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Subject: Quality Assurance (BP-606T)

Unit: III

Topic: ***Quality control testing of packaging materials***

# QUALITY CONTROL TESTING OF PACKAGING MATERIALS


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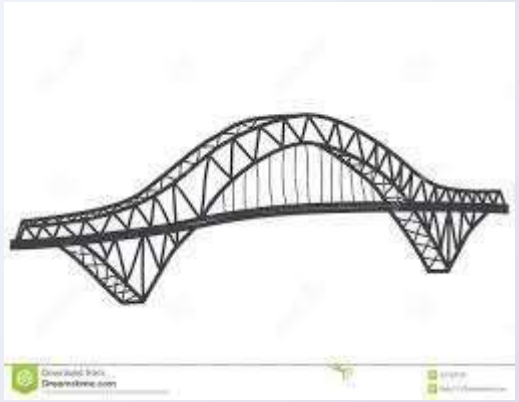
# CONTENTS

- INTRODUCTION
- OBJECTIVE
- QUALITY CONTROL AND TESTING STANDARDS
- SETTING THE STANDARDS
    1) Appearance
    2) Dimensions
    3) compatibility and customer usability
    4) Chemical testing
- STERILE PRODUCT VALIDATION
- NONSTERILE PRODUCT VALIDATION

# Packaging is a-

Production  marketing

# INTRODUCTION

- QC - backbone of pharmaceutical industry.
- Defects in packaging – harmful for dosage form
- Quality control of a packaging component starts at the design stage.
- All aspects of a pack development that may give rise to quality problems must be ***identified and minimized by good design***.

# Physical protection: eg ; shock, vibration

# Barrier protection: eg; oxygen, light

# Portion control: eg; single dose pack.

# Marketing

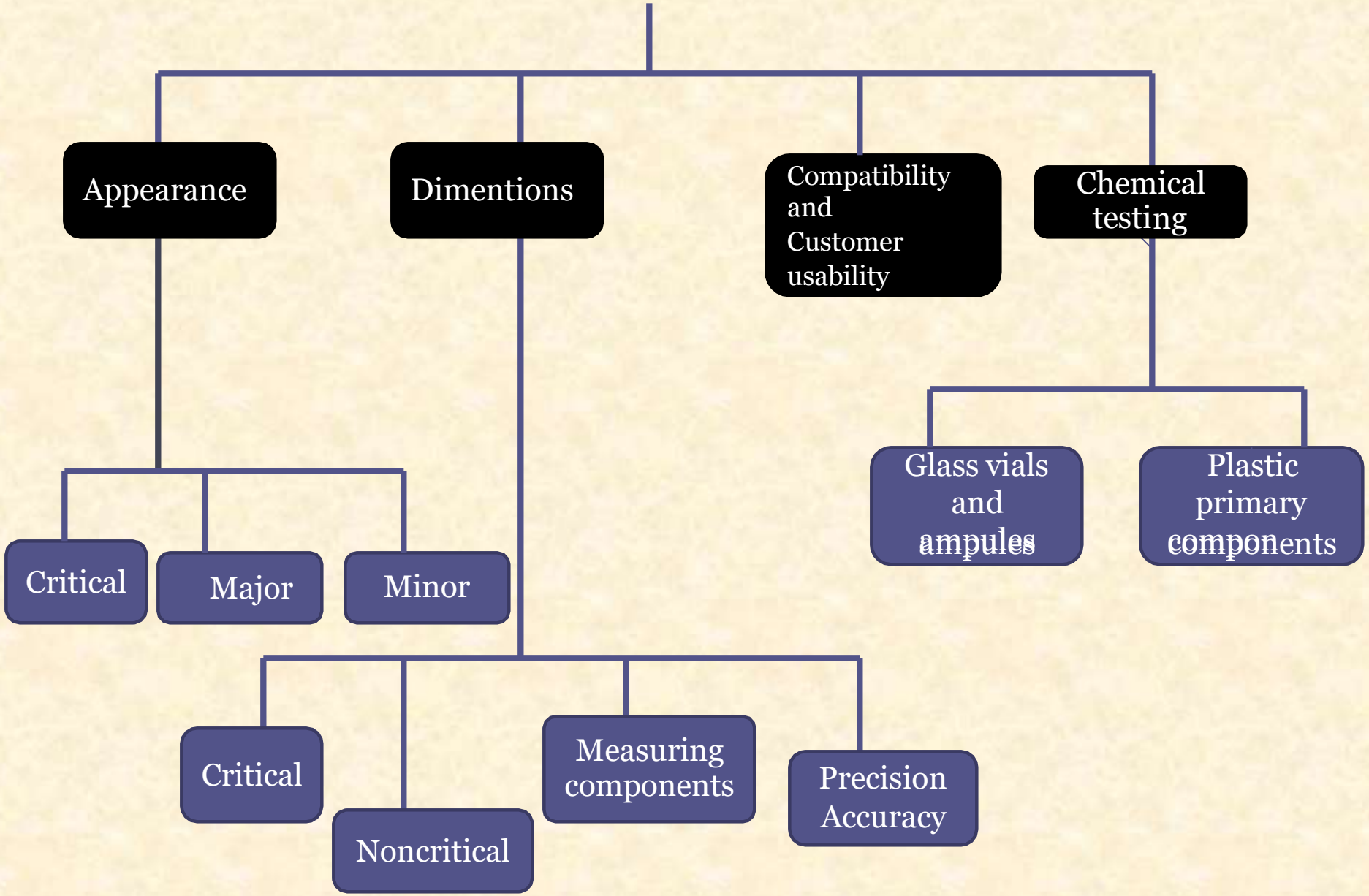

NAVEEN KUMAR P

# Which would you prefer ?

# QUALITY CONTROL AND TESTING STANDARDS

- It is to first determine which batch is for testing purposes.
- The basic ***testing system is the same*** for both the components, primary and secondary.
- Although component compatibility and chemical testing are required , in addition , for primary components.

# SETTING THE STANDARDS



# Appearance

- **Critical** :Unacceptable at any level , eg; rogue printed items in a delivery , incorrect printing of data such as the product name or concentration , insects in the bottles, etc.

- **Major**: Acceptable at low level; standard is decided by the pharmaceutical company. Very easy to ask for perfection if not possible so a reasonable compromise has to be reached .

  Two type standard will result in a supplier not supplying because the standard cannot be met or a 100% inspection of each consignment received by the pharmaceutical company.
  ***Too low standard – excessive complaint from market-loss of company image and orders.***

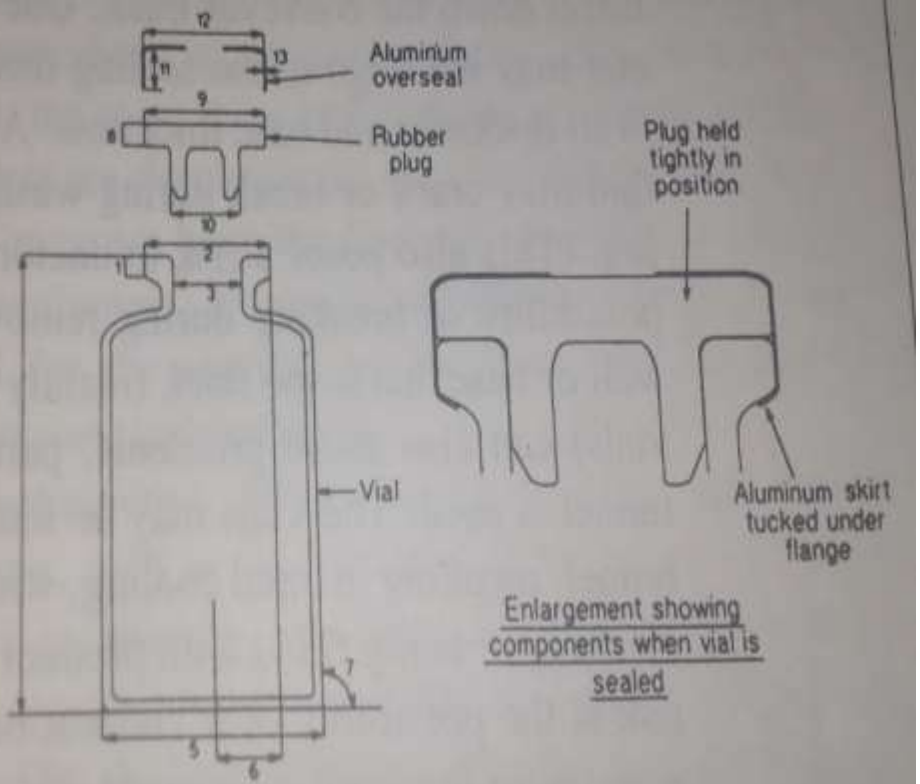
- **Minor:** acceptable at higher level then the major appearance defect this will detract from perfection and include marked components , slight colour variation ,etc.

# Dimensions

- **Critical** : requiring close control to insure that the components functions correctly and can be used satisfactorily by the packaging equipment.

- **Non critical** : necessary to maintain the component shape but not requiring close control . Eg  a vial containing injectable product. Components  are brought together by filling machine to give sterility to seal , rubber plug and aluminium overseal .

1. Flange Depth
2. Flange Diameter
3. Bore Diameter
4. Vial Height
5. Body Diameter
6. Concentricity - Flange Movement when Vial Rotated
7. Verticality - Maximum of Lean when Vial Rotated
8. Flange Depth
9. Flange Diameter
10. Plug Diameter
11. Internal Skirt Depth
12. External Diameter
13. Aluminum Thickness




Enlargement showing components when vial is sealed

- **Measuring component** :

  It is possible ***to accurately measure component without trained staff*** and variety of measuring equipment such as callipers , micrometer etc. the variety and types of equipment used are determined by materials to be measured.

  1) **Measuring tehniques**: Even when measuring something simple with a micromerter, such as thickness of a sheet of metal, it is possible to measure it incorrectly due either to not using the ratchet or using the ratchet incorrectly.

  2)**Precision and accuracy**: Firstly a set of recently calibrated gauging blocks are required, together with a certificate of calibration. The gauging blocks must cover the full measuring range of the equipment and must be periodically recalibrated at a frequency to be determined by the frequency of use.

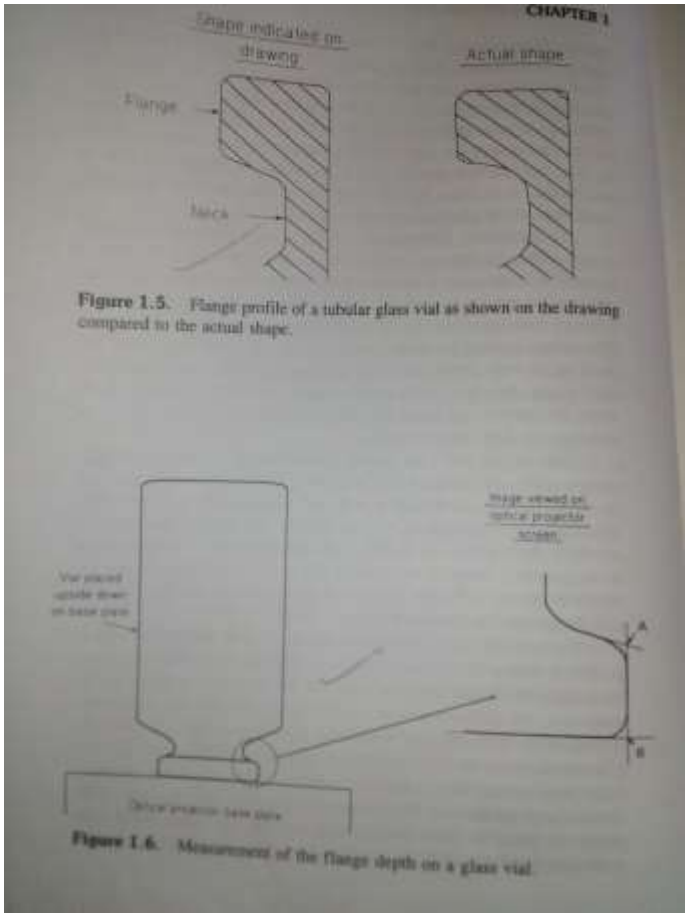



**Figure 1.5.** Flange profile of a tubular glass vial as shown on the drawing compared to the actual shape.



**Figure 1.6.** Measurement of the flange depth on a glass vial.



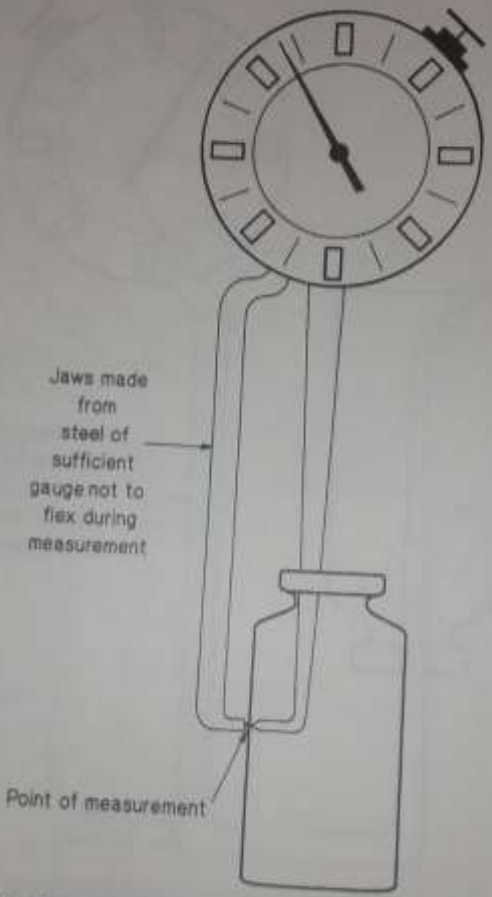



**Figure 1.7.** Bottle and vial measuring equipment used for side wall measurement.

# COMPATIBILITY AND CUSTOMER USABILITY

- This involves checking that each component forming a pack **fits together and functions correctly**.
- Consider an eye dropper pack as an example.
- The nozzle ,must have a interference fit in the bottle and allow 1 drop at a time delivery through the hole in the nozzle when inverted, but not leak from the fitted position.
- The cap must screw into position and leakage must not occur when the bottle is squeezed in the inveted position.

# Chemical testing

- The majority of chemical testing is required on primary component.
- The type of testing required depends on the type of component used.

  1) **glass vials and ampules**: The USPXXII requirements for glass containers are chemical resistance and light transmission.The requirements vary from country to country.

  2) **plastic primary components**: The testing is more extensive with plastic components, requiring both biological and physicochemical test. This is because the plastic components contain other substance such as plasticizers , stabilizers, antioxidants, pigment, lubricants ,etc.

# 3) 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 basis is acid-base titration.

| TESTS | CONTAINER | VOL.OF 0.02N $H_2SO_4$ |
|---|---|---|
| Powdered glass test | Type I | 1.0 |
| | | 8.5 |
| | Type II | 15.0 |
| | Type III | |
| Water attack test | | 0.07 |
| | Type II(100ml or below) | 0.02 |
| | Type II(above 100ml) | |

# QUALITY CONTROL TESTS FOR GLASS CONTAINERS: 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. 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.

# 2) HYDROLYTIC RESISTANCE OF GLASS CONTAINERS:

- Rinse each container at least 3times with $CO_2$ free water and fill with the same to their filling volume. Also fill & Cover the vials and bottles and keep in autoclave. Heat to $100^0$C for 10min and allow the steam to issue from the vent cork. Rise the temp from $100^0$C to $121^0$C over 20min. Maintain the temp at $121^0$C to $122^0$C for 60min.Lower the temp from $121^0$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.

# 3) 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 5min.Prep test as described in the test for hydrolytic resistance for an adequate no.of samples to produce 50ml.pipette out 10ml solution from
- combined contents of all ampoules to the flask.
  Add 10ml of $HNO_3$ to dryness on the water bath, dry the residue in an oven at $130^0C$ for 30min cool and add 10ml hydrogen molybdate reagent .Swirl to dissolve and heat under water bath and reflux for 25min. Cool to room temp and
- determine the absorbance at 840nm.
  Do the blank with 10ml hydrogen molybdate. The absorbance of the test solution should not exceed the absorbance obtained by repeating the determination using 0.1ml of arsenic standard solution (10ppm) in place of test soln.

# 4 ) 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, design and glass distribution. Small bottles withstand a temp differential of 60 to 80$^0$C and 1 pint bottle 30 to 40$^0$C.A typical test uses 45C temp difference between hot and cold water.

# 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 for predetermined pressure level and the test continues unteil the container finally bursts.

# 6 ) LEAKAGE TEST:

- Drug filled container is placed in a container filled with coloured solution (due to the addition of dye)which is at high pressure compared to the pressure inside the glass container so that the coloured solution enters the container if any cracks or any breakage is present.

# QUALITY CONTROL TESTS FOR RUBBERS :

- Fragmentation test for rubber closures :

Place a 4ml of water in each of 12 clean vials. Close a vial with closure and secure caps for 16 hrs.

↓

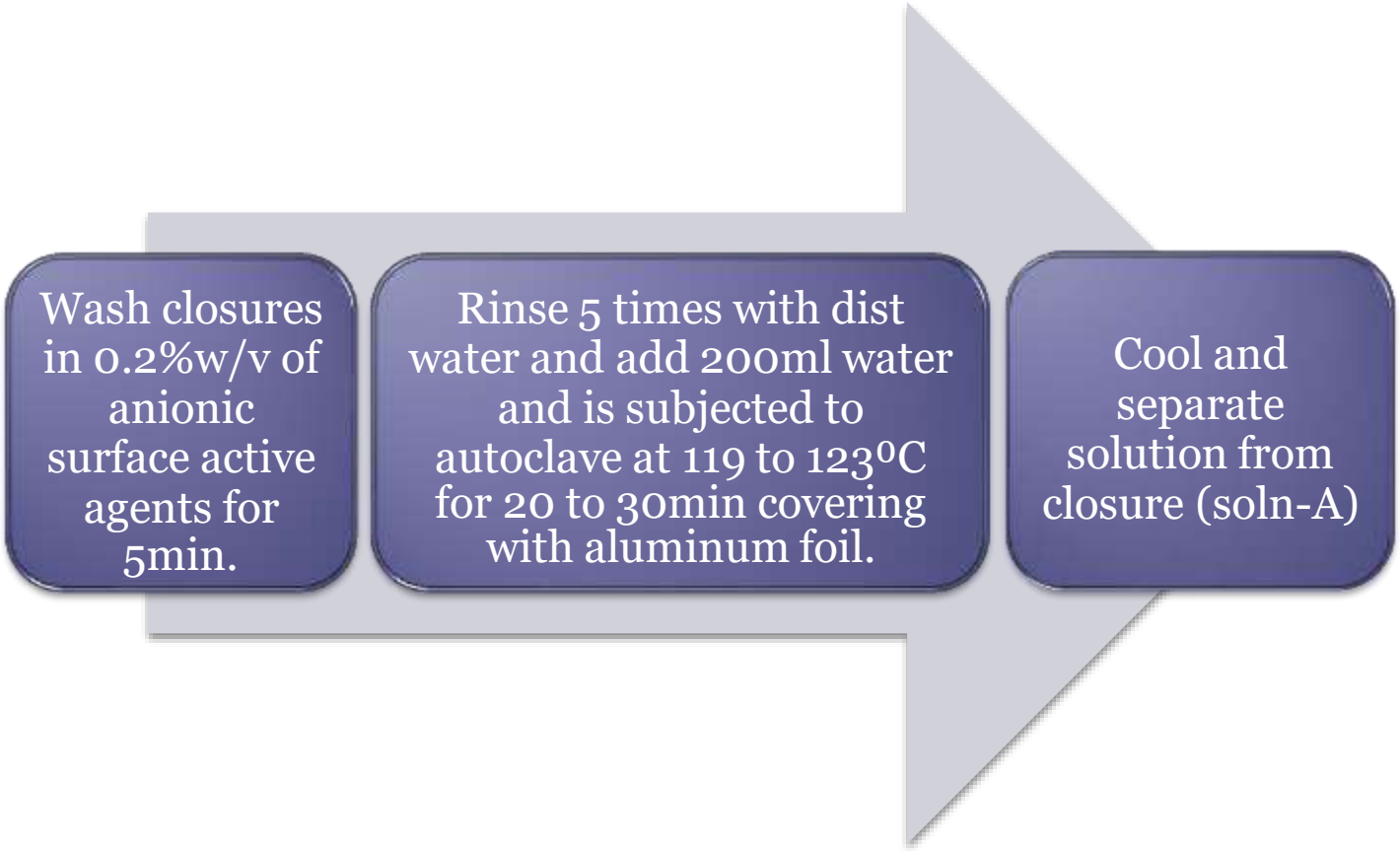
Pierce the closure with 21 SWG hypodermic needle. Repeat the operation 4 times for each closures.

↓

Count the number of fragment visible on the rubber . Total number of fragment should not be more than 10 except butyl rubber

# QUALITY CONTROL OF CLOSURES

- PREPARATION OF SAMPLE (SOL.-A) :



# 1) STERILITY TEST:

- When treated closures are subjected to sterilization test at 64-66$^0$C and a pressure of about 0.7 KPa for 24hr.

# 2) Fragmentation test

For closures for aqueous place a vol of water corresponding to the nominal vol minus 4 ml in each of 12 clean vials.

↓

close the vials with the ‘prepared’ closures & allow to stand for 16 hours.

↓

For closures for dry preparations close 12 clean vials with the ‘prepared’ closures.

↓

Using a hypodermic needle with an external diameter of 0.8 mm inject 1 ml of water into the vial and remove 1 ml of air.

↓

Carry out this operation 4 times with new needle each time Pass the liquid in the vials through a filter with a pores size of 0.5 µm.

↓

No. of fragments is NMT 10 except in the case of butyl rubber closures where the total no. of fragments is NMT 15

# 3)Self – sealability test:

- This test is applicable to closures intended to be used with water close the vials with the ‘Prepared’ closures
- For each closure, use a new hypodermic needle with an external diameter of 0.8 mm & pierce the closure 10 times, each time at a different site.
- Immerse the vials upright in a 0.1% w/v solution of methylene blue & reduce the external pressure by 27KPa for 10 min.
- 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 ) PH OF AQUEOUS EXTRACT:

- 20ml of solution A is added with 0.1ml bromothymol blue when it is added with a small amount of 0.01M NaOH which changes the colour from blue to yellow. The volume of NaOH required is NMT 0.3ml and if it is done with HCl, the volume of HCl needed should NMT 0.8ml.

# 5 ) LIGHT ABSORPTION TEST:

- It must be done within 4hrs of preparing solution A. It is filtered through 0.5µ filter and its absorbance is measured at 220 to 360nm.Blank is done without closures and absorbance is NMT 2.0.

# 6 ) REDUCING SUBSTANCES:

20ml of solution A is added with 1ml of 1M $H_2SO_4$ and 20ml of 0.002M $KMnO_4$ and boil for 3min then cool and add 1gm of potassium iodide which is titrated with sodium thio-sulphate using starch as an indicator. Blank is done and the difference between titration volumes is NMT 0.7ml.

# 7 ) RESIDUE ON EVAPORATION:

- 50ml of solution A is evaporated to dryness at 105$^0$C.Then weigh the residue NMT 4mg.

# TEST FOR PLASTIC CONTAINERS:

- **1.For non-injectable preparations:**

  **Leakage test** / **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. Fill 10 containers with water Fit with closures Keep them inverted at room temp. 24hrs No signs of leakage

# 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 121Ċ, 30min Colourless , free from turbidity

# NON VOLATILE RESIDUE TEST:

- Non volatile residue test 2. Injectable preparations: a. Leakage test b. Collapsibility test C. Transperancy: Fill 5 containers with dil. Suspension. The cloudiness of 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 Evaporate 100ml extract Allow it to dry at 105Ċ Residue weighs not more than 12.5mg

# 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. 20Ċ and 25Ċ. Reweigh the containers. Loss in wt in each container is NMT 0.2% Specifications and tests of plastic container materials: Barium Heavy metals Tin zinc 19

Quality test is designed to achieve-

1. Consistency
2. Purity
3. Stability

And to avoid-

1. Damage
2. Contaimination
3. degradation

# Laboratory Analysis

- Visual inspection
- Identification test
- Dimentional test
- Physical test
- Chemical test
- Microbiologcal test
- Permormance measurements

# 1. Sterile product validation:-

a) ***Product and pack compatibility-*** the components must be washed and sterilized through a validated procedure. The vials must be filled with the sterile product under sterile conditions and terminally sterilized if this is a part of the intended product operation. Components performance should be monitored during the compatibility trials to ensure that deterioration has not occurred.
b) *Seal integrity*- the

b) ***Seal integrity-*** the seals of each vial should be examined before the experiment to ensure that there are no defectives, and then each vial should be inserted into a tray containing the challenge bacteria. The samples should be cycled through temperature and pressure changes expected on the market for several weeks. Careful cleaning of the vials and examination of contents for sterility will determine the seal quality.

# 2. Nonsterile product validation:-

a) ***Water vapour permeability-*** the water vapour permeability of the pack containing the product is required. This is necessary because although the bottles will comply with the water vapour permeability test described in USP, permeation through the bottle wall will depend on wheather the product has a high or low affinity for the water. The test split into two parts to enable the maximum amount of information to be obtained and hence possibly eliminating the necessity to perform further time consuming experiments.

·Bottle wall permeation
·Bottle and cap permeation

b) ***Light transmission-*** this test is to determine the effect of light passing through the bottle wall on the product stability and appearance. The bottle wall thickness can have a significant effect on the results obtained.

c) ***Product stability-*** it is unlikely that a compatibility problem, particularly with the film coated tablet, will occur, although it is necessary to check up full life of the product. There is possibility that either the smell or taste of tablets will be affected.

# COMPONENT SPECIFICATIONS

- Every detail concerning a component specification must be communicated to and agreed upon with the manufacture, including packaging, transportation, and labeling requirements. If any of the details are missing confusion or mistakes may occur.
- The main specifications requirements are the component drawing, artwork (printed components only) and the quality control testing and standards.

# CONCLUSION

The testing of packaging materials is almost requirement for any pharmaceutical industry. The material of a package affects quality, stability and efficacy of drug product. The cost of material of a package should be as low as possible without compromising the quality of product. It should pass the specifications of tests before it reached the local markets and made available to the consumers of product. The type of test followed should be according to requirements of regulatory agencies.


THANK YOU
FOR
LISTENING