Name of Unit	Quality control and good laboratory practices
Subject/Course name	Quality Assurance
Subject/Course ID	BP 606T
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Learning Outcome of module-3

LO	Learning Outcome (LO)	Course Outcome Code
LO1	Students will able to know about Quality control test for containers	BP606.4
LO2	Students will able to understand the cGMP aspects in a pharmaceutical industry	BP606.4
LO3	Students will able to know about the importance of documentation	BP 606.5

MODULE CONTENT TABLE

Topic
Quality Control: Quality control test for containers rubber closures and secondary packing materials. **Good Laboratory Practices:** 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.

INTRODUCTION

Packaging is a process by which the pharmaceuticals are suitably packed so that they should retain their therapeutic effectiveness from the time of packaging till they are consumed. Packaging may be defined as the art and science which involves preparing the articles for transport, storage display and use. Pharmaceutical packaging is the means of providing protection, presentation, identification, information and convenience to encourage compliance with a course of therapy.

Composition of package:

(a) Container

(b) Closure

(c) Carton or Outer

(d) Box

PACKAGE TESTING PROCEDURES:-

The testing procedures may be divided into two groups according to whether the test is applied to the packaging material in isolation or to the entire package.

1. **Testing material:** Tests applied to packaging materials may be:

a. *Chemical* - The pH value of materials chloride and sulphate in paper or board, alkalinity of glass, compatibility test with chemicals or medicaments are typical of the chemical tests. **b. *Mechanical*-Standard** tests are available for the effect of creasing, folding and so on. **c. *Environmental*-** Materials may be tested by standard methods for absorption of water, permeability to water vapour, gases, oils, odours etc. and for characteristics such as light transmission.

2. **Testing Packages**

a. *Mechanical* – Mechanical tests are applied mainly to outer packaging for protection from transportation hazards. They consist of the use of a standardized test procedure to compare the effect of different protective materials to prevent damage to the contents. **b. *Environmental*-** Packages are subjected to conditions that reproduce the environment and some evaluation is made at suitable intervals. Such procedures may be applied to testing closures for water vapour transmission.

HAZARDS ENCOUNTERED BY A PACKAGE:-

a) Mechanical hazards – shock, compression, puncture, vibration etc.

b) Environmental Hazards-temperature, pressure, moisture, gases, light, contamination etc.

There are various tests to ensure that the resultant product will comply with its specification. Tests applied to the environment or to equipment, as well as to products in process, may also be regarded as a part of in-process control.

PRINCIPAL INSTRUMENTAL TECHNIQUES EMPLOYED FOR PACKAGING CONTROLS

i. Spectrophotometry

ii. Chromatographic Methods

iii. Thermal analysis techniques

iv. Gas transmission analysis

v. Leak detection

vi. Physical test methods

vii. X-ray Fluorescence Analysis

IDEAL REQUIREMENTS OF GOOD PACKAGE:-

1. They should be able to hold the product without loss on account of leakage, spoilage or permeation.
2. They should afford protect against environmental conditions like light, air and moisture during storage.
3. They should not have any permeability for gases.
4. They should possess sufficient strength to withstand shocks of handling, transportation etc.
5. They should facilitate efficient safe and convenient use of contents.
6. The material must not interact with the contents.
7. The containers should afford protection from moulds, bacteria etc.
8. The cost of material should be as low as possible without compromising the quality.
9. They should facilitate easy identification.
10. They should afford protection from moulds, bacteria etc.
11. The container should not absorb or adsorb any material containing.
12. The closure should provide air tight closing to the container.
13. The closure should be compatible with the preparation.

2. QUALITY CONTROL OF CONTAINERS

A container for a pharmacopoeia article is intended to contain a drug substance or drug product with which it is, or may be in direct contact. The closure is a part of the container.

Containers must be chosen with care and after taking into consideration the nature of the articles and the likely effects of transportation and storage, even for short periods of time.

A container should be designed so that the contents may be removed in a manner suitable for the intended use of the article in it. It should also provide an adequate degree of protection, minimize the loss of constituents and should not interact physically or chemically with the contents in a way that will alter their quality to an extent beyond the limits given in the individual monograph, or present a risk of toxicity.

Airtight container

A container that is impermeable to solids, liquids and gases under ordinary conditions of handling, storage and transport. If the container is intended to be opened on more than once, it must be so designed that it remains airtight after re-closure.

Hermetically Sealed container.

A container that is impervious to air or any other gas under normal conditions of handling, shipment, storage and distribution, e.g. sealed glass ampoule, gas cylinder etc.

Light-resistant container.

A container that protects the contents from the effects of actinic light by virtue of the specific properties of the material of which it is made.

Multidose container

A container that holds a quantity of the preparation suitable for two or more doses.

Sealed container.

A container closed by fusion of the material of the container.

Single-dose container.

A container that holds a quantity of the preparation intended for total or partial use as a single administration.

Tamper-evident container.

A container fitted with a device or mechanism that reveals irreversibly whether the container has been opened.

Tightly-closed container

A tightly-closed container protects the contents from contamination by extraneous liquids, solids or vapours, from loss or deterioration of the article from effervescence, deliquescence or evaporation under normal conditions of handling, shipment, storage and distribution. A tightly-closed container must be capable of being tightly re- closed after use.

Well-closed container

A well-closed container protects the contents from extraneous solids and liquids and from loss of the article under normal conditions of handling, shipment, storage and distribution.

2.1 GLASS CONTAINERS

Glass containers may be colorless or coloured. Neutral glass is a borosilicate glass containing significant amounts of boric oxide, aluminum oxide, alkali and/or alkaline earth oxides. It has a high hydrolytic resistance and a high thermal shock resistance.

Soda-lime-silica glass is a silica glass containing alkali metal oxides, mainly sodium oxide and alkaline earth oxides, mainly calcium oxide. It has only a moderate hydrolytic resistance.

According to their hydrolytic resistance, glass containers are classified as:

1. Type I glass containers which are of neutral glass, with a high hydrolytic resistance, suitable for most preparations whether or not for parenteral use,
2. Type II glass containers which are usually of soda-lime- silica glass with high hydrolytic resistance resulting from suitable treatment of the surface. They are suitable for most acidic and neutral, aqueous preparations whether or not for parenteral use,
3. Type III glass containers which are usually of soda- lime-silica glass with only moderate hydrolytic resistance. They are generally suitable for non-aqueous preparations for parenteral use, for powders for parenteral use (except for freeze-dried preparations) and for preparations not for parenteral use.

Glass containers intended for parenteral preparations may be ampoules, vials or bottles. The glass used in the manufacture of such containers complies with one of the requirements for hydrolytic resistance given below:-

Containers of Type II or Type III glass should be used once only. Containers for human blood and blood components must not be re-used. Glass containers with a hydrolytic resistance higher than that recommended for a particular type of preparation may generally also be used.

Containers for parenteral preparations are made from uncolored glass except that coloured glass may be used for substances known to be light - sensitive; in such cases, the containers should be sufficiently transparent to permit visual inspection of the contents.

Glass is a common material to be used in either no sterile or sterile liquid dosage forms. It leaches alkali from its surface. Leaching of alkali can be reduced but cannot be zero. Hence, a limit test for alkalinity is to be performed before using it for a particular product.

EVAUATION PARAMETERS:-

(A) Crushed – glass test:

This test is official in USP. The container is crushed and sieved to produce uniform particles of which a definite weight of taken. The control of the particle size and weight of powder ensures that a constant surface area is exposed to the solution. Because all of the glass (not just the surface layer) is examined and extraction is enhanced by the rough surfaces of the particles, this is a severe test, and, if a glass passes, it is unlikely that containers made from it will give trouble while is use. Nevertheless, the technique is tedious and is not applicable to surface treated containers (sulphured or siliconed) because crushing would expose the alkaline glass below the surface. This test can be used for determining the nature of a glass or for distinguish between two types of glasses, such as neutral or surface – treated.

(B) Whole-Container test:

This test is official in European, British and International Pharmacopoeias. it is used in the USP for treated soda-lime containers only. The containers are simply filled with the test solution and exposed to the test conditions. Glassware may pass the whole container test more easily because the surface layer of a container is smooth and less reactive.

In this test, surface area does not increase as much as volume with the increase in container size, consequently, the small sized containers are more attacked by the leaching of the alkali from the surface.

Container	**Surface area which supplies alkali to each milliliter of the solution.**
Ampoule (1 ml.)	5.9 cm2
Ampoule (10 ml.)	2.9 cm2
Bottle (1000 ml)	0.5 cm2

(C) Chemical resistance of test

USP and IP provide two tests to determine the chemical resistance of glass containers.

Table shows limits of alkalinity for glass containers:-

Tests	Containers	Limits ml of 0.02 N H2so4
1. Powdered Glass Test	Type I Type III Type NP	1.0 8.5 15.0
2. Water Attack Test	type II (100ml of less) type II (over 100ml)	0.7 0.2

(D) Powdered Glass Test

From the glass containers, alkaline constituents (oxides of sodium, potassium, calcium, aluminum, etc.) are leached into purified water under conditions of elevated temperatures. When the glass is powdered the leaching of alkali can be enhanced in the powdered is critical.

The principle involved in the powdered glass test in estimate the amount of alkali leached form the glass powder. The amount of acid that is necessary to neutralize the released alkali (a specified limit) is specified in the pharmacopoeia. The basic analysis is acid-base titration using methyl red indicator.

(E) Water Attack Test

This test is used only with containers that have been exposed to sulphur dioxide fumes under controlled humidity conditions. Such a treatment neutralizes the surface alkali. Now the glass becomes chemically more resistant. The principle involved in the water attack test is to determine whether the alkali leached form the surface of a container is within the specified limits or not. Since the inner surface is under test entire container (ampoule) has to be used. The amount of acid that is necessary to neutralize the released alkali from the surface is estimated, the leaching of alkali is accelerated using elevated temperature for a specified time. Methyl red indicator is used to determine the end point. The basic is acid-base titration.

2.2 PLASTIC CONTAINERS

Plastic containers for pharmaceutical products are made from plastics based on the following polymers: polyethylene (low or high density), polypropylene, polyvinyl chloride, polystyrene

and to a lesser extent polyethylene terephthalate. The containers consist of one or more polymers together with certain additives if necessary. They should be manufactured from materials that do not include in their composition any substances that can be extracted by any contents in such quantities so as to alter the efficacy or stability of the product or to present a toxic hazard. Additives may consist of antioxidants, lubricants, plasticizers and impact modifiers but not antistatic agents and mould- release agents.

Drug Plastic Consideration

1. Permeation: The transmission of gases, vapours or liquid through plastic packaging materials can have an adverse effect on shelf life of drug. Permeation of water vapour and oxygen through the plastic wall into the drug can present a problem if the dosage form is sensitive to hydrolysis and oxidation. Temperature and humidity are important factors influencing the permeability of oxygen and water through plastic. An increase in the temperature increases the permeability of gas.

2. Leaching: Since most plastic containers have one or more ingredients added in small quantities to stabilize a specific to the plastic the prospect of leaching or migration from the container to the product is present. Problems may arise with plastics when coloring agents in relatively small quantities are added to the formula. Release of a constituent from the plastic container to the drug product may lead to drug contamination and necessitate removal of the product from the market.

3. Sorption: It may be defined as bonding of solutes to a plastic .This process involves the removal of constituents from the drug product by the packaging material. Sorption may lead to serious problem for drug preparation in which important ingredients are in solution. Since drug substances of high potency are administered in small doses, losses due to sorption may significantly affects therapeutic efficacy of the preparation.

4. Chemical Reactivity: Certain ingredients that are used in plastic formulations may react chemically with one or more components of a drug product. At times ingredients in the formulation may react with the plastic. Even micro quantities of chemically incompatible substance can alter the appearance of the plastic or the drug product.

A. TESTS ON PLASTIC CONTAINER

Parenteral and non-parenteral preparations:-

1. Leakage test: Fill ten containers with water. Fit with intended closures and keep tem inverted at room temperature for 24 hour. There are no signs of leakage from any container.

2. Collapsibility Test: This test applicable to containers. Which are to be squeezed in order toe 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. Clarity of aqueous extract: Select unlabelled, unmarked and non-laminated portions from suitable containers, 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 cm2. Wash the strips free from extraneous matter by shaking them with at least two separate portions of distilled water for about 30 seconds in each case, then draining off the water thoroughly.

4. Transparency test: Fill five 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.

5. Water vapour permeability test: Fill five containers with nominal volume of water and heat seal the bottles with an aluminum foil-poly ethylene laminate or other suitable seal. Weigh accurately each container and allow standing (without any overwrap) for 14 days at a relative humidity of 60+5% and a temperature between 20 and 25ºC reweigh the containers. The loss in weight in each container is not more than 0.2%.

PLASTIC CONTAINERS FOR OPHTHALMIC PREPARATIONS:

Plastic containers for ophthalmic preparations comply with the following tests: Leakage test; Collapsibility test Clarity of aqueous extract; Non-volatile residue

1. Comply with the tests described under Plastic containers for Non-parenteral Preparations.
2. Systemic injection test; Intracutaneous test Comply with the tests described under Plastic containers for Parenteral Preparations.
3. Eye irritation test. This test is designed to evaluate responses to the instillation of extracts of material under examination in the eye of a rabbit.

B. TESTS ON PLASTIC MATERIAL

Physico-Chemical Tests:-

The following tests are based on the extraction of the plastic material, and it is essential that the designated amount of the plastic be used. Also, the specified surface area must be available for extraction at the required temperature.

1. Appearance

2. Light absorption
3. pH
4. Non-volatile matter
5. Residue on ignition
6. Heavy metals
7. Buffering capacity
8. Oxidisable substances

METAL CONTAINERS

The materials used for various pharmaceutical drug delivery systems include tin plated steel, mild steel, stainless steel, tin free steel, aluminum and its various alloys. Tin is frequently used in the production of aerosol cans by electroplating it onto sheet steel to improve corrosion resistance and facilitate soldering. In contrast; aluminum is used in its pure form as foil. Often, aluminum foil is used as an impermeable layer in a multilayer laminate that may include paper and plastics as well. Aluminum foil can be formed into rigid containers, semi rigid containers, blister construction, or laminates.

Metals have a number of advantages over other packaging materials. Like glass, metal is nearly totally impermeable to gas and water. In addition, metal containers are extremely strong and are shatterproof. For applications requiring malleability such as collapsible tubes, metal offers relatively easy manufacturing and very easy use .Metals can also be fashioned into more complex delivery systems such as metered-dose inhalers, dry powder inhalers, aerosol administration devices, and even ready-to-use needles. The primary disadvantages of metals relate to their cost and quality control. Metals are inherently more expensive to purchase and to fabricate into a useful container. Metals also are prone to the development of ‘‘pinhole’’ defects during manufacturing that can drastically compromise their barrier properties—especially in particularly thin sections. Not only can these defects be deleterious to the container, but they can also compromise the quality of the pharmaceutical.

PAPER, PAPERBOARD, AND CARDBOARD

The most common applications of paper, paperboard, and cardboard are in blister lidding stock and in over-the-counter (OTC) outer packaging. Because paper, paperboard, and cardboard offer virtually no moisture or gas barrier, they are typically part of the secondary pharmaceutical container. To provide additional protection, paper can be laminated or coated with a variety of materials. More commonly, when paper is involved in critical packaging functions, it is the only

one component of a multicomponent system that offers optimal environmental protection to the drug environment. .Although paper does not offer high shear strength, its relatively high tensile strength makes it an easy barrier to overcome if one intends to do so, but is an exceedingly confounding one for a child. Paper also simplifies printing on the blister itself. Other uses of paper, paperboard, and cardboard are as secondary packaging or for shipping packaging (e.g., corrugated cardboard).

4. QUALITY CONTROL OF CLOSURES

The closure is normally the most vulnerable and critical component of a container as far as stability and compatibility with the product is concerned.

Suitable closing of the container is necessary because

1. It prevents loss of material by spilling or volatilization.
2. It prevents the deterioration of product from the effects of environment such as moisture, oxygen, or carbon dioxide.
3. It avoids contamination of the product from dirt, microorganism or insects.

Types of closures:-

1. Thread screw cap
2. Lug cap
3. Crown cap
4. Pilfer proof closures

Materials used for making closures:-

1. Cork
2. Glass
3. Plastic
4. Metal
5. Rubber

A closure for a container for an aqueous parenteral preparation or for a sterile powder is a packaging component which is in direct contact with the drug. A rubber closure is made of materials obtained by vulcanization (cross-linking) of elastomers with appropriate additives. The elastomers are produced from natural or synthetic substances by polymerization, poly addition or poly condensation. The nature of the principal components and of the various additives such as vulcanizes, accelerators, stabilizing agents, pigments, etc. depends on the properties required for the finished closure.

Rubber closures are used in a number of formulations and consequently different closures possess different properties. The closures chosen for use with a particular preparation should be such that the components of the preparation in contact with the closure are not adsorbed onto the surface of the closure to an extent sufficient to affect the product adversely.

TEST FOR CLOSURES:-

1. **Penetrability:** This is measured to check the force required to make a hypodermic needle penetrate easily through the closure. It is measured by using the piercing machine. The piercing force must not exceed a stated value. If it exceeds that stated value, the hypodermic needle can be damaged as a result of undesirable hardness of the closures.

2. Fragmentation test: This test is performed on 20 closures. Each closure is penetrated with hypodermic needle in a piercing machine five times within a limited area and needle is washed to transfer any fragment present. The contents are filtered through coloured paper that contrasts with the rubber and the fragments counted. On an average there should not be more than three fragments per unit.

3. Self salability test: Applicable to multidose containers fill 10 vials with water close them with prepared closures and secure with a cap. For each closure use a new hypodermic needle and pierce 10 times each time at different site immerse the vials upright in methylene blue (0.1%) solution and reduce external pressure 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 contains any trace of coloured solution.

4. Extractive test: In this test, the closure is boiled with water for four hours under reflux and the water evaporated to dryness. The residue must not exceed the specified amount.

5. Compatibility test: This test is performed to check the compatibility of the rubber closures with various types of the substances, since it is necessary to ensure that there is no interaction between the contents of the bottle and the closure.

6. Light absorption Filter solution A through membrane filter. Measure the light absorbance of filtrate in the range 220 to 360 nm using a blank solution (prepared in the same manner as solution A). The absorbance is not more than.

7. Light absorption: Filter solution A through membrane filter. Measure the light absorbance of filtrate in the range 220 to 360 nm using a blank solution (prepared in the same manner as solution A). The absorbance is not more than.

GOOD LABORATORY PRACTICE (GLP)

The Good Laboratory Practice standards (GLPs) are federal regulations promulgated in the United States by both the Food and Drug Administration in 21 CFR Part 58 and the Environmental Protection Agency both for FIFRA in 40 CFR Part 160 and for TSCA in 40 CFR Part 792.

In Japan, the Ministry for Agriculture, Forestry and Fisheries (MAFF) has also adapted a version of the GLPs.

The main purpose of the role of the Good Laboratory Practice (GLP) Quality Assurance (QA) professional is to assure management of the compliance with the GLP regulations within their departments. GLP is the quality system applied to non-clinical safety and environmental studies during the development of new products such as medicines, industrial chemicals and pesticides. GLP gives assurance that study data submitted to government assessors is accurate, valid and of sound integrity. Monitoring for GLP compliance by the QA Professional involves conducting audits of the facilities, of ongoing work in the facilities and of various documents.

The GLP regulations require that QA conduct audits of the following types

- Facility audits – to assure the facility is fit for purpose and documents to support processes are in place
- Process and Study audits – observing personnel in the laboratory to assure they are following relevant procedures and working in compliance with GLP
- Study Plan reviews – review of the document which outlines the work to be conducted
- Study Report reviews – review of the report to check it accurately reflects the data generated during the study and contains everything required under GLP
- Computerized Systems used to generate and/or manipulate study data and facility GLP records– review of documents associated with validation of new systems plus audits of ongoing maintenance and validation status of the system

The role also involves proactive input into changes in policies and working practices within the departments. As a QA professional, you will be asked for suggestions on how to improve processes and policies within the department with a view to improving the quality of the work.

Work with a variety of internal and external companies

A GLP QA professional typically works with many parts of the organization. It really is a cross departmental role. Additionally your organization may be involved in contracting out work or in

collaborations with other organizations. You may be involved in auditing quality systems within these external organizations as well as auditing other parts of your own organization.

Share knowledge through consultancy and training

You may be expected to deliver training in the basic principles of GLP to new staff within your organization as well as training for staff taking on particular GLP roles in what their responsibilities are (for example, computer system owners, Study Directors). It is also expected that all staff working in GLP areas receive periodic refresher training so you may be involved in putting together material for this as well as running training workshops. All of this training needs to be organized and documented so organization skills are also key.

Provide opportunities for personal and professional development

A career as a GLP QA professional will mean that you will be constantly developing your knowledge and skills. In order to perform audits, you will need a good understanding of the science behind the work being conducted. Therefore as scientific techniques evolve and develop, you will be aware of this and learn about these exciting developments.

You will also get opportunities to gain a broad understanding of the pharmaceutical or agrochemical industry and the drug development process to understand how your role fits in.

You will also get the opportunity to attend professional development courses such as auditing skills, observation and report writing, risk management and process mapping, and you may get the opportunity to study for a MSc in Quality Management.

Travel

Many organizations that are involved in GLP work are large global companies that have sites on many locations. You may be required to travel to other locations in order to participate in joint audits or attend meetings.

You may also be required to be involved in due diligence activities at a location of another company of which your organization is considering a buy out or buying a drug in mid development.

The laboratory within your organization may decide to contract some work to other organizations. You may be required to audit these 3rd party organizations, which could be located anywhere in the UK or abroad. The purpose of these audits will be to assess the standards that they are working to and whether this is acceptable to your organization.

Additionally you may be required to audit supplier companies who provide materials and/or services that are key to the work being conducted in your organization. This is to ensure that the

systems in the supplier company are adequate to ensure quality of those products that are being supplied.

General Provisions

Scope

This part prescribes good laboratory practices for conducting non-clinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by the FDA, including food and colour additives, animal food additives, human and animal drugs, medical devices for human use, biological products, and electronic products.

Inspection of a testing facility

A testing facility shall permit an authorised employee of the FDA, at reasonable times and in a reasonable manner, to inspect the facility all records and specimens required to be maintained regarding studies within the scope of this part..

If the testing facility refuses to permit inspection the Food and Drug administration will not consider a non-clinical laboratory study in support of an application for a research or marketing permit.

SUBPART B – ORGANIZATION AND PERSONNEL

PERSONNEL

Each individual engaged in the conduct of or responsible for the supervision of a non-clinical laboratory study shall have education, training, and experience

There shall be a sufficient number of personnel for the timely and proper conduct of the study according to the protocol.

Personnel shall take necessary personal sanitation and health precautions designed to avoid contamination of test and control articles and test systems.

Personnel engaged in a non-clinical laboratory study shall wear clothing appropriate for the duties they perform.

Any individual found at any time to have an illness that may adversely affect the quality and integrity of the non-clinical laboratory study shall be excluded from direct contact with test systems, test and control articles

Testing facility management

For each non-clinical laboratory study, testing facility management shall:

Replace the study director promptly if it becomes necessary to do so during the conduct of a study.

Assure that test and control articles or mixtures have been appropriately tested for identity, strength, purity, stability, and uniformity, as applicable.

Assure that personnel, resources, facilities, equipment, materials and methodologies are available as scheduled.

As sure that any deviations from these regulations reported by the quality assurance unit are communicated to the study director and corrective actions are taken and documented.

Study director

For each non-clinical laboratory study, a scientist or other professional of appropriate education, training, and experience, or combination thereof, shall be identified as the study director.

The study director has overall responsibility for the technical conduct of the study, as well as for the interpretation, analysis, documentation and reporting of the results, and represents the single point of study control. The study director shall assure that:

The protocol including any change is approved and is followed. All experimental data, including observations of unanticipated response of the test system are accurately recorded and verified. All applicable good laboratory practice regulations are followed.

Quality assurance unit

Responsibilities of The quality assurance unit

Monitoring each study to assure management that the facilities, equipment, personnel, methods, practice, records, and controls are in conformance with the regulations in this part.

For any given study, the quality assurance unit shall be entirely separate from and independent of the personnel engaged in the direction and conduct of that study.

Functions of the quality assurance unit:

- Maintain a copy of a master schedule sheet
- Inspect each non-clinical laboratory study at intervals adequate to assure the integrity of the study and maintain written and properly signed records of each periodic inspection
- Determine that no deviations from approved protocols or standing operating procedures were made without proper authorisation and documentation.
- A designated representative of the FDA shall have access to the written procedures established for the inspection and may request testing facility management to certify that inspections are being implemented, performed, documented, and followed-up in accordance with this paragraph.

Subpart C –Facilities

General

Each testing facility shall be of suitable size and construction to facilitate the proper conduct of non-clinical laboratory studies. It shall be designed so that there is a degree of separation that will prevent any further function or activity from having an adverse effect on the study.

Animal care facilities

A testing facility shall have sufficient number of animal rooms or areas

Separate areas shall be provided, as proposed, for the diagnosis, treatment, and control of laboratory animal disease.

When animals are housed, facilities shall exist for the collection and disposal of all animal waste and refuse or for safe sanitary storage of waste before removal from the testing facility.

Facilities for handling test and control articles

As necessary to prevent contamination or mix-ups, there shall be separate areas for Receipt and storage of the test and control articles, Mixing of the test and control articles with a carrier, Storage of the test and control article mixtures.

Storage areas for the test and or control article and test and control mixtures shall be separate from areas housing the test systems and shall be adequate to preserve the identity, strength, purity, and stability of the articles and mixtures.

Laboratory operation areas

Laboratory space shall be provided, as needed, for performance of the routine and specialized procedures required by non- clinical laboratory studies and data storage facilities

Space shall be provided for archives, limited access by authorized personnel only, for the storage and retrieval of all raw data and specimens from completed studies.

Subpart D – Equipment

Equipment design

Equipment used in the generation, measurement, or assessment of data and equipment used for facility environmental control shall be of appropriate design and adequate capacity to function according to the protocol and shall be suitability located for operation, inspection, cleaning and maintenance.

Maintenance and calibration of equipment

Equipment shall be adequately inspected, cleaned, and maintained. Equipment used for the generation, measurement, or assessment of data shall be adequately tested, calibrated or standardized

Written records shall be maintained of all inspection, maintenance, testing, calibration and standardizing operations.

Subpart E - Testing Facilities Operation

Standard operating procedures.

Standard operating procedures shall be established for

- Animal room preparation.
- Animal care.
- Receipt, identification, storage, handling, mixing, and method of sampling of the test and control articles.
- Test system observations.
- Laboratory tests.
- Handling of animals found moribund or dead during study.
- Necropsy of animals or post mortem examination of animals.
- Collection and identification of specimens.
- Histopathology.
- Data handling, storage, and retrieval.
- Maintenance and calibration of equipment.
- Transfer, proper placement, and identification of animals.

Reagents and solutions

All reagents and solutions in the laboratory areas shall be labelled to indicate identity, titre or concentration, storage requirements, and expiration date. Deteriorated or outdated reagents and solutions shall not be used.

Animal care

- There shall be standard operating procedures for the housing, feeding, handling, and care of animals.
- All newly received animals from outside sources shall be isolated and their health status shall be evaluated
- At the initiation of a non-clinical laboratory study, animals shall be free of any.

- If, during the course of the study, the animals contract such a disease or condition, the diseased animals shall be isolated, if necessary
- These animals may be treated for disease or signs of disease provided that such treatment does not interfere with the study.
- The diagnosis, authorisation of treatment, description of treatment, and each date of treatment shall be documented and shall be retained.
- Animals of different species shall be housed in separate rooms when necessary.
- Animal cages, racks and accessory equipment shall be cleaned and sanitised at appropriate intervals.
- Feed and water used for the animals shall be analysed periodically to ensure that contaminants known to be capable of interfering with study and reasonably expected to be present in such feed or water are not present in levels above those specified in the protocol. Documentation of such analyses shall be maintained as raw data.
- If any pest control materials are used, the use shall be documented. Cleaning and pest control materials that interfere with the study shall not be used.

Subpart F– Test and Control Articles

Test and control article characterization

- The identity, strength, purity, and composition or other characteristics which will appropriately define the test or control article shall be determined for each batch and shall be documented.
- Methods of synthesis, fabrication, or derivation of the test and control articles shall be documented by the sponsor or the testing facility.
- Each storage container for a test or control article shall be labelled by name, chemical abstract number, or code number, batch number, expiration date, if any, and, and, where appropriate, storage conditions necessary to maintain the identity, strength, purity, and composition of the test or control article. Storage containers shall be assigned to a particular test article for the duration of the study.
- Test and control article handling Procedures shall be established for a system for the handling of the test and control articles to ensure that:} There is proper storage.} Distribution is made in a manner designed to preclude the possibility of contamination, deterioration, or damage.} Proper identification is maintained throughout the distribution

- The receipt and distribution of each batch is documented. Such documentation shall include the date and quantity of each batch distributed or returned.

Subpart G - Protocol for and Conduct of a Non- clinical Laboratory Study

Protocol

Each study shall have an approved written protocol that clearly indicates the objectives and all methods for the conduct of the study.

The protocol shall contain:

- A descriptive title and statement of the purpose of the study.
- Identification of the test and control articles by name, chemical abstract number, or code number.
- The name of the sponsor and address of the testing facility
- The number, body weight range, sex, source of supply, species, strain, sub strain, and age of the test system.
- The procedure for the identification of the system.
- A description of the experimental design, including the methods for the control bias.
- Each dosage level to be administered and the method and frequency of administration.
- The records to be maintained.

Conduct of nonclinical laboratory study.

- The non-clinical laboratory study shall be conducted in accordance with the protocol.
- The systems shall be monitored in conformity with the protocol.
- Specimens shall be identified by test system, study, nature, and date of collection.
- Records of gross findings for a specimen from post-mortem observations should be available to a pathologist when examining that specimen histopathologically.
- Any change in these entries shall be made so as not to obscure the original entry, shall indicate the reason for such change, and shall be dated and signed or identified at the time of the change.

Subparts J- Records and Reports

Reporting of non-clinical laboratory study results

A final report shall be prepared for each non- clinical laboratory study and shall include

- Name and address of the facility performing the study and the dates
- Statistical methods employed for analysing data.

- The test and control articles identified by name, code number, strength, purity, and composition or other characteristics.
- Stability of the test and control articles under the conditions of administration.
- A description of the methods used.
- A description of the test system used.
- A description of the dosage, dosage regimen, route of administration, and duration.
- The name of the study director, other scientists, supervisory personnel involved in the study.
- A description of the transformations, calculations, or operations performed on the data, a summary and analysis of the data, and a statement of the conclusions drawn from the analysis.
- The locations where all specimens, raw data, and the final report are to be stored.
- The statement prepared and signed by the quality assurance Unit.
- The final report shall be signed and dated by the study director.
- Corrections or additions to a final report shall be in the form of an amendment by the study director. The amendment shall clearly identify that part of the report that is being added to or corrected and the reasons for the correction or addition, and shall be signed and dated by the person responsible.

Storage and retrieval of records and data

- All raw data, documentation, protocols, final reports, and generated as a result of a non-clinical laboratory study shall be retained.
- There shall be archives for orderly storage and expedient retrieval of all raw data, documentation, protocols, specimens, and interim and final reports.
- An individual shall be identified as being responsible for the archives.
- Only authorised personnel shall enter the archives.
- Material retained or referred to in the archives shall be indexed to permit expedient retrieval

QUESTION BANK

Short questions (2marks)

1. Write different tests for closures.
2. What are the different types of plastics?
3. What is temper resistant packaging?
4. Enlist the critical dimensions of a vial.
5. Write the important chemical tests for glass container.
6. Enlist different QC test for collapsible tubes.
7. Define GLP.
8. What are principles of GLP?
9. Describe any two responsibilities of study director.
10. List the types of studies covered under GLP.
11. What do you mean by test facility?
12. Write about storage and retrieval of records and data.

Long questions (5 marks)

1. Discuss different types of packaging material used in plasma industries with their advantages and disadvantages.
2. Write a note on quality control tests for secondary components.
3. What is closure? Enlist different types of closures. Discuss their quality control tests.
4. Explain the disqualification of a facility.
5. Write about organization and personnel requirements in GLP.

Very Long questions (10 marks)

1. Write about organization and personnel requirements in GLP.
2. Discuss different types of packaging and packaging material in details.