# Sampling Guideline for Pharmaceutical Products and Related Materials, 2019

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Post-Marketing Control Division

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# SAMPLING GUIDELINES

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## 1. Introduction

It would be impossible and often impractical to test every individual product received in a consignment primarily owing to financial and time constraint. However, sampling provides the representative section of the entire consignment, which can be defined as subset of a consignment. This can be extrapolated back to the entire population of the consignment.

Sampling may be required for different purposes such as assessing the quality, identity, acceptance of consignments; inspection for customs clearance; or obtaining a retention sample.

The tests intended to be applied to the sample may include, but not limited to:

i. Verifying the identity
ii. Performing the assay
iii. Complete pharmacopoeial test
iv. Special test
v. Official test for individual dosage forms

## 2. Scope

This guideline describes the sampling operations to be followed for the sampling of:

i. Starting materials for use in the manufacture of finished pharmaceutical products;
ii. Pharmaceutical products (in-process as well as before and after packaging);
iii. Health supplements or herbal products
iv. Primary and secondary packaging materials; and
v. Cleaning and sanitizing agents, compressed gases and other processing agents.

## 3. Objective

This guideline is designed to guide sampler(s) on sampling of pharmaceutical products and related materials for a defined purpose.

## 4. Definition

**4.1** **Batch:** a quantity of any drug produced during a given cycle of manufacture. If the manufacturing process is continuous, the batch originates in a defined period of time during which the manufacturing conditions have not been modified.

**4.2** **Clean:** It means free of dust, rust and soil materials.

**4.3** **Consignment:** quantity of a drug product, made by one manufacturer that is supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include product belonging to more than one batch.

**4.4** **Extreme sample:** A selected sample that is likely to contain deteriorated, contaminated, adulterated or otherwise unacceptable material.

**4.5** **Homogeneity:** A product is regarded as homogeneous when it is all of the same origin (for example, from the same batch) and as non-homogeneous when it is of differing origins.

**4.6** **Sampling procedure:** It is the complete sampling operation to be applied to a defined product for a specific purpose. A detailed written description of the sampling procedure is provided as the sampling protocol.

**4.7** **Sampling method:** section of the sampling procedure dealing with the method prescribed for withdrawing samples.

**4.8** **Sampling plan:** description of the number of units or quantity of material that must be collected.

**4.9 Sampling record:** written record of the sampling operations carried out on a particular product for a defined purpose. This should be clearly recorded by sampler in the specified sample collection form.

**4.10 Sample:** a portion of a product collected according to a defined sampling procedure. The size of any sample should be sufficient to carry out all anticipated test procedures, including all repetitions. If the quantity of product available is not sufficient for the intended analysis and for the retention samples, the sampler must record that the sampled product is the available sample (see below) and the evaluation of the results must take account of the limitations deriving from the insufficient sample size.

**4.11 Random sample:** sample in which the different fractions of the product have equal probability of being represented.

**4.12 Representative sample:** sample obtained according to a sampling procedure designed to ensure that the different properties of a non-uniform material are proportionately represented.

**4.13 Retention sample:** sample collected and reserved for future controls. The size of a retention sample should be sufficient to allow at least two confirmatory analysis.

**4.14 Sampling unit:** discrete part of a consignment, such as an individual package, drum or container.

**4.15 Sampler:** person responsible for performing sampling operations.

**4.16 Uniformity:** A product may be considered uniform when samples drawn from different layers do not show significant differences in the quality-control tests. The assumption of uniformity is strengthened by homogeneity, i.e. when the consignment is derived from a single batch. Signs of non-uniformity include differences in shape, size or colour of particles in crystalline, granular or powdered solid substances, moist crusts on hygroscopic substances, deposits of solid material in liquid or semi-liquid products, and stratification of liquid

products. Such changes, some of which may be readily reversible, can occur during prolonged storage or exposure to extreme temperatures during transportation.

**4.17 Well-known source:** It refers to the Multi National Pharmaceutical firms and to the Pharmaceutical firms with no record of the quality defects for the past three years in the country.

## 5. Agencies concerned for sampling

The following agencies or entities may be responsible for sampling:

i. Drug Regulatory Authority

ii. Drug Testing Laboratory,

iii. Government or nongovernmental agencies involved in the acquisition of drug products;

The sampling agency may form a team to perform the sampling which should comprise of at least one member as witness from other relevant governmental agency as deemed necessary for proceedings having legal liabilities.

## 6. General precautions to be taken during sampling operations

### 6.1 Sampling Facility

All operations related to sampling should be performed with care, using proper equipment and tools as necessary. Any contamination of the sample by dust or other foreign material can affect the validity of the subsequent analysis and results. The sampling should be carried out in an area which reduces the risk of:

i. Contamination of the opened container, the materials and the operator,

ii. Cross contamination by other materials, products and environment,

iii. Harm to the individual who samples during the sampling procedure.

Sampling of sterile products should be carried out with great care. For the manufacturing firms, sample should be drawn from the dedicated sampling booth.

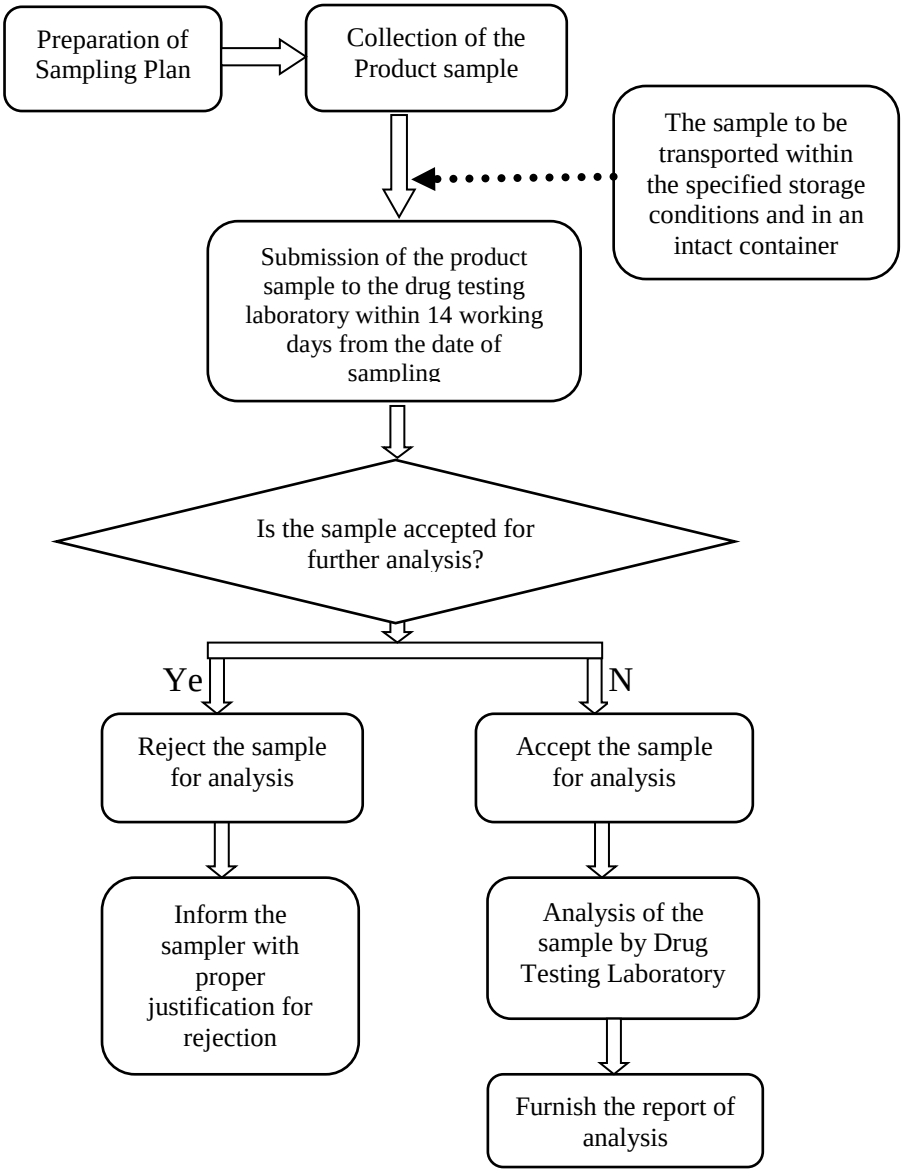
Generally, taking the original sales pack as a sample from outlets such as pharmacies or hospitals does not present problems. However, the inspector should ensure that the quantity of sample taken is sufficient for the intended analyses and for the retention samples, and that all units sampled are derived from the same batch and preferably from the same location. When Drug Inspector(s) draw sample from private pharmacies an amount equivalent to the MRP of the product should be compensated.

### 6.2 Health and safety

It is the responsibility of the sampler to read the relevant health and safety information (e.g. Safety data sheet etc.) before the sampling of the product. Necessary safety precautions and requirements for both the operator and the environment should be followed carefully.

The storage of samples should satisfy the requirements of safety as well as any other special precautions arising from the characteristic of the product being sampled.

## 7. Sampling process



## 7.1 Preparation for sampling

For the sampling of products at warehouses, the responsible person should have at his or her disposal necessary tools required to open the packages, barrels, containers, etc and necessary tools to label the containers to indicate that a part of the content has been removed from a package or container.

A variety of pipettes fitted with suction bulbs, cups or beakers, dippers and funnels are needed for liquids of low viscosity. The use of glass should be avoided. A suitable inert rod can be used for highly viscous liquid, and spatulas or scoops are needed for powdered and granular solids. Sterile pharmaceutical products should be sampled under aseptic conditions, and only when deemed absolutely essential, to avoid the risk of loss of sterility. All sampling tools and implements should be made of inert materials and kept scrupulously clean. After use or before reuse, they should be thoroughly washed, rinsed with water or suitable solvent, and dried. They should be stored in clean conditions.

## 7.2 Sampling operations and precautions

7.2.1 Sampling should be done in accordance with the approved written procedure that describes:

i. Method of sampling

ii. Equipment to be used

iii. Amount of sample to be taken

iv. Type and condition of sample container to be used

v. Identification of containers sampled

vi. Special precautions to be observed, especially with regard to sampling of sterile and noxious materials

vii. Storage conditions

viii. Instruction for cleaning of sampling equipments

7.2.2 All sampling procedures and operations should be documented using sample collection form (annexure I). Sampling should ensure that the representative samples are taken in sufficient quantity for testing in accordance with the specifications. Closures and labels should preferably be such that unauthorized opening can be detected. Samples should never be returned to the bulk. Supervision of the sampling process should be provided for new samplers.

7.2.3 The sampling procedure should take account of official and non official test required for individual dosage form. Non-official test include testing for adulteration and counterfeiting. The sampling procedure should also take account of the past experience, with the pharmaceutical product, the supplier, and number of sampling units in the consignment.

7.2.4 Labeling of the samples should provide appropriate details and may include product name, manufacturer, manufacturing date and expiry date, identification code, batch/lot no., quantity, date of sampling, place of sampling, purpose of sampling, storage conditions, handling, safety precautions etc. The container containing sample(s) should be labeled at the time of sampling.

7.2.5 The container has been punctured to take a sample, then the sampling hole should be closed appropriately and identified as made by authorized sampler. Sampled container should be labeled as they don't contain pre-claimed quantity.

### 7.3 Storage and retention of samples

7.3.1 The container used to store a sample should neither interact with the sampled material nor allow contamination. It should protect the sample from light, air, moisture, etc., as required by the manufacturer's storage directions for the product sampled. As a general rule, the container should be sealed, tamperproof and properly labeled.

7.3.2 If one sample is divided into several sample containers, they should be labeled individually with all the required details.

7.3.3 All samples should be packaged adequately and transported in such a way as to avoid any breakage, instability and contamination during transport. Security and adequate storage conditions should be ensured for the rooms where samples are stored.

7.3.4 Storage conditions of the retention sample(s) should be monitored.

### 7.4 Sampling during pharmaceutical inspections

7.4.1 For the purpose of the inspection of the deteriorated dosage forms by Drug Inspectors, the sample should consist of samples from one or several retail containers of the product from different locations.

7.4.2 When a complaint has been received about a drug product, the sample should be taken from the original container and, if possible, from one or more unopened containers of the same product bearing the same batch number.

### 7.5 Sampling during regular surveillance program

7.5.1 Drug Testing Laboratory and Drug Regulatory Authority should determine the extent to which routine surveillance should be undertaken considering the capacity of the drug testing laboratory; the extent to which the quality of products is assessed during registration; the extent to which the requirements for good manufacturing practice are implemented and; the number of products that are imported.

7.5.2 A systematic program of drug quality surveillance should be aimed at regular sampling of all marketed products. While sampling, priority should be accorded to products that are of prime importance to public health programmes; that are potentially dangerous and unstable; or difficult to formulate properly.

7.5.3 This surveillance programme should list the products to be sampled during a given period. Specify the sampling procedures and the size of the samples to be collected, taking into account the need for retention samples.

## 7.6 Sampling for acceptance of consignments

8.6.1 An appropriate sampling method of the consignments should be followed considering the following conditions:

i. Presumed homogeneity or nonhomogeneity

ii. Uniformity or nonuniformity

8.6.2 A consignment of a product from a single manufacturer labelled with a single batch number is assumed to be homogeneous. This assumption is further strengthened in the case of imported products provided with a batch certificate issued in the country of origin.

8.6.3 If the conditions of homogenity apply and if the size of the batch is reasonable, required number of sample for the intended analysis and retention should suffice. The size of such samples should be determined by the requirements of the analytical procedure according to which the product should be tested.

8.6.4 Depending upon the type of product, the size of the consignment, and the way in which the material is packaged, a sampling unit may be regarded as a box of vials or a box of jars of tablets rather than one of the individual vials or jars. The required number of unit dosage forms is then withdrawn from any individual container in the selected box.

8.6.5 If the consignment consists of one very large batch, or if little experience has been obtained with the product to be sampled, samples should then be taken from different sampling units.

## 8. Sampling of Starting materials

Testing of starting materials should be undertaken using samples collected in accordance with an appropriate procedure. If the material of a consignment can be regarded as uniform, the sample can be taken from any part of the consignment. If, however, the material is not physically uniform, special sampling tools may be required to withdraw a cross-sectional portion of the material. Alternatively, where applicable, a validated procedure can be followed to restore the uniformity of the material before sampling, based on information concerning the subsequent handling and manufacturing steps. For example, a stratified liquid may be stirred or a solid deposit in a liquid may be dissolved by gentle warming and stirring. Such interventions should not be attempted without adequate knowledge of the properties of the contents and appropriate discussions with the consignee of the goods. All partially processed natural products, both animal, herbal (dried plants and their parts) and mineral, should be treated as intrinsically non-uniform. Special procedures requiring considerable practice are needed to prepare representative samples from such consignments,

## 9. Sampling of Finished products

The quality of finished pharmaceutical products frequently needs to be verified at the time of their importation or purchase. The necessary sampling should be performed using an appropriate method and with regard to the presumed uniformity.

Sampling and testing may be adjusted according to experience with the specific source (e.g. manufacturer or supplier) of the product. If the consignment consists of one very large batch, or if little experience has been obtained with the product to be sampled, it may be prudent to carry out two independent analyses. Two independent final samples should then be taken from different sampling units.

Conversely, when a consignment is composed of two or three batches from the same manufacturer, a single sample taken from each batch may suffice, provided that favorable documented experience has previously been gained

with the product and the manufacturer, and that there is evidence from the expiry date, or other information, that the batches were produced at approximately the same time.

## 10. Sample size

Sample size plays a pivotal role in sampling. Choosing sample size depends on statistical and non-statistical considerations. Non-statistical considerations may include availability of resources, manpower, budget and ethics. Similarly, Statistical considerations may include level of precision, confidence level and degree of variability. The sample quantity must be big enough to perform analysis and to keep reserve samples.

## 11. Sampling plans for starting materials and finished products

Samples should be withdrawn from a single sampling unit if the consignment is intact and uniform without any signs of damage as it is not prudent to open all containers of products liable to deteriorate under the influence of moisture or oxygen. When this is not possible, a number of sampling units should be randomly selected for sampling. However, materials in damaged containers or found to be non-uniform should be individually sampled for a complete quality control. Unlabelled sampling units should be rejected.

Number of samples taken for the preparation of a representative sample should be determined statistically and specified in a sampling plan. The number of individual samples which may be blended to form a composite sample should be also be defined, taking into account the nature of the material, knowledge of the supplier and homogeneity of the composite sample.

For random sampling, whenever possible each sampling unit should be consecutively numbered. The required numbers of sampling units are then selected randomly using tables of random numbers. The number of units depends on different assumptions and three plans in this regard are given below.

### 11.1 The "n plan"

The "n plan" should be used with great caution and recommended only when the product is considered uniform and is supplied from a well-known source. The samples can be withdrawn from any part of the container (preferably from the top layer). A minimum number of containers needs to be sampled, e.g. if N is less than or equal to 4, then every container is sampled. According to this plan, original samples are taken from n sampling units selected at random and these are subsequently placed in separate sample containers. The control laboratory inspects the appearance of the material and tests the identity of each original sample according to the relevant specification. If the results are concordant, the original samples are combined into a final, composite sample from which an analytical sample is prepared, the remainder being kept as a retention sample.

The "n plan" is based on the formula

$$n = 1 + \sqrt{N}$$

Where:

"N" is the total number of sampling units in the consignment;

"n" is number of sampling units from where samples can be drawn.

If the value of n comes as a decimal place, it should be rounded up to the next higher whole number integer. According to this plan, original samples are taken from n sampling units selected at random.

### 11.2 The "p plan"

The "p plan" may be used when the product is uniform and is received from a source that is well known and tested by laboratories recognized by Drug Regulatory Authority. For this plan, samples are drawn using the formula:

$$p = 0.4\sqrt{N}$$

"p" samples are first tested for identity. If the results are concordant, it is further subjected for analytical tests.

Where:

"N" is the total number of sampling units in the consignment;

"p" is number of sampling units from where samples can be drawn.

### 11.3 The "r plan"

The "r plan" may be used when the product is suspected to be nonuniform and/or is received from a source that is not well known. The "r" plan" may also be used herbal medicinal products as starting materials. Samples are taken from N sampling units of the consignment and placed in separate sample containers. These N samples are transferred to the control laboratory and tested for identity. If the results are concordant, r samples are randomly selected and individually subjected to testing. If these results are concordant, the r samples are combined for the retention sample.

This plan is based on the formula

$$r = 1.5\sqrt{N},$$

Where:

"N" is the total number of sampling units in the consignment;

"r" is number of sampling units from where samples can be drawn.

The accompanying table gives the values of n, p and r according to the different plans.

Values of n, p or r for N sampling units;

| Value of n, p or r | Values of N | | |
|---|---|---|---|
| | **n plan** | **p plan** | **r plan** |
| 2 | up to 3 | up to 25 | up to 2 |
| 3 | 4-6 | 26-56 | 3-4 |
| 4 | 7-13 | 57-100 | 5-7 |
| 5 | 14-20 | 101-156 | 8-11 |
| 6 | 21-30 | 157-225 | 12-16 |
| 7 | 31-42 | | 17-22 |
| 8 | 43-56 | | 23-28 |
| 9 | 57-72 | | 29-36 |
| 10 | 73-90 | | 37-44 |

**Examples of use of sampling plans n, p and r**

Consider a consignment of 40 containers of a starting material.

**n Plan**

Assuming a uniform material from a recognized source where there is a high degree of confidence in the source. Using the n plan, samples would be taken from seven containers selected at random. The appearance and identity of each of these seven samples is checked. If the results are concordant, the seven samples are combined to produce a single, composite sample from which an analytical sample is prepared for full testing.

**p Plan**

Assuming a uniform material from a recognized source with the main purpose of checking the identity. Using the p plan, samples would be taken from three containers. The appearance and identity of each of these samples

is checked. If the results are concordant, the samples are used for retention (or full testing if required).

**r Plan**

Assuming the material is non-uniform and/or from a source that is not well-known

Using the r plan, samples would be taken from each container. The appearance and identity of each of these samples is checked. If the results are concordant, 10 samples are selected at random and individually subjected to full testing.

## 12. Sampling of inner container from a tertiary package

| Sl. No. | Total number of tertiary package per consignment | Number of inner cartons to be checked |
|---|---|---|
| **1.** | 1-2 | 1 |
| **2.** | 3-50 | 3 |
| **3.** | 51-100 | 4 |
| **4.** | 101-150 | 5 |
| **5.** | 151-200 | 6 |
| **6.** | 201-250 | 7 |
| **7.** | >250 | 8 |

## 13. Submission of sample for analysis

**13.1** At the time of submission of the sample for analysis by the sampler to the Drug Testing Laboratory, the sample should at least have 12 months shelf life. And for special cases an expiry of not less than 6 months can be accepted.

**13.2** The sample should reach the Drug Testing Laboratory within 2 weeks from the date of sampling with packaging specification as described in the section 6.3 of this guideline.

**13.3** The samples sent to the laboratory should be accompanied by a completely filled sample collection form (annexure I).

## 14. Reports for the Analysis

The Drug Testing Laboratory should furnish the analytical report to the sampler in the specified format.

## 15. Training of Samplers

Personnel who take samples should receive initial and on-going regular training in the disciplines relevant to correct sampling. The training should include:

i. Sampling plans

ii. Written sampling procedure

iii. Techniques and equipment for sampling

iv. Risks of cross-contamination

v. Precautions to be taken with regard to unstable and/or sterile substances

vi. Importance of considering the visual appearance of materials, containers and labels

vii. Importance of recording any unexpected or unusual circumstances.

## 16. Reference

***16.1*** *WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report. Geneva, World Health Organization, 2005 (WHO Technical Report Series No. 929), Annex 4.*

***16.2*** *Good practices for national pharmaceutical control laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report. Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902), Annex 3.*

***16.3*** *Guidelines on packaging for pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report. Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 929), Annex 9.*

**16.4** *EU GMP Annex 8: Sampling of starting and packaging materials,*

***16.5*** *SOP for finished product inspection and release in pharmaceuticals from pharmastate blog,*

**16.6** *Food, Health and Medicine (fhm-unlimited.blogspot.com)*

***Annexure I: Drug product Sample Collection Form***

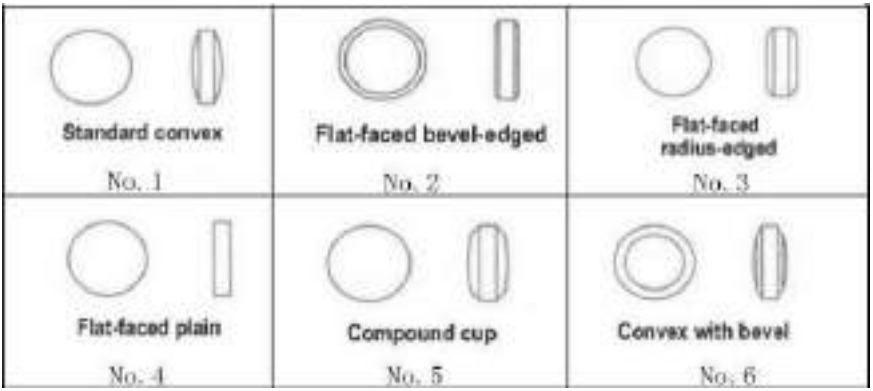
| **A. SAMPLE INFORMATION** | |
|---|---|
| Sample Serial Number/Identification code: _____ | |
| Name of place where sample was taken: | |
| Address of the sampling collection source (with telephone and fax number, if applicable) | |
| Date of sampling (dd/mm/yy): | |
| Drug Name (trade or brand name): | |
| Generic or INN name: | |
| Pharmacopoeial standard of the product: | |
| Dosage form and strength: | |
| Manufacturer's Batch or Lot Number | |
| Manufacturing date: | |
| Expiry date : | |
| Registration number (if applicable): | |
| Manufacturer name and address: | |
| Number of sample units taken (minimum 50 tablets or capsules; and 10 for injectables) | |
| □ taken in original package | □ taken from bulk container |
| Brief physical/visual description of sample(if any): | |

| B. PHYSICAL/VISUAL INSPECTION TEST | |
|---|---|
| | Remarks (Yes/ No) |
| **Labeling (requirements)** | |
| Brand Name of the drug sample (if applicable) | |
| Generic or INN name of active ingredient(s) | |
| Dosage form and strength | |
| Name of reference standard used (as claimed on label e.g. USP, BP, IP, EP) | |
| Manufacturer's Batch or Lot Number | |
| Name of manufacturer and address (with telephone and fax number if applicable) | |
| Manufacturing date | |
| Expiry date | |
| Storage conditions | |

| **Packaging** | Remarks |
|---|---|
| Material (blister pack/card, bottle, others specify) | |
| Unit dose per blister card or container stated | |
| Any print on the backing foil (if packed in blister pack or card) | |

| **Description of dosage form** | |
|---|---|
| Shape (circular, oval, flat sides, other) | |
| Uniformity of shape | |
| Uniformity of color | |
| No physical damage (cracks, breaks, erosion, abrasion, sticky) | |
| Other observations (no foreign contaminant, dirty marks, proper seal - for capsule) | |
| **C. LABORATORY TESTS REQUESTED:** | |
| | |
| Name of sampler(s):<br><br>Address (telephone no. and fax no.):<br><br>Dated signature of the sampler: | |
| Name of representative of establishment where sample was taken:<br><br>Dated signature: | |

## *Annexure II: Reference for tablet shapes*

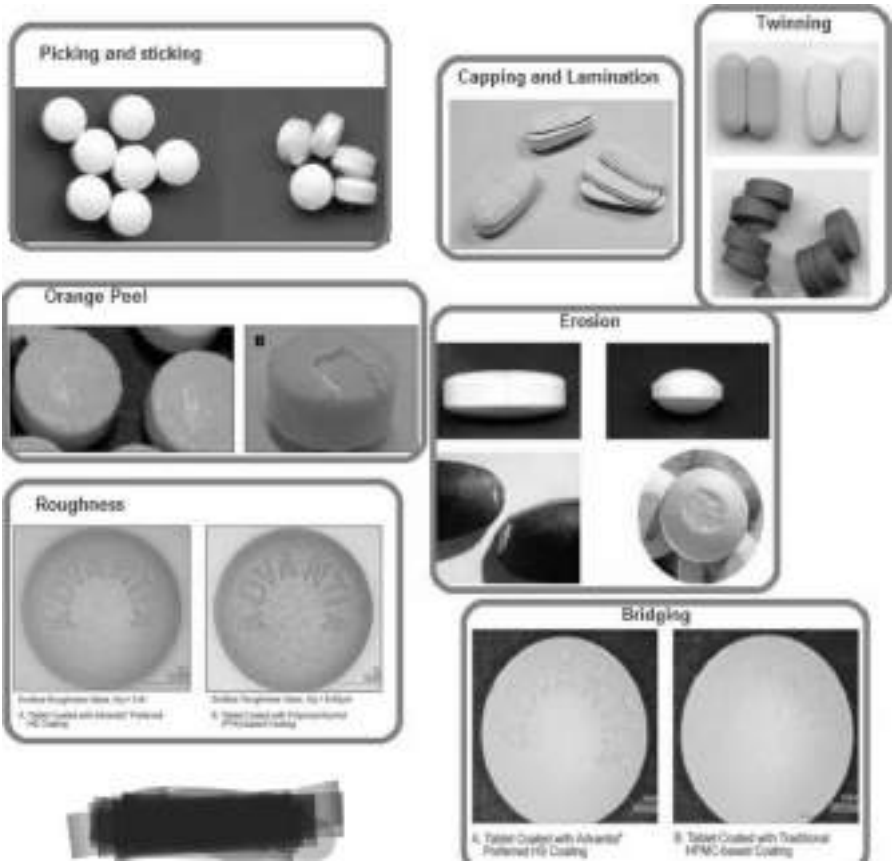


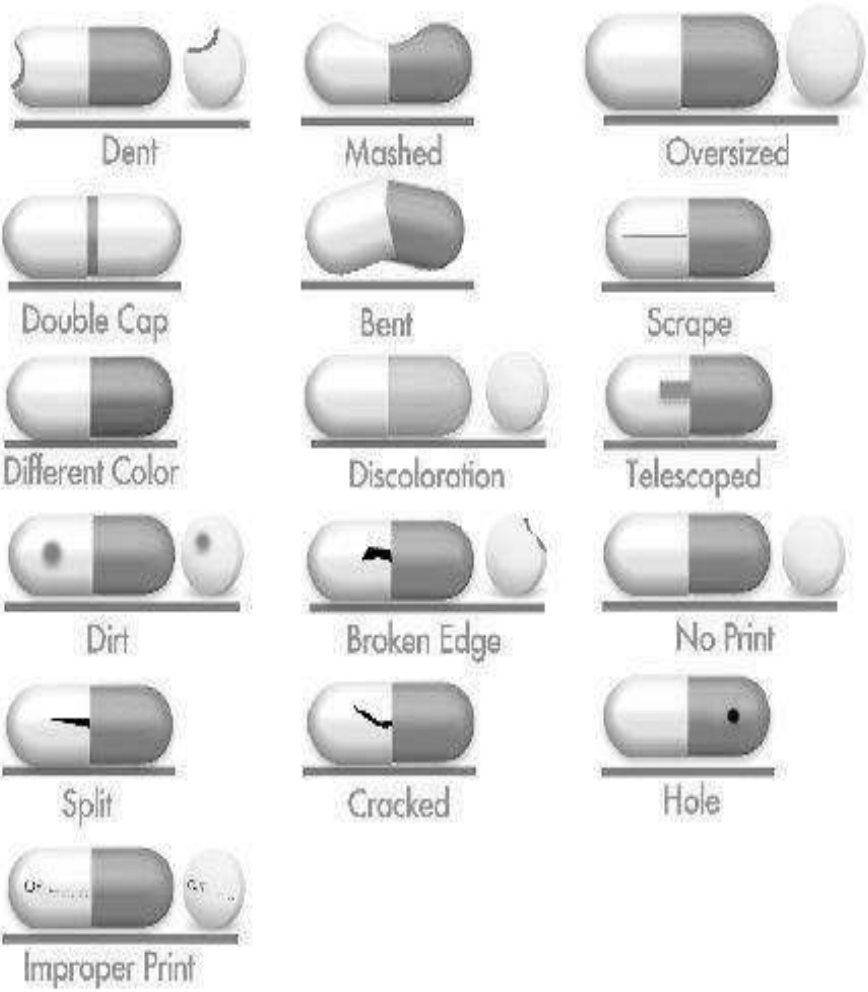
***Annexure-III: General and specific test requirements for pharmaceutical dosage forms.***

| Sl. No | Types of dosage forms | General test requirement | Specific test requirement |
|---|---|---|---|
| 1. | Tablets/capsules/ suppositories | -Visual inspection<br>-Identification of active ingredient | -Disintegration test<br>-Dissolution test<br>- Uniformity of mass<br>- Hardness test<br>- Friability test<br>- Assay<br>-Uniformity of content |
| 2. | Parenteral preparations | -Visual inspection<br>-Identification of active ingredient | -Test for sterility<br>-Pyrogen test<br>-Particulate matter<br>-Extractable volume<br>-Uniformity of weight (powders for inj.)<br>-Clarity of the solution<br>-Assay<br>-Uniformity of content |
| 3. | Eye, ear and nasal preparations | -Visual inspection<br>-Identification of active ingredient | -Test for sterility<br>-Particle size test<br>-Uniformity of volume<br>-Uniformity of consistency for ointments.<br>-Uniformity of delivered dose for inhalations.<br>-Assay<br>-Uniformity of content |

| | | | |
|---|---|---|---|
| 4. | Topical semi-solid preparations | -Visual inspection<br><br>-Identification of active ingredient | -Sterility test as required<br>-Uniformity of weight<br>-Uniformity of consistency<br>-pH<br>-Dissolution test for patches<br>-Assay<br>-Uniformity of content |
| 5. | Oral liquids | -Visual inspection<br><br>-Identification of active ingredient | -Weight/volume<br>-Specific gravity<br>-pH<br>-Assay<br>-Uniformity of content. |
| 6. | Powders | -Visual inspection<br><br>-Identification of active ingredient | -Powder finesse<br>-Flowability<br>-Uniformity of weight<br>-Assay<br>-Uniformity of content. |

## *Annexure IV: Common defects of tablet and capsules*




Dent
Mashed
Oversized
Double Cap
Bent
Scrape
Different Color
Discoloration
Telescoped
Dirt
Broken Edge
No Print
Split
Cracked
Hole
Improper Print

**Drug Regulatory Authority**

*Promoting availability of quality, safe and efficacious medicinal products for consumers*

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