffered aq. Solutions with pH below 7.0 Dry powder, oleaginous solutions
III	Soda -lime glass	Powdered glass	Dry powders, oleaginous solutions
IV(NP)	General- purpose soda- lime glass	Powdered glass	Not for Parenteral oral solutions. For tables and suspensions, Ointments and external liquids

❖ TESTS ON CONTAINERS AS PER INDIAN PHARMACOPOEIA

1) CHEMICAL RESISTANT OF GLASS CONTAINERS

A) Powdered Glass Test:

- It is done to estimate the amount of alkali leached from the powdered glass which usually happens at the elevated temperatures. When the glass is powdered, leaching of alkali is enhanced, which can be titrated with 0.02N sulphuric acid using methyl red as an indicator.

✓ **Step-1: Preparation of glass specimen:**

- Few containers are rinsed thoroughly with purified water and dried with stream of clean air.
- Grind the containers in a mortar to a **fine powder and pass through sieve no.20 and 50.**

✓ **Step-2: Washing the specimen:**

- 10gm of the above specimen is taken into 250 ml conical flask and wash it with 30 ml acetone.

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- Repeat the washing, decant the acetone and dried after which it is used within 48hr.

✓ **Procedure:**

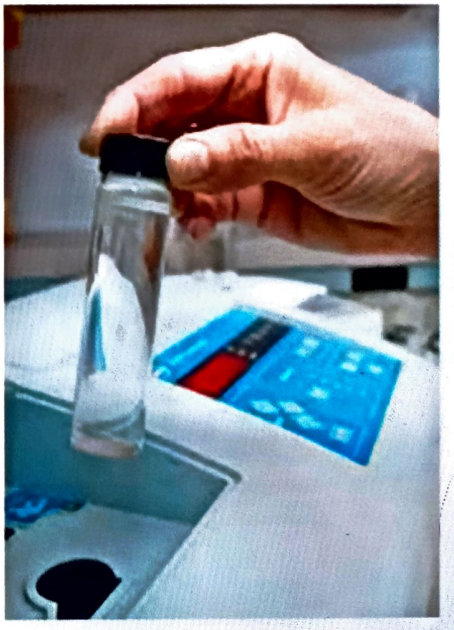
- 10gm sample is added with 50ml of **high purity water in a 250ml flask.**
- Place it in an **autoclave** at $121^0C \pm 2^0C$ for 30min. Cool it under running water.
- Decant the solution into another flask, wash again with 15ml high purity water and again decant.
- Titrate immediately with 0.02N sulphuric acid using methyl red as an indicator and record the volume.

B) Water Attack Test:

- This is only for **treated soda lime glass containers** under the controlled humidity conditions which neutralize the surface alkali and glass will become chemically more resistant.
- Principle involved is whether the **alkali leached or not from the surface** of the container.

✓ **Procedure:**

- Rinse thoroughly with high purity water.
- Fill each container to **90% of its overflow capacity** with water and is autoclaved at 121^0C for 30min then it is cooled and the liquid is decanted which is titrated with 0.02N sulphuric acid using methyl red as an indicator.
- The volume of sulfuric acid consumed is the measure of the amount of alkaline oxides
- present in the glass containers



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Test Limits		
Tests	Container	Vol. Of 0.02N H_2SO_4
Powdered glass test	Type-I Type-II Type-III	1.0 8.5 15.0
Water attack test	Type-II (100ml or below) Type-II (above 100ml)	0.7 0.2

(2) HYDROLYTIC RESISTANCE OF GLASS CONTAINERS:

- Rinse each container at least 3times with distilled water and fill with the same to their filling volume.
- Heat to 100°C for 10min and allow the steam to issue from the vent cork. Rise the temp from 100°C to 121°C over 20min. Maintain the temp at 121°C to 122°C for 60min.
- Lower the temp from 121°C to 100C over 40min venting to prevent vacuum.
- Remove the container from autoclave, cool and combine the liquids being examined.
- Measure the volume of test solution into a conical flask and titrate with 0.01M HCl using methyl red as an indicator. Perform blank with water and the difference between the titration represents the volume of HCl consumed by the test solution.

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Nominal Capacity Of container (ml)	Number of containers to be used	Volume of test solution to be used for titration (ml)
5 or less	at least 10	50.0
6 to 30	at least 5	50.0
More than 30	at least 3	100.0

Capacity of container [corresponding to 90 per cent average overflow volume (ml)]	Volume of 0.01M hydrochloric acid per 100 ml of test solution	
	Type I or II glass (ml)	Type III glass (ml)
Not more than 1	2.0	20.0
More than 1 but not more than 2	1.8	17.6
More than 2 but not more than 5	1.3	13.2
More than 5 but not more than 10	1.0	10.2
More than 10 but not more than 20	0.80	8.1
More than 20 but not more than 50	0.60	6.1
More than 50 but not more than 100	0.50	4.8
More than 100 but not more than 200	0.40	3.8
More than 200 but not more than 500	0.30	2.9
More than 500	0.20	2.2

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(3) Thermal Shock Test:

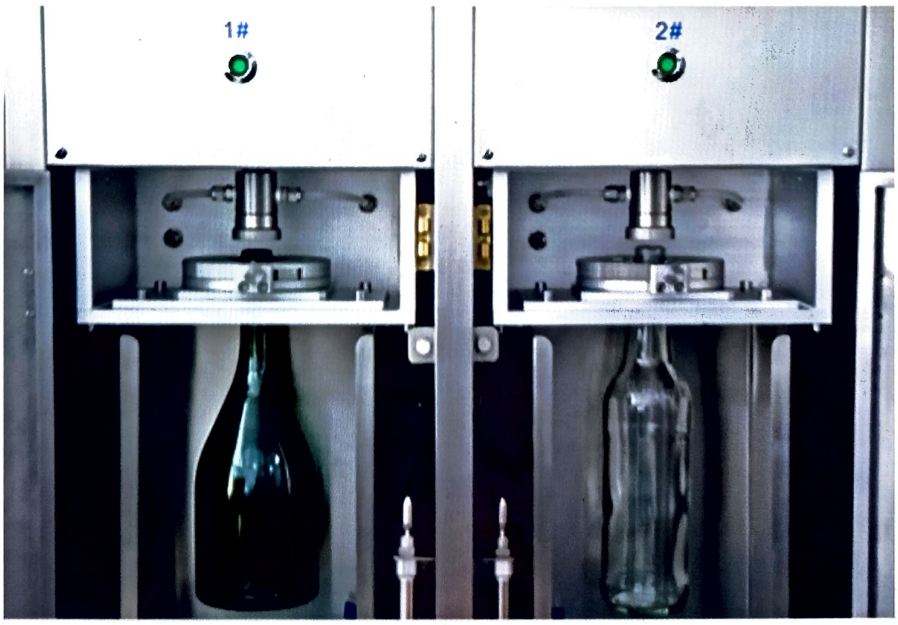
- Place the samples in **upright position in a tray.** Immerse the tray into a **hot water for a given time and transfers to cold water bath**, temp of both are closely controlled.
- **Examine cracks or breaks before and after the test.** The amount of thermal shock a bottle can withstand depends on its size and design. Small bottles withstand a temp differential of 60 to 80^{0}C and large bottle 30 to 40^{0}C.
- A typical test uses 45°C temp difference between hot and cold water.

(4) Leakage Test:

- Fill **10 containers with water**, fit with intended closures and keep them inverted at room temperature for 24hr.The test is said to be passed if there is no signs of leakage from any container.

(5) Internal Bursting Pressure Test

- The most common instrument used is **American glass research increment pressure tester.** The test bottle is filled with water and placed inside the test chamber.
- A **scaling head is applied and the internal pressure automatically raised by a series of increments each of which is held for a set of time.** The bottle can be checked to a preselected pressure level and the test continues until the container finally bursts.



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❑ TEST FOR PLASTIC CONTAINER:

(a) For non-injectable preparations

✓ Collapsibility test :

- Applicable to containers which are to be **squeezed in order to remove contents.** yield 90%of its contents at required rate of **flow at ambient temp.**

✓ Clarity of aqueous extract:

- Clarity of aqueous extract **Select unlabelled portion** from a suitable containers.
- **Cut** these portions into strips.
- **Wash it with extraneous matter by shaking** with two separate portions of distilled water
- Transfer to flask – previously washed with chromic acid.
- Rinse with distilled water add 250ml d.w.
- Cover the flask autoclave at 121°C, 30min Colourless , free from turbidity

✓ Non-volatile residue

- Evaporate 100 ml of the extract obtained in the test for Clarity of aqueous extract to dryness and dry to constant weight at 105º.
- The residue weighs not more than 12.5 mg.

(b) For injectable preparations

- **Leakage test, Collapsibility test**
- **Clarity and colour of solution**
- **Acidity or alkalinity**
- **Light absorption**
- **Reducing substances**
- **Transparency**

❑ SOLUTION S

- Fill a container to its nominal capacity with water and close it, if possible using the usual **means of closure**; otherwise close using a sheet of pure

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aluminium. Heat in an autoclave so that a temperature of 121 ± 2° is reached within 20 to 30 minutes and maintain at this temperature for 30 minutes.

- If heating at 121° leads to deterioration of the container, heat at 100º for 2 hours.
- Use solution S within 4 hours of preparation

✓ Blank

- Prepare a blank by heating water in a borosilicate glass flask closed by a sheet of pure aluminum at the temperature and for the time used for the preparation of solution S.

✓ Clarity and colour of solution S

- Solution S is clear and is colorless.

✓ Acidity or alkalinity.

- To a volume of solution S corresponding to 4 per cent of the nominal capacity of the container add 0.1 ml of phenolphthalein solution.
- The solution is colorless.
- **Add 0.4 ml of 0.01M sodium hydroxide**. The solution is pink. Add 0.8 ml of 0.01M hydrochloric acid and 0.1 ml of methyl red solution. The solution is orange-red or red.

✓ Light absorption.

- The light absorption in the range 230 nm to 360 nm of solution S using a blank prepared as described under Solution S is not more than 0.20.

✓ Reducing substances.

- To 20.0 ml of solution S add 1 ml of dilute sulphuric acid and 20.0 ml of 0.002M potassium permanganate. Boil for 3 minutes. Cool immediately.
- Add 1 g of potassium iodide and titrate immediately with 0.01M sodium thiosulphate, using 0.25 ml of starch solution as indicator.
- Carry out a titration using 20.0 ml of the blank prepared as described under Solution S. The difference between the titration volumes is not more than 1.5 ml.

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✓ Transparency

- Fill the container previously used for the preparation of solution S to its **nominal capacity with a 1 in 200 dilution** of the standard suspension for a container made from polyethylene or polypropylene.
- For containers of other materials, **use a 1 in 400 dilution.** The cloudiness of the suspension is perceptible when viewed through the container and compared with a similar container filled with water

❑ Water Vapour Permeability

- Fill **5 containers with nominal volume of water** and heat seal the bottles with aluminium foil.
- Weigh accurately each container and allow to stand **for 14 days humidity-60±5% temp 20°C and 25°C.**
- Reweigh the containers.
- Loss in wt in each container is NMT 0.2%

❑ Biological Tests

- These tests are designed to **determine the biological response of animals to plastics and other polymeric material by the injection** or instillation of specific extracts from the material under test. Some of the tests performed include:

✓ Systemic Injection Test

- To measure the irritation and toxicity caused by administration of sample orally, on the skin and by inhalation.
- **Test animal:** Albino **Mice Inject each of 5 mice** in test group with sample or blank observe the animals immediately, again after **4 hours, and then at 24, 48 and 72 hours.**
- If none of animals shows significant greater biological reactivity than the blank, the sample meets the requirements.
- If abnormal behavior such as prostration or convulsions occur or if there is a loss of body weight greater than 2g, the sample does not meet the requirements.

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✓ Intracutaneous Test

- To measure **localized irritation and toxicity** when sample comes into contact with live subdermal tissues. Test **animal- Rabbit Administer intracutaneous injection of doses of the sample and the blank.**
- Examine the sites of for any tissue reaction like erythema, edema, neurosis at 24, 48, 72 hours after injection. Limit- difference between the scores of sample and blank should be lesser than 1.0.

❑ Plastic Containers for Ophthalmic preparations

- They should comply with the following tests described under **plastic containers for non-parenteral preparations.**
  - ✓ **Leakage tests**
  - ✓ **Collapsibility tests**
  - ✓ **Clarity of aqueous extract**
  - ✓ **Non-volatile residue**
  - ✓ **Comply with the**
- **Systemic injection test and intracutaneous tests** under plastic containers for parenteral preparations.
- **Eye irritation Test**
- **Test animals:** Healthy rabbits without visible eye irritation.
- **Extracting media:** Sodium chloride injection or vegetable oil.

❑ Rubber Closures for Parenteral Product Containers

- Rubber closures are generally used for vials and need to be thoroughly tested because they come into **direct contact with the injectable preparations.**
- Due to their complex composition, problems may be found with rubber stoppers such as absorbing of the active ingredient or excipients, and leaching of the rubber ingredients into the drug product.
- This may affect the **safety of the product for its intended use.** Therefore, a series of tests are performed to evaluate the quality of rubber closures. These include:

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- Identification – using IR spectroscopy.
- Total ash – using compendial methods.

✓ Other Tests:

- **Sample preparation (Solution A):** Wash the closures in 0.2% w/v of anionic surface active agents for 5 min.
- Rinse 5 times with distilled water and add 200 ml water and is subjected to autoclave at 119°C to 123°C for 20 to 30 minutes covering with aluminum foil.
- **Cool and separate solution** from closure to obtain Solution A.

✓ Sterilization Test

- When treated closures are subjected to sterilization test at 64°C to 66°C and a **pressure of about 0.7 kPa for 24 hours**, the closures must not soften or become tacky and there shall be no visual change in the closure.

✓ Fragmentation Test

- This is applicable to closures intended to be **pierced by a hypodermic needle.**
- For closures that are intended to be used for **aqueous preparations**, place a volume of water corresponding to the nominal volume – 4 ml in each of the 12 clean vials, close the vials with the prepared closures, secure with a cap and allow to stand for 16 hours.
- For closures that are intended to be used for dry preparations, close 12 clean vials with the prepared closures.
- Use a new needle for each **closure and check that the needle is not blunted during the test.** Pass the liquid in the vials through a filter with a nominal pore size of 0.5 micrometer.
- Count the number of fragments visible to the naked eye. The total number of fragments is not more than 10 except in case of butyl rubber closures where the total number of fragments is not more than 15.

✓ Self-sealability Test

- This is applicable to closures intended to be used with multidose

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- containers.
- **Fill 10 suitable vials** with water to the nominal volume, close the vials with the prepared closures and secure with a cap. For each closure, use a new hypodermic needle with an external diameter of **0.8 mm and pierce the closure 10 times, piercing each time at a different site.**
- Immerse the vials upright in a 0.1% w/v solution of methylene blue and reduce the external pressure by 27 kPa for 10 minutes. **Restore the atmospheric pressure and leave the vials immersed for 30 minutes.** Rinse the outside of the vials. None of the vials contain any trace of coloured solution.

✓ pH of Aqueous Extract

- 20 ml of solution A is mixed with **0.1 ml bromothymol blue** and a small amount of 0.01 M sodium hydroxide is added to change the colour from blue to yellow.
- The **volume of sodium hydroxide required is not more than 0.3 ml** and if it is done with 0.01 M hydrochloric acid, the volume of acid needed should be not more than 0.8 ml.

✓ Reducing Substances

- 20 ml of solution A is mixed with 1 ml of 1 M sulphuric acid and 20 ml of 0.002 M potassium permanganate and boiled for **3 minutes, and cooled immediately.**
- 1 g of potassium iodide is added and solution is titrated against sodium thiosulphate using starch as an indicator. Blank is done and the difference between titration volumes is not more than 0.7 ml.

✓ Residue on Evaporation

- 50 ml of solution A is evaporated to **dryness at 105°C. The residue weight must be not more than 4 mg.**

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❖ SECONDARY PACKAGING

- Secondary packaging designates the packaging used to group various **pre-packaged products together.**
- As secondary packaging is not in **direct contact with the actual product**, its use and application usually differ distinctly from those of primary packaging, although the purpose of both type may at times converge.

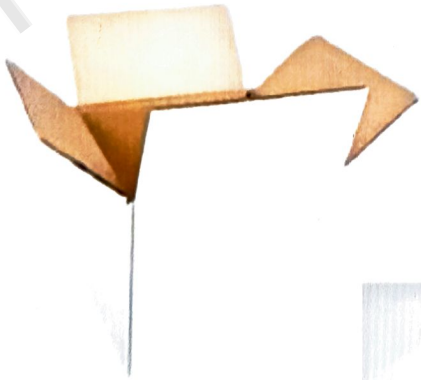
✓ **Secondary packaging said to have two central functions:**

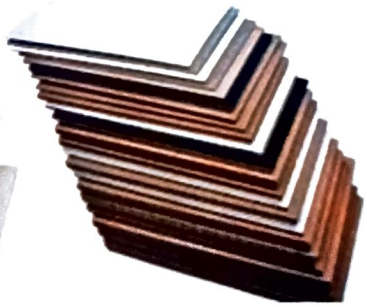
- **Branding & Display:** Secondary packaging plays a vital role in the **marketing strategy surrounding the product.** This is especially relevant in case of display packaging.
- **Logistics:** secondary packaging serves to group several products together for ease of **handling, transport and storage**. This means that secondary packaging must be able to.

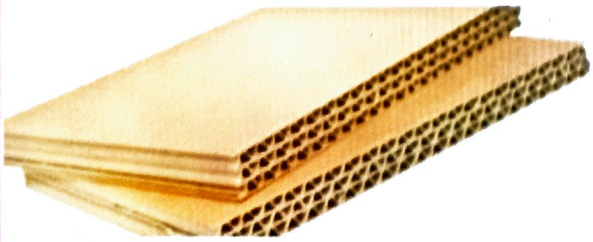
- Contain relatively large volume of primary packaged product
- Transport the product safely to the retailer or consumer destination
- Keep the primary packaging in its original condition during storage

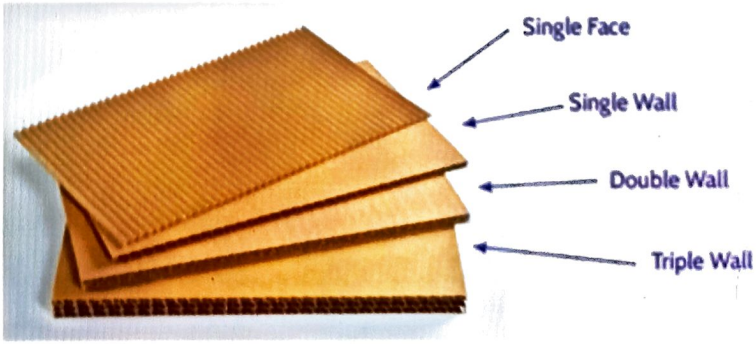
✓ **Different type of Secondary Packaging materials**

- **Paper and boards**
- **Cartons**
- **Corrugated fiberboard**









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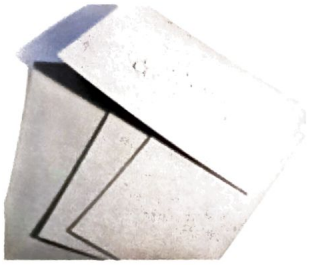
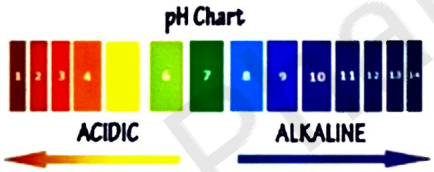
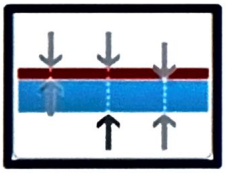
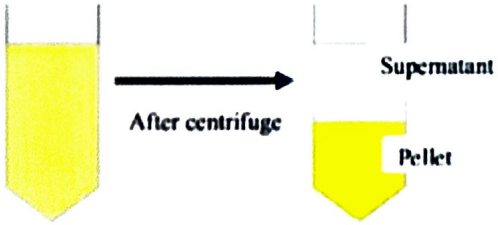
✓ Ideal Properties of Secondary Packaging Material

- The dimensions should be appropriate to withstand the **stress during transportation.**
- It should not effect the **primary packaging.**
- It should have sufficient strength to hold the material. Thickness should be appropriate to have mechanical strength.

➢ Testing of Paper & Board

DIMENSIONS	The **physical dimensions** of the given paper board is taken and recorded
GRAMMAGE 	A test piece of **suitable size (10cm x 10cm) is cut and weighed.** The grammage of the sample is determined by Grammage 10^4 x w/a x b w-weight in grams a - length b- breadth
SURFACE PH 	**Acidity in paper** may be caused by the presence of residual chemical left in the pulp. A drop of distilled water is placed on the top of the test piece and the electrode of pH meter is placed in the drop touching the paper. The reading is taken after 2 min.
THICKNESS 	Thickness is related to grammage of paper and its bulk density. It **directly influences the physical property of paper like stiffness, varnishing and cutting.**
PH AFTER EXTRACTION 	Cut **1gm of paper & place in a 100 ml flask, fitted with condenser, add 20 ml of boiling distilled water** in small portions till the paper is wet. Add 50 ml of distilled water. Reflux and digest with occasional shaking at

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PH AFTER EXTRACTION	95- 100°c for 1 hr. Cool to 40-45°c, remove the condenser and shake, cool in water bath. Determine the pH of the supernatant with pH meter.
MOISURE CONTENT	Conditioned specimen is weighed and heated to a constant weight to expel the moisture. The difference of the two weights gives the moisture content of the paper. **% moisture = 100(A-B) / B** A - Original weight B - Weight after drying.
ASH CONTENT Desiccator	Take about 1g of specimen and make it in to shreds and place in a previously weighed crucible (C). Heat carefully over a **burner till completely charred.** Transfer the crucible in to a muffle furnace at 800°c untill all the carbonaceous matter are burnt off. Cool in desiccator, weigh and repeat the experiment to constant weight (D). **%Ash- 100 (C-D)/D**
ALKALINITY	Place about 5g (w) of accurately weighed sample, cut into pieces in a stoppered flask containing **250 ml of 0.02N HCl.** Allow to stand for 1 hr with occasional shaking. Decant and titrate a measured quantity (v) against 0.1 N NaOH using methyl orange as indicator. Carry out blank (B). $\% \text{ Alkalinity} = \frac{1250\,(B-A) \times N}{V \times w}$ **A- Sample reading** **N- Normality of NaOH**

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COBB TEST	Fold the test piece back and forth until rupture occurs
FOLDING ENDURANCE	The maximum tensile force per unit width that a paper or board will withstand before breaking
TENSILE STRENGTH	The mean force required to continue the tearing of an initial cut in a single sheet of paper
BURST STRENGTH	The maximum uniformly distributed pressure, applied at a right angle to surface that a test piece of paper & board will stand under condition of test
DENSITY	For rigid cellular materials
PUNCTURE RESISTANCE	Energy required to make initial puncture
RUB RESISTANCE	Resistance of printed test piece to withstand rubbing against another similar test piece.
ROUGHNESS OR SMOOTHNESS	Important for printability of paper
INK ABSORBENCY	Determination of ink absorbency by K& N ink

Test for cartons

Compression	This method is used to assess the strength of erected package
Carton opening force	The method is used to hold the flat carton as delivered, by its creases between thumb & first finger press.
Coefficient of friction	Both static and kinetic coefficients of friction are determined by sliding the specimen over itself under specific test conditions

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Crease Stiffness	This involves testing a carton board **piece & folding it through 900.** It will then try to recover its position when bending force is removed
Joint Shear Strength	This is a method **of testing glued lap seam on the side of a carton for strength of the adhesive using** a tensile testing machine.

UNIT-III

Good Laboratory Practices

Points to be covered in this topic

- General provisions
- Organization and personnel
- Facilities
- Equipment
- Testing facilities Operation
- Test and Control Articles
- Protocol for conduct of a Nonclinical Laboratory study
- Records and reports
- Disqualification of testing Facilities

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Good Laboratory Practices

Introduction

- In 1976, the **United States Food and Drug Administration (USFDA)** received information from a whistleblower about some problems in data submitted by a **company called Syntex.**
- Erroneously, an FDA official picked up a file on a contract laboratory called **IBT (Industrial Bio- Test Laboratories)** which was under contract to Syntex.

Definition of glp

- FDA defines GLP as, **"A set of principles intended to assure the quality and integrity of non-clinical laboratory studies that are intended to support research or marketing permits for products regulated by government agencies."**
- The term non-clinical laboratory study refers to the in-vitro or in-vivo experiments where item being tested is studied in systems under laboratory conditions to evaluate how safe it will be.

Scope of GLP

- The term **GLP applies to the non-clinical testing required** for approval of new drug products for human and animal use.
- Its scope also extends to cover non-pharmaceutical compounds like **food additives, colour additives, food packaging, food contamination limits, biological products, electronic products and medical devices.**
- If a firm hires the services of a contract laboratory or a **consultant laboratory service for the testing, that laboratory must also abide by GLP.**
- The testing laboratory must permit an inspection of their facility and records of the studies being conducted by a **duly authorized employee of the FDA.**

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- GLP does not cover human clinical studies, discovery-related toxicology studies, nonclinical pharmacology studies to study efficacy and drug action and bioanalysis of samples drawn from clinical trials.

❖ GENERAL PROVISIONS

1) It prescribes **GLP for conducting non-clinical laboratory** studies that support research and marketing permits of products regulated by FDA.
2) Applicability to studies performed under **grants and contracts.**
3) Inspection of the **testing facility.**

❖ ORGANIZATION AND MANAGEMENT OF TEST FACILITY

❑ Study Director

- Before start of a study, the management of the facility should appoint a study director.
- This person should be either a scientist or a professional who has the necessary **education, training and experience to manage the technical aspects of the study and also interpret, analyze, document and report** the study results.

❑ Systems

- Test protocol should be prepared and approved by authorized person. All data collected during experiments must be **recorded accurately and verified, including unanticipated responses.**
- If any situation occurs that may affect the quality and integrity of the study, it must be noted, and corrective action must be taken and documented. All **GLP regulations that apply to the study must be followed and testing must be carried out as laid out in the protocol.**
- At the close of the study, all data, documents, samples and final reports must be archived safely.

❑ Management

- The management of test facility must make sure that **all materials, facilities, resources, equipment and personnel required for testing are**

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available. It must also assure that **tests for identity, purity, strength, stability and uniformity, as applicable, have been performed adequately.** Personnel must understand the functions they are to perform. Deviations if observed must be reported by QA unit directly to the study director; corrective actions must be taken and documented.

❑ QA Unit

- A quality assurance unit must be set up in a manner as to be **independent of the persons involved with the study**. There must be written procedures, and details of **responsibilities and records to be maintained by this unit.**
- This unit must monitor **that equipment, facilities, personnel, practices, methods, records and controls match the GLP regulations.** It is this unit's responsibility to have all information – a master schedule sheet, protocols etc – of the studies performed by the lab.
- The QA unit must inspect the study regularly to verify the **study integrity**, and these inspections must be documented with signatures. Any problems that can compromise the integrity of the study must be reported to the study director and the management at once.
- The unit must also ensure that no deviations from the **standard operating procedures (SOPs) or protocol occur without duly documented authorization.**
- It is also the responsibility of QA unit to review the study report at the end and check that it gives an accurate description of the methods, and that the results being reported match the findings as per the raw data generated in the study.
- All QA documents must be made available for inspection by the authorized FDA representative.

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❖ PERSONNEL

- Persons involved in conducting or **supervising the study in the non-clinical laboratory** must have the necessary **education, training and experience to ensure that they can perform their functions adequately.**
- The details of these must be **maintained in current condition.**
- **Sufficient personnel** must be employed for conducting the study as per the protocol.

- They must take all due precautions with respect to personal health and sanitation to **prevent contaminating the test systems and articles.**
- Clothing of personnel must be apt for their duty; it must be changed as required to avoid chemical, microbiological or radiological contamination during testing.
- Any person with an illness that could **adversely affect the integrity and quality of the study must be excluded from it until full recovery.**

❖ FACILITIES

- The testing facility must be of a suitable size and constructed to allow **proper conduct of the study, without any adverse effect on the study.**

❑ Animal Care Facilities

- There must be **enough animal areas or rooms to allow separation** of different species/test systems. Each project must be run in isolation. **Housing and quarantine requirements** of the animals must be sufficiently met.

- There must be entirely **separate rooms and areas to carry out studies** on materials that are biohazardous (such as aerosols, infectious agents, volatile substances and radioactive materials).
- Separate areas must be kept for isolation of animals who are carriers of disease or that have been diagnosed with any disease. Proper arrangements must be made to dispose animal waste without causing odor, environmental contamination, vermin infestation or disease hazards.

❑ Animal Supply Facilities

- Space must be provided for storage of animal supplies such as **bedding, feed, supplies and equipment.**
- These areas must be kept **separate from the test system housing areas, and kept free of contamination or infestation.** Perishable supplies must be duly protected.

❑ Test and Control Handling Facilities

- Separate areas must exist for **receiving and storing control and test articles, and test and control article mixtures,** to prevent any contamination or mix-up.
- These storage areas must be designed to prevent any change in the purity, strength, identity and stability of the articles and mixtures.

❑ Laboratory Operation Areas

- There must be **separate space for the laboratory** where the study is to be performed including routine as well as specialized procedures.

❑ Specimen and Data Storage Facilities

- There must be enough space **to archive specimens and data. Access to this area shall be restricted to only authorized personnel.**

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❖ EQUIPMENT

❑ Design and Location

- All equipment used to generate, measure or **assess data and to control the facility environment must be of a design and capacity sufficient** to perform its expected function.
- The equipment must be **located in a manner suitable for operation, cleaning, maintenance and inspection.**

❑ Calibration and Maintenance

- All equipment in the laboratory must be **cleaned, inspected and maintained as per written procedures.**
- Any equipment that generates, measures or assesses data must be **regularly calibrated or standardized as required.** There must be written **SOPs for equipment operation, cleaning, inspection, maintenance and testing/calibration/standardization.**
- All inspections, testing/calibration/standardization procedures and maintenance actions must be recorded. Any non-routine repair work done after malfunction or failure of the equipment must also be documented with details of nature of defect and the remedial action taken..

❖ TESTING FACILITIES OPERATION

❑ Standard Operating Procedures (SOPs)

- Written SOPs and laboratory manuals must be present describing the study methods to be adopted to **ensure data quality and integrity.** The study director must authorize any deviations from the **SOPs and the same must be documented.**

➢ **Minimum required SOPs in a non-clinical laboratory:**

- Preparation of animal room.
- Animal care.
- Test and control articles receiving, identification, handling, storage, mixing and sampling methods.
- Laboratory tests.

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- Test system observations.
- Handling of animals found dead in the course of the study.
- Necropsy/post-mortem examination of such animals.
- Collecting and identifying specimens.
- Histopathology study.
- Storage, handling and retrieval of data.
- Calibration and maintenance of equipment.
- Placement and identification of animals and their transfer.

❑ Solutions and Reagents

- **All solutions and reagents kept and used** in the lab must be labeled to show the identity, concentration, **expiry date and storage requirements. Outdated substances must not be used.**

❑ Animal Care

- **Care, handling, feeding and housing of animals must be done in keeping with written procedures.** When animals are newly received at the laboratory, they must be isolated until their health status is evaluated as per standard veterinary medical practice.
- Only animals without any disease or condition that may interfere with the conduct or purpose of the study must be used when the study begins. If a **disease is contracted by the animals during the study, such animals must be isolated if required.**
- They may be treated for the disease but the treatment should not interfere with the study. Details of all such diagnoses, treatment authorization, its description and the treatment dates must be documented and archived.

❑ Characterization of Test and Control Articles

- For every batch **of control and test articles, their purity, strength, identity and composition** must be determined and documented. Their synthesis method must be documented by either the study sponsor or the testing laboratory.
- **Stability of these articles must be evaluated either before the study begins or along with the study, as per written SOPs.**

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- The containers in which test and control articles are stored must be labeled with appropriate **information such as name, code number, batch number, storage conditions and expiry date.** Containers must not be changed until the end of the study.
- When the **study duration is longer than 4 weeks,** reserve samples must be drawn and retained from each batch of the control and test articles.

❑ Handling of Control and Test Articles

- Test and control articles must be handled in a way that they are stored, **identified and distributed in a way that avoids contamination or deterioration, and their receiving and distribution** (with quantities) is to be documented.

❑ Article-carrier Mixtures

- When **control or test article is mixed with a carrier**, there must be tests performed to ensure mixture uniformity, concentration and stability of the articles in the mixture.
- Stability may be assessed either before the **study commences, or during course of the study according to written SOPs. The expiry date of the mixture must be indicated.**

❖ PROTOCOL FOR AND CONDUCT OF NON-CLINICAL LABORATORY STUDY

❑ Protocol

- Written and approved protocols must exist for each study, and they must indicate the purpose of the study and methods to be adopted in conducting the study.

✓ **The following information must form a part of the protocol:**

- **Title and purpose** statement for the study.
- Test and control articles identified by **name, code number** or chemical abstract number.
- Study **sponsor name, and testing facility name and address.**

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- **Test system being used** – number, sex, age, body weight range, species, strain, sub-strain and supplier details.
- Procedure to **identify test system.**
- Experimental design **description, methods used for bias control.**
- Description of items to be used in study – **diet of animals, solvents or emulsifiers, and limit values for contaminants** likely to be found in these that may interfere with study
- **Dosage levels** (in mg/kg body weight) of control and test articles; the **frequency and method of administration.**
- **Tests, measurements, analyses** to be performed and their frequency.
- Information regarding the statistical methods that will be used in the study.
- Date when study protocol was approved by sponsor, and signature with date by study director.
- **Any changes/revisions** in an approved protocol must be documented along with the reason; it must be signed and dated by the study director and this document must be kept along with the protocol.

❑ Conduct of the Study

- The non-clinical laboratory study must be conducted according to the protocol. **All specimens must be labeled with details of study, test system, nature and date of collection**.
- If a specimen is to be examined histopathologically by a pathologist, the gross findings from post-mortem examination must be also available.
- Data generated during the course of a study (except automatically collected data) must be recorded at once, directly, and in legible ink.
- **Dates and initials of the person making the entry should be affixed**. If any change is to be made, it shall be done in a manner to not deface the original entry. **The reason for the change must be documented, and dated and signed.**
- In case of automated data collection systems, the person responsible for data input must be identified. Any changes in data must follow the **same procedure as for other means of data collection.**

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❖ RECORDS AND REPORTS

❑ Reporting Study Results

- **Final report must be prepared for each study, containing the following information:**
  - **Name** of the facility, address, and dates of study commencement and completion.
  - **Details of purpose** and procedure as per approved protocol, and any changes in protocol.
  - Statistical data **analysis methods.**
  - **Test and control articles** – names, code numbers, purity, strength, composition etc.
  - **Stability parameters** of control and test articles under study conditions.
  - **Methods** used in the study.
  - **Test system description** – details of animal numbers, sex, species, strain and substrain, body weight range, age, identification procedure.
  - **Details** of dose, dosage regimen, duration, route of administration.
  - All circumstances that may have had an **effect on the data quality** or integrity.
  - Names of study director, other **scientists or professionals,** and supervisory personnel who participated in the study.
  - Details of calculations and other procedures performed with the data, data analysis and summary, and conclusions inferred from the analysis.
  - Dated and signed reports of each scientist/professional who was part of the study.
  - **Locations** of storage of raw data, specimens and final report.
  - Prepared statement signed by QA unit.
- The study's final report must have the date and signature of study director.
- Any corrections in the final report must be reported separately as an amendment, and the reasons for correction must be specified, along with date and signature by the person responsible for the correction.

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❖ DATA AND RECORDS STORAGE AND RETRIEVAL

- All **documents, protocols, raw data, specimens and final reports generated** during the study must be retained except wet specimens of **urine, blood, feces and biological fluids** and the ones from mutagenicity tests.
- These reports must be stored in an **orderly manner to allow easy retrieval when required, with adequate precautions against deterioration** of the documents or specimens. Such storage may be done off-premises and details of where it has been stored must be retained in the laboratory.

❑ Retaining Records

- Records must be retained for whichever of the following is the shortest duration:
- **At least 2 years after the date** when application for **research or marketing** permit (for which the study was conducted) is approved by FDA.
- **At least 5 years after the date** when results of the study were submitted to FDA to support an application for research or marketing permit.
- At least **2 years after date of study** completion or discontinuation or termination, in cases where the study results are not **used to support an application for research or marketing permit.**
- Wet specimens (except from mutagenicity tests) and wet specimens of **urine, blood, biological fluids and feces, and other samples** that are fragile and deteriorate on storage must be kept only until their quality allows evaluation.
- **Protocol copies, master schedule sheet and QA inspection** reports must be stored by the QA unit so as to be easily accessible.
- Job descriptions, summaries of employee training and experience must be retained with other employment records for duration as mentioned in first two points.
- Reports of equipment calibration, inspection and maintenance must be

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retained.

- Records must be kept either in original form or true copies as photocopies, microfiche, microfilm etc.

In the event that the facility conducting the study goes out of business, all the documentation, raw data and other records must be transferred to the study sponsor for storage, and the FDA must be given written notice of this.

❖ DISQUALIFICATION OF TESTING FACILITIES

❑ Purpose

Disqualification may serve the following purposes:

1. To exclude from being considered the **completed studies that were performed by a facility that has failed to comply with GLP regulations** until it can be proved that such non-compliances did not occur during a particular study or that the non-compliances did not affect the acceptability of **data generated during that study.**
2. To exclude from being considered, all the studies that have been completed following disqualification until **the facility undertakes to conduct studies according to GLP regulations.**

If a testing facility is disqualified, the sponsor of the study that was performed (and disqualified) cannot use that as an excuse to not submit the study in their application for research or marketing permit. They must get the study repeated and submit with the application.

❑ Disqualification Grounds

Reasons why a testing facility may be disqualified include:

- Failure to comply with **one or more of the GLP regulations.**
- The non-compliance has created an **adverse effect on the validity of the study.**
- Previous **incidents of warnings or individual study rejections have not helped to achieve compliance with GLP guidelines.**

When the FDA has relevant information to justify a test facility disqualification, the Commissioner issues a written notice to the concerned facility proposing the disqualification.

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A regulatory hearing will then be conducted as per legal guidelines.

❑ Final Disqualification Order

- After the **regulatory hearing, or after time permitted** for a contest by the facility passes without such action, the **Commissioner of FDA evaluates the records of the proceedings and issues** the final order to disqualify the facility, with the reason for the disqualification.
- A copy of this order must be sent to the testing facility.

❑ Actions Following Disqualification

- After disqualification of a testing facility, **scrutiny is done of every application for research or marketing permit** that contains data from a study conducted by the disqualified testing facility.
- It is determined if that study is acceptable or not. If the study is considered unacceptable, the onus lies on the study sponsor to prove that the study was unaffected by the non-compliances that led to the disqualification. This may include validating the data by a repeat study.
- Any study done by a **disqualified testing facility will be invalid for the purpose of application for a research or marketing permit,** unless the facility has been reinstated after due procedure.

❑ Public Disclosure of Disqualification

- After a testing facility has been disqualified by the **final order, the FDA Commissioner notifies all interested persons at his discretion** if he believes the disclosure is in public interest, or that it will promote compliance with GLP.
- If **public notice** is given, it must include a copy of final disqualification order along with the statement that the FDA will not consider any studies done by the said facility in support of any application for research or marketing permit.

❑ Termination or Suspension of Testing Facility by Sponsor

- If a sponsor suspends or **terminates a laboratory from further participation in the study, it must notify the FDA in writing within 15 working days,** along with the reasons for such action.

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❑ Reinstatement of a Disqualified Testing Facility

- The disqualified testing facility may apply to the **FDA Commissioner assuring that it will comply with GLP regulations in the future**, along with details of the corrective actions that have been taken or are intended to be **taken, and the reasons why it believes** it must be reinstated.
- On examining this submission, and following an inspection, if the **Commissioner determines that GLP regulations are being followed**, he may reinstate the testing facility as a source for the study.
- The testing facility must be notified and any other involved persons, such as the **sponsor, and information about the reinstatement is publicly disclosed.**
- Before a new drug is introduced into the market, it has to undergo certain in-vitro and in-vivo experiments in a non-clinical setting.

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