# Unit - 3

## Quality Control :

Quality Control Test for Containers :-
Different types of container are -
(a) Glass Container
(b) Plastic Containers
(c) Metal Containers

## # Quality Control test for Glass Containers -

### (i) Chemical resistant test :

(a) Powdered Glass Test -:
It is done to estimate the amount of alkali from powdered glass with happen at elevated temperature. When glass is powdered, leaching of alkali is enhanced, which can be titrated with 0.02 N Sulphuric acid using methyl red as an indicator.

Step-1 : Preparation of glass specimen
Step-2 : washing the specimen.

Procedure :-
10 gm of specimen + 50 ml of highly purified water. Autoclave it at 121°C.

↓

Cool it & decant sol" in another flask again add 15ml of water & decant sol".

↓

Titrate the decant sol" with 0.02 N Sulphuric acid using indicator & record the volume.

Limits :-

| Test | Containers | Volume of 0.02N $H_2SO_4$ (ml) |
|---|---|---|
| Powdered Glass Test | Type I | 1.0 |
| | Type II | 8.5 |
| | Type N.P. | 1.5 |

(b) Water Attack Test -:
This test is for Type II glass. The principle involve in this is whether the alkali leaches from surface of container.

Procedure:-
Rinse thoroughly containers with high purity water. Fill it by 90% of its capacity with water.

↓

Autoclave it at 121°C for 30 minutes. Then its is cooled & liquid is decanted.

↓

Decanted liquid is titrated with 0.02 N Sulphuric acid using Methyl red as an indicator.

↓

The volume of Sulphuric acid consumed is recorded & compare with limits.

Limits :-

| Test | Containers (Type II) | Volume of 0.02N $H_2SO_4$ (ml) |
|---|---|---|
| Water Attack test | 100 ml or below | 0.7 |
| | More than 100 ml | 0.2 |

(2) Hydrolytic Resistant Test ; Procedure :-

Rinse the containers with $CO_2$ free water for 3 times. Fill till a particular volume. Autoclave it

↓

At 100°C for 10 min., allow to rise temperature to 121°C for 60 min. Low down temperature to 100°C. Remove the containers from autoclave & cool it.

↓

Specific amount of liquid sol$^n$ is titrated with 0.01N HCl using methylred as an indicator.

↓

Perform the blank with water & difference between the titration represents volume of HCl consumed by test liquid.

Limits :- * NMT → Not more than ,

| Capacity of container (corresponding to 90% average flow volume) (ml) | vol. of 0.01M HCl Type I or Type II glass (ml) | vol. of 0.01M HCl Type III glass (ml) |
|---|---|---|
| Not more than 1 | 2.0 | 20.0 |
| More than 1 but NMT 4 | 1.8 | 17.6 |
| More than 2 but NMT 5 | 1.3 | 13.2 |
| More than 5 but NMT 10 | 1.0 | 10.2 |
| More than 10 but NMT 20 | 0.80 | 8.1 |
| More than 20 but NMT 50 | 0.60 | 6.1 |
| More than 50 but NMT 100 | 0.50 | 4.8 |
| More than 100 but NMT 200 | 0.40 | 3.8 |
| More than 200 but NMT 500 | 0.30 | 2.9 |

(3) Arsenic Test: This is for glass containers intended for aqueous Parenteral.

Procedure:
- Wash inner & outer surface of contain with distilled water for 5 mins.
- Test sol$^{n}$ is same as that of hydrolytic resistant test(50ml)
- Pipette out 10 ml of sol$^{n}$ & add 10 ml of nitric acid on the water bath maintaining the temperature.
- Dry the residue in oven at 130°C for 30 mins & add 10 ml of hydrazine molybdate reagent & reflux for 25 min.
- Cool the sol$^{n}$ & determine absorbance at 840 nm.
- Perform blank with only 10 ml of hydrazine molybdate.
- The absorbance of test sol$^{n}$ should not exceed the absorbance obtained by repeating the determination using 0.1 ml of arsenic standard sol$^{n}$ in place of test sol$^{n}$.

Limits:- The absorbance of test sol$^{n}$ should not exceed the absorbance of arsenic standard sol$^{n}$ of 10 ppm.

(4) Internal Bursting Pressure Test: Instrument used American glass research incremental pressure tester

The test bottle is filled with water & placed inside the test chamber.

↓

The internal pressure automatically raised by series of increment at set time.

↓

Bottles are checked at pre-selected pressure level until container finally burst.

(5) Thermal Shock Test:-

Place sample containers in upright position in a tray.
Immerse the tray into a hot water for a given time.

↓

Transfer the container in cold water bath. Temperature should be controlled. Examine cracks before & after the test.

↓

The amount of thermal shock a bottle can withstand is based on construction.

⇒ Small bottle - 60 to 80°C, large bottle - 30 to 40°C & temperature - 45°C b/w hot & cold water.

# Quality control test for Metal Container -

Procedures:-

Take 50 empty tubes filled with ointment base, sealed & kept overnight at 15-20°C

↓

A metal bacteriological filter assembly fitted with 4.25 cm filter paper & heated it above melting range of ointment base.

↓

Base from all tubes squeezed at certain rate & passed through filter under vaccum & further wash with $CHCl_3$ & observed for particles.

Observation:-

| | |
|---|---|
| Particles 1mm & above | 50 |
| Particles 0.5mm to 1mm | 10 |
| Particles 0.2mm to 0.5mm | 2 |
| Particles less than 0.2mm | Nil |
| Total | 62 |

Limits :-

- Lot of tube passes test if total score is less than 100
- Lot of tubes fail if total score is above 150
- If it is between 100-150 test it is repeated again with 50 more tubes.

# Quality Control test for Plastic Containers -

(1) Leakage Test : Fill 10 containers with water. Fit with intended closures & keep them inverted at room temp. for 24 hours. There are no signs of leakage from any container.

(2) Compatibility Test : This test applicable to containers which are to be squeezed in order to remove the contents. A container by collapsing inwards during use yields at least 90% of its nominal contents at the required rate of flow at ambient temperature.

(3) Transparency Test : Fill 5 empty containers to their nominal capacity with diluted suspension as described in IP 1966. The cloudiness of the diluted suspension in each container is detectable when viewed through the containers as compared with a container of the same type filled with water.

(4) Clarity of aqueous extract : Select unlabelled, unmarked & non-laminated portions from suitable container taken at random sufficient to yield a total area of sample required taking into account the

Surface area of both sides. Cut these portions into strips none of which has a total area of more than 20 $cm^2$. Wash the strips free from extraneous matter by shaking them with atleast two separate portions of distilled water for about 30 seconds in each case, then draining off the water thoroughly.

(5) Water vapour permeability Test: Fill 5 containers with nominal volume of water & heat seal the bottles with an aluminium foil-poly ethylene laminate. Weigh accurately each container & allow to stand for 14 days at a relative humidity of 50 ± 5%. & a temperature between 20 & 25°C. Reweigh the containers. The loss in weight in each container is not more than 0.2%.

Quality Control test for closures :-

∴ Preparation of Sample Soln -
wash closures in 0.2% w/v of anionic surface active agents for 5 mins.

↓

Rinse 5 mins with distilled water. Add 20 ml water then Autoclave at 119-123°C for 20-30 mins, covered with aluminium foil.

↓

Cool & Separate Soln from closure. (Soln A)

(1) Sterility Test:
When treated closures are subjected to sterilization test at 64–66°C & pressure of about 0.7 kPa for 24 hours.

(2) Fragmentation Test:
Take 12 clean vials & place closures containing 4ml of water. Allow to stand for 16 hours.

↓

use hypodermic needle inject 1ml of water into the vial & remove 1ml of air

↓

Carry this operation for 4 times with new needle each time.

↓

Pass the water present in vial through a filter with pore size of 0.5 μm.

↓

No. of fragment is not more than 10 except in the case of butyl rubber closures where the total no. of fragment is not more than 15.

(3) pH of aqueous extract:
Take 20 ml of sample sol" & add 0.1 ml of bromothymol blue.

↓

Add 0.01M of NaOH till colour change from Blue to yellow. volume required is measured.

Limits:
- The vol. of NaOH is NMT 0.3 ml
- If it is done with HCl, the vol. of HCl is NMT 0.8 ml

(4) Self-Sealability Test:

Fill in vials with nominal vol. of water & place closures.

↓

Pierce cap for 10 times at different sites with hypodermic needle.

↓

Immerse vials in 0.1% w/v sol$^n$ of methylene blue under pressure.

↓

Keep the containers immersed for 30 minutes.

↓

Wash the vials & none of vials should contain traces of color sol$^n$.

(5) Light Absorption Test:

It must be done within 4 hours of preparing sol$^n$ A.

It is filtered through 0.5 μ filter & its absorbance is measured at 220 to 360 nm. Blank is done without closures & absorbance is NMT 2.0.

(6) Reducing Substances:

20 ml of sol$^n$ A is added with 1M $H_2SO_4$ & 20ml of 0.002 M $KMnO_4$ & boil for 3 mins then cool & add 1 gm of KI which is titrated with Sodium thio-Sulphate using starch as an indicator. Blank is done & the difference b/w titration vol. is NMT 0.7 ml.

(7) Residue of Evaporation:

50 ml of sol$^n$ A is evaporated at 105°C. Residue obtained should be NMT 4 mg.

## Quality Control test for Secondary Packaging materials :-

Different types of Secondary packaging material are -

(a) Paper & Board.

(b) Cartons.

### # Test for Paper & Board -

The test pieces of paper & board are taken for test to be carried out in standard condition :

(a) Temperature : 23°C ± 1°C

(b) Relative humidity : 50% ± 2%.

| Sno. | Name of the test | Description |
|---|---|---|
| 1. | Moisture Content | All the substances will be measured at temperature specified for test. |
| 2. | Folding endurance | Fold the test piece back & forth until rupture occurs. |
| 3. | Air permeability | Important for using light weight uncoated paper on machine having vaccum pickup system. |
| 4. | Tensile strength | The maximum tensile force per unit width that a paper or board will withstand before breaking. |
| 5. | Tear strength | The mean force required to continue the tearing of initial cut in a single sheet of paper. |

| | | |
|---|---|---|
| 6. | Stiffness | Degree of resistance offered by paper/board when it is bent. |
| 7. | Burst Resistance | The maximum uniformly distributed pressure, applied at right angles to the surface, that a test piece of paper & board will stand under condition of test. Hydraulic pressure is applied to diaphragm, bulging it until test piece bursts. |

# Test for Cartons -

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

(2) Carton opening force: This test is used to hold the flat carton as delivered, by its creases b/w thumb & first finger press.

(3) Coefficient of Friction: This test is used in static as well as Kinetic coefficients of friction are determined by sliding the sample over itself under specific test condition.

(4) Crease Stiffness: This test is used for testing a carton board piece, folding it through 90°, & then trying to recover its former position when bending force is removed.

(5) Joint Shear Strength: This test is used for testing the glued lap seam or the side of carton for strength of the adhesive using a tensile testing machine.

## Good Laboratories Practices:

GLP is a formal regulation created by USFDA as these regulation were proposed on November 19, 1976 & designated as a new part of chapter 21 of the Code of Federal Regulation (CFR) as 21 CFR Part 58 in 1976.

In 1981, an organization named Organization for Economic Cooperation & Development (OECD) produced GLP principles that are international Standards.

GLP in OECD principles is defined as, "a quality System concerned with the organizational process & the condition under which the non-clinical health & environmental safety studies are planned, performed, monitored, recorded, archived & reported".

## Why GLP was Created?

(1) GLPs were initially invoked in a reaction to malpractices in the laboratories Conducting Safety experiments of medicines.

(2) In the early 1970s, Research laboratories in the USA found doing work in unethical ways, like:
- Data generation without Conduct of the body.
- Falsification of the laboratory work.
- Replacement of dead animals & fabrication of test results, etc.

## Advantages -

- Assures that the data are a true reflection of results obtained from studies.

- Precinical Safety & residue safety.
- Mutual acceptance of data.
- Increases public confidence.

Disadvantages -
- More man power is required
- Expensive process.
- Time consuming process.

Objectives -
(1) GLP makes sure that the data submitted are true reflection of the results obtained from studies
(2) GLP makes sure that data is traceable.
(3) Promotes international acceptance of tests.

How to practice GLP?

(A) General Provisions:
- It prescribes GLP for conducting non-clinical laboratory studies that support research & marketing permits of products regulated by FDA.
- Applicability to studies performed under grants & contracts
- Inspection of the testing facility.

(B) Organization & Personnel:
(i) Organization function -
- Identification of quality activities
- Dividing the jobs among the personnel.
- Define the authority & responsibility of each job & relationship of each job with other jobs.
- Coordinate the work of internal departments & outside agencies.

(ii) Personnel -
Each individual engaged in the conduct or supervision of non-clinical laboratory study shall have:
(a) Education
(b) Training : (i) General training (ii) Specific training
(c) Experience or combination
(d) Personal sanitation & health publication.

(iii) Testing Facility Management -
- A sufficient no. of qualified personnel, appropriate facilities, equipment & materials are available for conductance of the study.
- Maintenance of records of qualification, training & experience of personnel & their job description.
- Appointment of study directors.
- Quality Assurance program with designated personnel.

(iv) Study Director -
A scientist or other professional of appropiate education, training & experience.

Responsibilities of the study director are -
(a) Approval of protocol & study plans including ammendants.
(b) Technical conduct of the study.
(c) Ensure that the QA personnel & study personnel are updated with the study plan & SOPs.
(d) Interpretation, analysis, documentation & reporting of the results.
(e) Also checks that experimental data is accurately recorded & verified.
(f) Sign & date the final report for acceptance of data.

(v) Quality Assurance Unit -

- An individual or a group designated by management to assure that the studies are in compliance with GLP principles.
- Monitors the study to assure management that the facilities, equipment, personnel, methods, practices, records, & controls are in conformance with the regulations.
- Maintain the copies of master schedule sheet, protocol & SOPs.
- Access to updated study plans & SOPs.
- Documentation verification of compliance of the study with GLP principles.
- Inspection to determine the compliance of the study with GLP principles & 3 type of inspection are:
(i) Study based inspection (2) Process based inspection
(iii) Facility based inspection.
- Determines any deviation from the approved protocol & report to SD, PI & management.
- Prepare statements to be included in the final report containing dates & types of inspection.

(C) Facilities:

(i) General facilities -

(a) Archieve facilities: Secure storage & retrieval of study plan, raw data, final report & specimen to prevent untimely deterioration.

(b) Waste disposal: Appropriate collection, storage & disposal facilities & decontamination procedures.

(c) Testing System facilities:
- Suitable size, construction & location.
- Adequate degree of separation of different activities.
- Laboratories should be well ventilated, free of dust, draft & extreme temperatures.
- Minimum 150 sq feet of floor space & minimum 6 linear feet of usable bench space should be providing for each analyst.

(iii) Animal Care Facilities -
- located away from testing laboratories preferably in a separate building.
- Contamination risk is reduced by 'barrier' system as well as by providing 'clean' & 'dirty' corridors.
- Separate areas for animal of different species & studies.
- Separate areas for diagnosis, treatment & control of laboratory animal diseases.
- lightening should be proper as light intensity & noise level is sufficient.
- Maintain room temperature, humidity, air changes in animal quarters.

(D) Equipments:
(a) Appropriate design & adequate capacity.
(b) Equipment shall be adequately inspected, cleaned & maintained
(c) Equipment used for generation, measurement or assessment of data shall be adequately tested, calibrated & standardized.
(d) log books for each equipment should be there.

(6) Testing facilities operations :

(i) Standard operating procedures (SOPs) -

- written documentation specifying procedures for laboratories programs.
- Testing facility should have a written SOP approved by management.
- SOPs should be available wherever applicable. eg- test & reference items, apparatus, materials & reagents, recording keeping, reporting, storage & retrieval, test systems & quality assurance procedure.
- Any deviations from SOP should be authorized by SD & documented in the raw data.
- Routine inspection, cleaning, maintenance, testing & calibration.
- Actions to be taken in response to routine failure.

(ii) Reagents & Solutions -

- Reagents used in the operation should be specified in the SOPs.
- Reagents & sol^n should be labelled.
- Deteriorated or outdated reagents should not be used.
- Store under ambient temperature.

(iii) Animal Care -

- SOPs for housing, feeding, handling & care of animals.
- Animals should be free of any disease & if, during the course of study, animals contract a disease then the diseased animals shall be isolated.
- Diagnosis, authorization of treatment, description & date of treatment shall be documented & retained.
- Animals of different species should be housed in separated rooms where necessary.
- The animal cages, racks & accessory equipment shall be cleaned & sanitized at appropriate interval.

(f) Test & Control Articles :

(i) Test & Control characterization -

- The identity, strength, purity & composition or other characterized of test & control article shall be determined & documented for each batch.
- Methods of synthesis, fabrication or derivation shall be documented by the sponsor or the testing facility.
- Stability of each test & control article is determined.
- Storage conditions are maintained & each storage container shall be labelled by name, chemical abstract no..

(ii) Test & Control Article Handling -

Handling procedures of test & control articles ensures-

- Proper storage.
- Minimum risk of contamination & deterioration or damage.
- Receipt & distribution of each batch is documented.
- Documentation include date & quantity of each batch distributed or returned.

(iii) Mixture of Article with Carriers -

- Appropriate analytical methods shall be conducted for determination of uniformity of mixture & conc^n. of test or control article in mixture.
- Stability of mixture is determined.
- Expiration date should be written on the container.

(g) Protocol for Conduct of a non-clinical laboratory study :

(i) Protocol -

(1) Identification.

(2) Title & Statement of purpose.

(3) Identification of test (or control) items.
(4) Name & address of the Sponsor, test facility & test site.
(5) Name of the study director & other personnel.
(6) Proposed dates
(7) Justification for selection of the test system.
(8) Description of the test system.
(9) Experimental design.

(ii) Conduct of a Non-Clinical Laboratory Study -
(1) Study shall be conducted in accordance with the protocol.
(2) Information of the specimen should be present on the container to avoid error in recording & storage of data.
(3) All the data generated shall be recorded directly, promptly & legibly by ink.

(H) Records & Reports :
(i) Reporting of Non-Clinical Laboratory Study Results -
Final report shall contains :
(1) Information on Sponsor & test facility.
(2) Experimental starting & completion dates.
(3) objectives & procedures stated in protocol (including the changes in protocol).
(4) Description of materials & test methods.
(5) A quality assurance program statement.
(6) Storage.

(ii) Storage, Retrieval & Retention of Records & Data -
(1) Archives should be therefor orderly storage & expedient of all raw data, documentation, protocols, specimens & final report.
(2) Index of materials required.

(3) Master schedule sheet, copies of protocols & records of quality assurance inspection shall be maintained by QAU
(4) Wet specimens & samples of test & control articles shall be retained until the quality of prep" afford evaluation.
(5) If any study plan is disposed of before expiry the reason to justified & documented.

(I) Disqualification of Testing Facilities :
These are regulatory provision & are not relevant to India. In India, if a manufacturer is found not complying with provisions of the drugs & Cosmetics Act & rules made there under either in respect of manufactures or testing or both; licensing authority under the said rules can suspend or cancel the licenses of the manufacturer.

However, before doing that licensing authority is required to give the manufacturer a notice in writing of such action. Explanations & reasoning are also to be heard before such action is taken.

Similarly, in case of approved drug testing laboratory, approval can be suspended or cancelled; if the necessary is not found complying with the statuary provision relating to approval. A similar procedure is to be followed in case of approved testing laboratory.