UNIT-3

Quality Control

→ Any material that is used for packaging of products for their distribution and sale is said to be packaging material.

→ Pharmaceutical packaging is the means of providing protection, presentation, identification, information and convenience to encourage compliance with a course of therapy.

→ The commonly used packing materials are containers, closures, etc.

→ The containers mostly made up of glass, plastic, metal or paper. The material for closure may include cork, Glass, plastic, metal or rubber.

There are three types of packaging materials:

1. Primary Packaging Material :- The packaging materials that comes in direct contact with the product.
   e.g. bottles, vials, ampoules, tin, etc.
2. Secondary Packaging Materials :- Used to cover primary packaging materials.
   e.g. Cartoons, boxes, etc.
3. Tertiary Packaging Materials :- It is used to bulk-handling and shipping.
   e.g. barrel, container, edge protector.

→ There are various tests for determination of quality, integrity and compatibility of packaging materials. The specification and requirement of quality testing depends on type of pharmaceutical materials used.

Types of glass used in pharmaceutical industry

Type-I :- Neutral or borosilicate glass with high hydrolytic resistance, suitable for most preparations not for parenteral use.

Type-II :- Treated soda-lime silica glass (with high hydrolytic resistance, suitable for most acidic and neutral, aqueous preparations.

Type-III :- soda-lime silica glass (with only moderate hydrolytic resistance, suitable for non-aqueous preparations for parenteral use, for powders for parenteral use.

Type-IV :- General purpose soda-lime glass, used for non-parenteral products, to be taken orally or by inhalation.

Quality Control Tests for Containers

Following tests are performed to evaluate glass containers:

1) Crushed glass test

→ The container is crushed and seived to produce uniform particles of definite weight.
→ Inspect the particles for any impurities.
→ Conduct chemical analysis to check for composition consistency.
→ Perform tests for strength and durability.
→ Evaluate optical properties such as clarity and transparency.
→ Compare results with industry standards to determine quality.

2) Whole Container Test

→ It is used only for treated soda-lime containers.
→ In this test, the test containers are filled with test solution and is exposed to test conditions.
→ Due to the smooth and less reactive surface layer of the container, glassware may pass the whole container test more easily.

3) Powdered Glass Test :-

→ Under elevated conditions of temperature, alkaline constituents like oxides of sodium, potassium, calcium, aluminium, etc. leach out from the glass containers into purified water. The leaching of alkali is enhanced if the glass is powdered.
→ This test is based on the principle that the amount of alkali leached from the powdered glass is estimated. The concentration of acids required to neutralise the released alkali is prescribed in the Pharmacopoeia.

4) Water Attack Test :-

This test is only for treated soda-lime (type-III) glass containers.

→ Rinse the container thoroughly with high purity water.
→ Fill container to 90% of its overflow capacity with water and is autoclaved at 121°c for 30 minutes.
→ Then, it is cooled and liquid is poured out in a flask.
→ This 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.
→ Principle involved is whether the alkali leached or not from the surface of container.

Sulphuric acid neutralise the surface alkali and the glass will become more resistant.

5) Arsenic Test :- This test is for glass containers intended for aqueous parenterals.

→ Wash the inner and outer surface of container with fresh distilled water for 5 minutes.
→ Fill and cover the containers and keep in autoclave at 100°C for 10 minutes and allow the steam issue from the vent cork.
→ Rise the temperature from 100°C to 121°C for 20 minutes.
→ Lower the temperature from 121°C to 100°C.
→ Remove the container from autoclave, cool and combine the liquids being examined.
→ Pipette out 10 ml solution from combined contents of all containers to a flask.
→ Add 10 ml of HNO_3 to dryness on the water bath.
→ Dry the residue in an oven at 130°C for 30 min
→ cool and add 10 ml hydrogen molybdate reagent.
→ swirl to dissolve and heat under water bath and reflux for 25 minutes.

→ Cool to room temperature and determine the absorbance at 840 nm.

→ Do the blank with 10 ml hydrogen molybdate.

→ The absorbance of test solution should not exceed the absorbance obtained by repeating the determination using 0.1 ml of arsenic standard solution (10 ppm) in place of test solution.

6) Thermal shock Test :-

→ In this test, the samples are kept in a tray in an upright position and then immersed into hot water for a given time period.

→ Then, the tray is transferred to cold water bath.

→ Sample containers are examined before and after the tests are performed for outside surface cracks or breakage.

Quality Control Tests for Rubber closures

1) Penetrability :- This test measures the force needed for easy penetration of needle through the closure. Piercing machine is used to measure penetrability. The piercing force should not be more than the standard value, otherwise, the needle can be damaged due to undesirable hardness of closures.

2) Fragmentation Test :- 20 closures are selected and each is penetrated with needle in a piercing machine five times within a limited area. Then, the needle is washed to transfer any fragment present.
A coloured paper that contracts with the rubber is used to filter the contents so that the fragments can be counted. There should not be more than three fragments per unit on an average.

3) self-Sealability Test :- This test is applicable to multiple dose containers.

→ 10 vials are filled with water, closed with prepared closures and secured with a cap.

→ A new needle is used for each closure and each time piercing is made 10 times at different site.
→ Thereafter, the vials are immersed upright in 0.1% methylene blue solution and external pressure is reduced for 10 minutes.
→ The atmospheric pressure is restored and the vials are left immerged for 30 minutes.
→ The outer side of the vials is rinsed and it is ensured that none of the vials contain any trace of coloured solution.

4) Extractive Test :- In this test, the closure is boiled in water for 4 hours under reflux and the water is evaporated to dryness. The test is successful if any residue does not exceed the specified amount.

5) Compatibility Test :- This test determines the compatibility of the rubber closures with various types of substances because it is important to ensure that the contents of the bottle do not interact with the closure.

Quality Control Tests for Secondary Packaging Materials

(A) Paper and Board Tests

1) Moisture content :- At a specified temperature, moisture content is measured.
2) Folding endurance :- Test piece is folded back and forth until rupture occurs.
3) Paper and board density :- suitable for rigid cellular materials.
4) Grammage :- It is the weight of material measured per unit area of sample.
5) Thickness :- It directly influences the physical property of paper like stiffness, varnishing and cutting.
6) Tensile strength :- It is the maximum tensile force measured per unit width that a paper or board can withstand before breaking.
7) Tear strength :- It is the mean force applied for continuous tearing of an initial cut in a single sheet of paper.

8) Stiffness of thick paper and boards : when paper/ board is bent, a degree of resistance is offered.

9) Cobb test (g/m^2) :- This test measures water absorbency.

10) pH, chloride or sulphate :- The acidity and alkalinity (pH) is important to measure the life of paper/ board.

11) Roughness/ smoothness :- It determines the printability of the paper.

12) Wet burst strength :- It determines wet bursting strength of any paper or board when immersed in water.

13) Ash in paper and board :- It determines the ash content.

14) Opacity :- It is the ratio expressed as percentage of luminous reflactance factor of a single sheet of paper with a black backing to intrinsic luminous reflactance factor.

(B) Tests for Cartoons

1) Compression :- This test determines the strength of erected package.

2) Opening force :- This test is used to hold the flat cartoon as delivered, by its creases between thumb and first finger press.

3) Coefficient of Friction :- By this test, static as well as kinetic coefficients of friction are determined by sliding the sample over itself under specific test conditions.

4) Crease stiffness :- This test is used for testing a cartoon board piece, folding it through 90°, and then trying to recover its former former position when bending force is removed.

5) Joint shear strength :- This test is used for testing the glued lap seam on the side of a carton for strength of the adhesive using a tensile testing machine.

Good Laboratory Practices

Good Laboratory Practice is a quality system concerned with the laboratory studies and the conditions under which a study is planned, performed, monitored, recorded, achieved and reported.

→ GLP applies to non-clinical studies conducted for the assessment of the safety and efficacy of pharmaceutical agents. GLP applies to many other non-pharmaceutical agents also such as colour additives, food additives, food contamination limits, food packaging and medical devices.

→ GLP helps assure regulatory authorities that the data submitted are true.

→ GLP was first introduced in New Zealand and Denmark in 1972 and later in US in 1978 in response to the "Industrial BioTest Labs" scandal.

→ It was followed a few years later by the organisation for Economic Co-operation and Development (OECD). OECD produced GLP principles that are international standards, in 1981.

Reason behind GLP creation

→ In the early 70s, FDA became aware of cases of poor laboratory practices all over the United states.

→ FDA decided to do an in-depth investigation on 40 toxicology labs.

→ They discovered a lot of fraudulent activities and a lot of poor lab practices.

→ Examples of some of these poor lab practices found were:

(i) Equipment not even calibrated to standard form, therefore giving wrong measurements.

(ii) Incorrect / inaccurate accounts of the actual lab study.

(iii) Inadequate test systems.

Objectives of GLP

→ GLP makes sure that the data submitted are a true reflection of the results that are obtained during the study.
→ GLP also makes sure that the data is traceable.
→ Promote international acceptance of tests.
→ Prevent human errors in the performance of the job.
→ Prevention of equipment errors in measurements.
→ Prevention of unsafe and hazardous acts which could affect individuals.

Organisation and Personnel

There should be an organisational chart, and responsibilities and duties at various levels should be well-defined and documented.
→ Every individual in the laboratory should have the desired educational qualification, training and experience to perform the assigned tasks.
→ A sufficient number of personnel should be available for performing the studies in accordance with protocols.
→ The personnel should take necessary precautions to avoid contamination of tests.
→ The personnel should be provided with appropriate clothing that will prevent contamination.
→ The personnel should undergo medical examination to check health status and ensure they do not have any infection which might cause contamination.
→ The test facility manager should have sufficient qualification, experience, training and authority to ensure that the test facility is following the GLP principles.

Facilities

→ The test facility should have a direct access to personnel working area, so that they do not need to enter the facility through the manufacturing area.

→ Proper lighting, temperature, humidity and ventilation should be maintained such that they do not affect the products and equipments.
→ If sterility testing is to be performed, aseptic conditions should be maintained.
→ Sufficient space should be available to prevent mix-ups and cross contamination.

Equipment

→ The laboratory equipments and instruments should be educated and calibrated as per pharmacopoeial recommendations.
→ Sensitive instruments should be placed in separate climate-controlled rooms to protect from electrical interference, humidity, vibrations, etc.
→ Records of repair and routine maintenance and any non-routine work should be maintained.
→ The equipment should be properly maintained to ensure their constant performance and to reduce unexpected errors.

Testing Facilities Operations

Test facility operation requires written, accurate, current, approved, available and reviewed SOPs that follow all the routine procedures required for a GLP study.

Standard Operating Procedures (SOPs)

SOPs are a set of written procedures that provides directions on how tasks and processes should be carried out in laboratories.

→ A complete set of good SOPs is an essential requirement for successful compliance of GLP guidelines.
→ For implimenting SOPs successfully, the following requirements are necessary:

(1) Support from all management levels, alongwith the mindset to establish SOPs as an essential element in the organisation and culture of the laboratory.

(2) SOP-based education and training of personnel so that everyone in the staff performs the procedures in the same manner.

(3) A good SOP management system so that current SOPs are available in the right place and at the right time.

Test and control Articles

→ Records of test item and standard item, date of receipt, expiry date, quantities received and used in studies should be maintained.

→ Handling, sampling and storage procedures should be identified so that mix-up and contamination does not occur.

→ storage containers should have identification information, expiry date and specific storage instructions.

Product for Conduct of a Non-clinical Laboratory study

The laboratories should develop a well-defined protocol to conduct the tests. They should have prescriptive documents to direct the scientific studies.

The document is of three main times, i.e., policy statements, SOPs describing routine laboratories activities and study plans or protocols detailing on how to organise the work for each study.

study Plan or Protocol

Protocol is a document that the study director uses to communicate his planned study organisation to the staff and to the third parties (sponsor).

Protocol describes the study design, contains a time schedule and various stages of the study, and indicates the methods and materials to be used in the study. Protocol is the principal means of instruction for the staff about how to perform

the study, and its contents, and a suitable style and layout.

Records and Reports

Records contains the complete process of experimentation. These records are the qualitative and quantitative results of the study. The study Director uses the records as the basis for scientific interpretation of the study.

→ After the study is complete, all the prescriptive and descriptive documents are archived so that so that whenever there is a need of full new study, the archived material can be examined.

Disqualification of Testing Facilities

The commissioner can disqualify a testing facility on the following grounds:

1) The testing facility failed to comply with the GLP guidelines.
2) Such a non-compliance adversely affected the validity of the non-clinical laboratory studies.
3) Ignorance of other lesser actions of regulatory authorities (like warnings or rejections of individual studies) by the testing facilities.