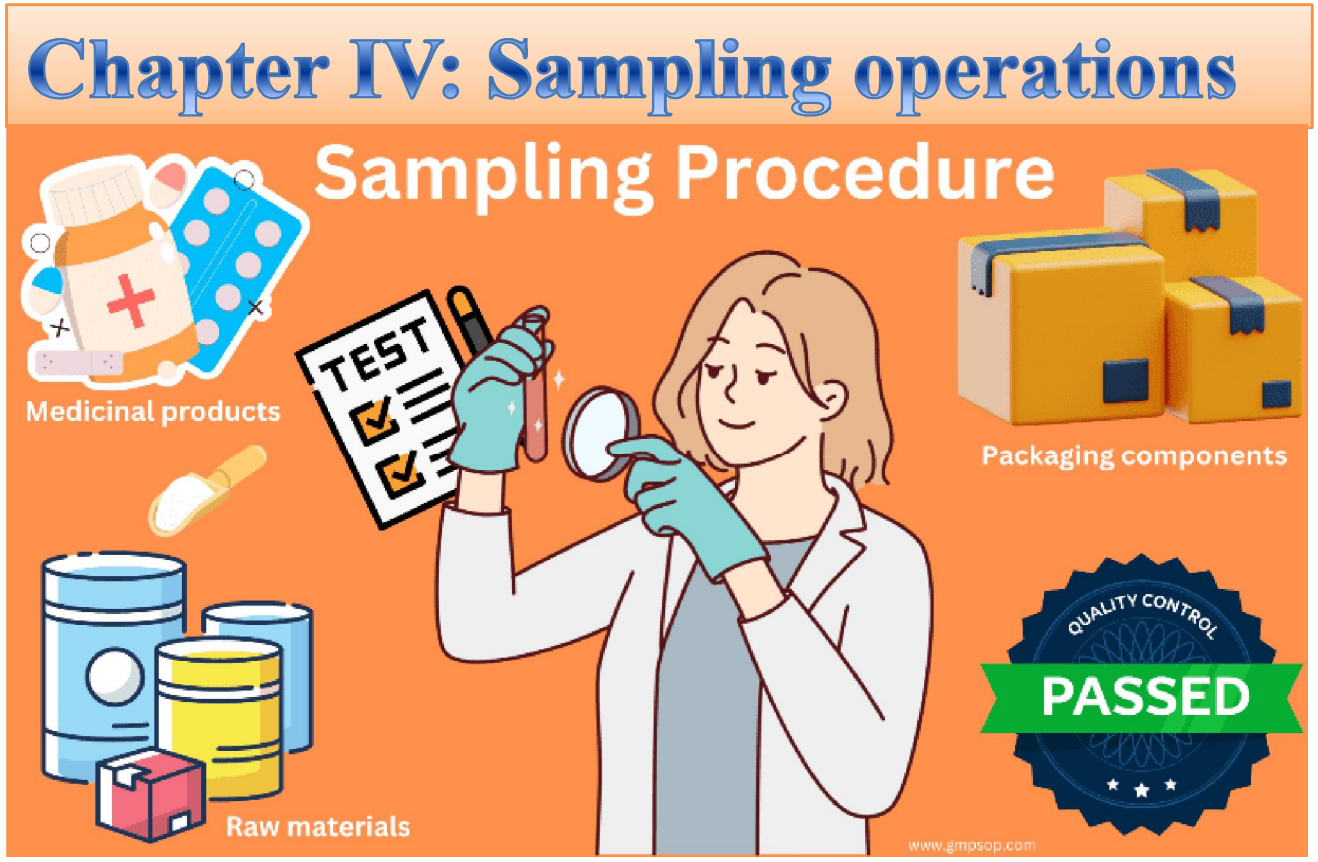
Master 2: Pharmaceutical Chemistry

Module: Drug Analysis and Control



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1. Introduction

Sampling comprises the operations designed to select a portion of a pharmaceutical product for a defined purpose. The sampling procedure should be appropriate to the purpose of sampling, to the type of controls intended to be applied to the samples and to the material to be sampled. All operations related to sampling should be performed with care, using proper equipment and tools. Any contamination of the sample by dust or other foreign material is liable to jeopardize the validity of the subsequent analyses.

2.Glossary

Available sample

Whatever total quantity of sample materials is available.

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 are stable and have not been modified.

Original sample

Sample collected directly from the material.

Final sample

Sample ready for the application of the test procedure.

Random sample

Sample in which the different fractions of the material have an equal probability of being represented.

Representative sample

Sample obtained according to a sampling procedure designed to ensure that the different parts of a batch or the different properties of a non-uniform material are proportionately represented.

Retention sample

Sample collected as part of the original sampling process and reserved for future testing. The size of a retention sample should be sufficient to allow for at least two confirmatory analyses. In some cases statutory regulations may require one or more retention samples, each of which should be separately identified, packaged and sealed.

Combined sample

Sample resulting from combining all or parts of two or more samples of the material.

Consignment

The quantity of a bulk starting material, or of a drug product, made by one manufacturer or supplied by an agent, and supplied at one time in response to a particular request or order. A consignment may comprise one or more lot identified packages or containers and may include material belonging to more than one lot-identified batch.

Homogeneity

A material is regarded as homogeneous when it is all of the same origin (e.g. from the same batch) and as non-homogeneous when it is of differing origins.

Uniformity

A starting material may be considered uniform when samples drawn from different layers do not show significant differences in the quality control tests which would result in non-conformity with specifications. The following materials may be considered uniform unless there are signs to the contrary: organic and inorganic chemicals; purified natural products; various processed natural products such as fatty oils and essential oils; and plant extracts. The assumption of uniformity is strengthened by homogeneity, i.e. when the consignment is derived from a single batch.

Sample

A portion of a material collected according to a defined sampling procedure. The size of any sample should be sufficient to allow all anticipated test procedures to be carried out, including all repetitions and retention samples. If the quantity of material available is not sufficient for the intended analyses and for the retention samples, the inspector should record that the sampled material is the available sample (see Sampling record) and the evaluation of the results should take account of the limitations that arise from the insufficient sample size.

Sampler

Person responsible for performing the sampling operations.

Sampling method

That part of the sampling procedure dealing with the method prescribed for withdrawing samples.

Sampling plan

Description of the location, number of units and/or quantity of material that should be collected, and associated acceptance criteria.

Sampling procedure

The complete sampling operations to be performed on a defined material for a specific purpose. A detailed written description of the sampling procedure is provided in the sampling protocol.

Sampling record

Written record of the sampling operations carried out on a particular material for a defined purpose. The sampling record should contain the batch number, date and place of sampling, reference to the sampling protocol used, a description of the containers and of the materials sampled, notes on possible abnormalities, together with any other relevant observations, and the name and signature of the inspector.

Sampling unit

Discrete part of a consignment such as an individual package, drum or container.

Selected sample

Sample obtained according to a sampling procedure designed to select a fraction of the material that is likely to have special properties. A selected sample that is likely to contain deteriorated, contaminated, adulterated or otherwise unacceptable material is known as an extreme sample.

Prequalification

The activities undertaken in defining a product or service need, seeking expressions of interest from enterprises to supply the product or service, and examining the product or service offered against the specification, and the facility where the product or service is prepared against common standards of good manufacturing practice (GMP). The examination of the product or service and of the facility where it is manufactured is performed by trained and qualified inspectors against common standards. Once the product is approved, and the facility is approved for the delivery of the specified product or service, other procurement agencies are informed of the approval. Prequalification is required for all pharmaceutical products regardless of their composition and place of manufacture or registration, but the amount and type of information requested from the supplier for use in the assessment by the procurement agency may differ.

Pharmaceutical product

Any material or product intended for human or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in the exporting state and/or the importing state.

Production

All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing, packaging and repackaging, labelling and relabelling, to completion of the finished product.

3. Purpose of sampling

Sampling may be required for different purposes, such as pre-qualification; acceptance of consignments; batch release testing; in-process control; special controls; inspection for customs clearance, deterioration or adulteration; or for obtaining a retention sample.

The tests to be applied to the sample may include:

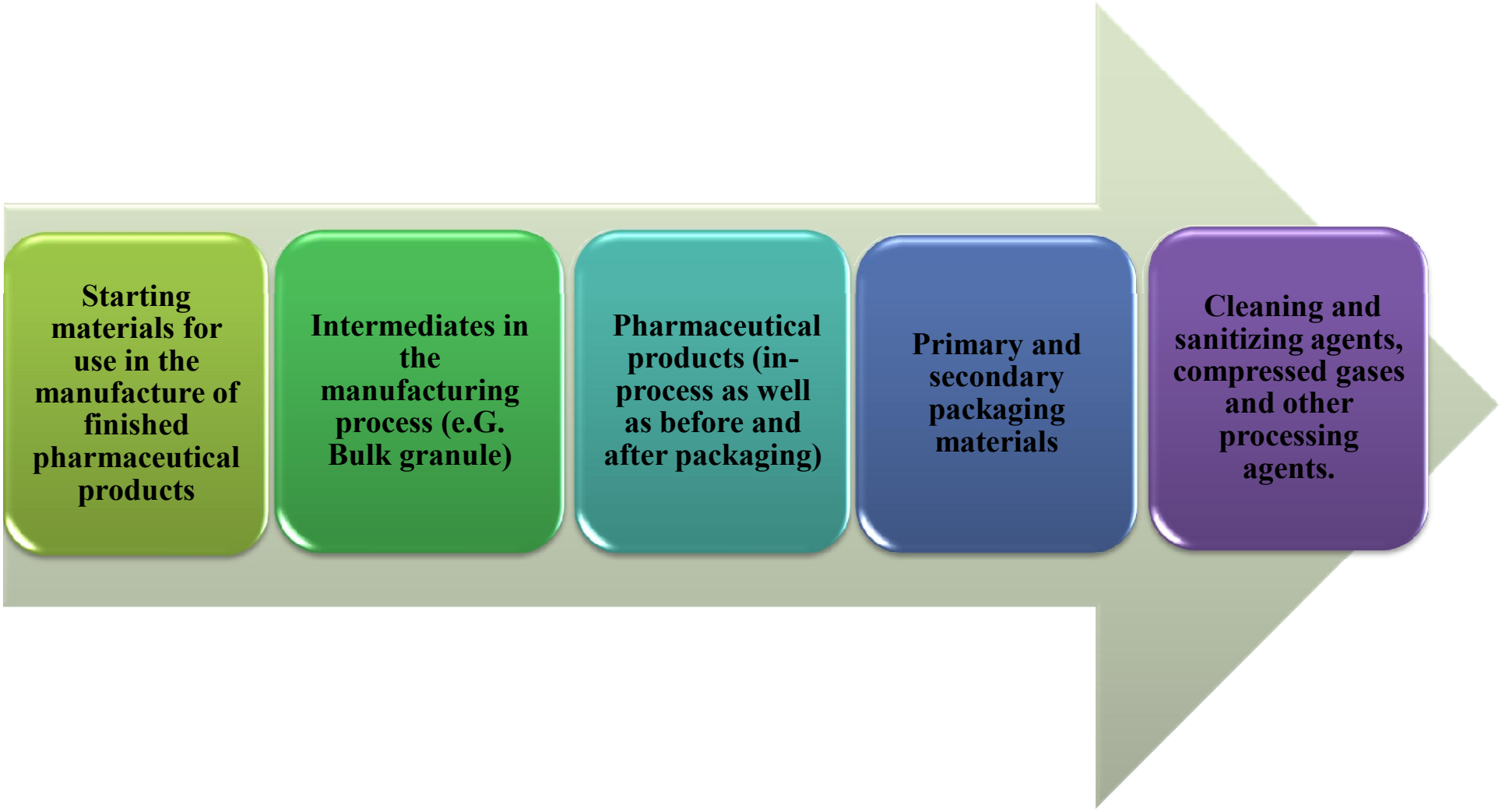
— verifying the identity;

— performing complete pharmacopoeial or analogous testing; and

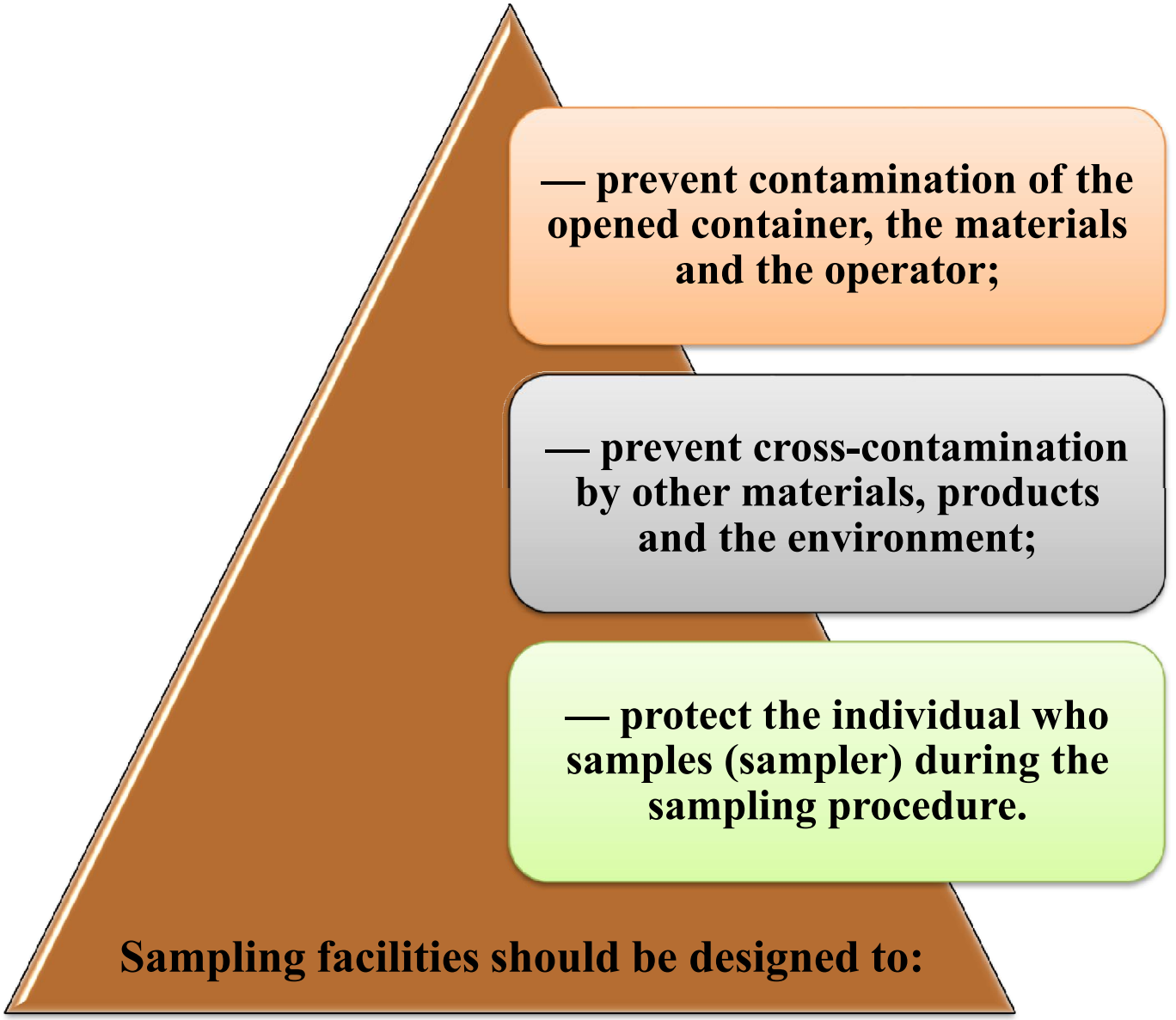
— performing special or specific tests.

4. Classes and types of pharmaceutical products and related materials

The materials to be sampled may belong to the following classes:



5. Sampling facilities



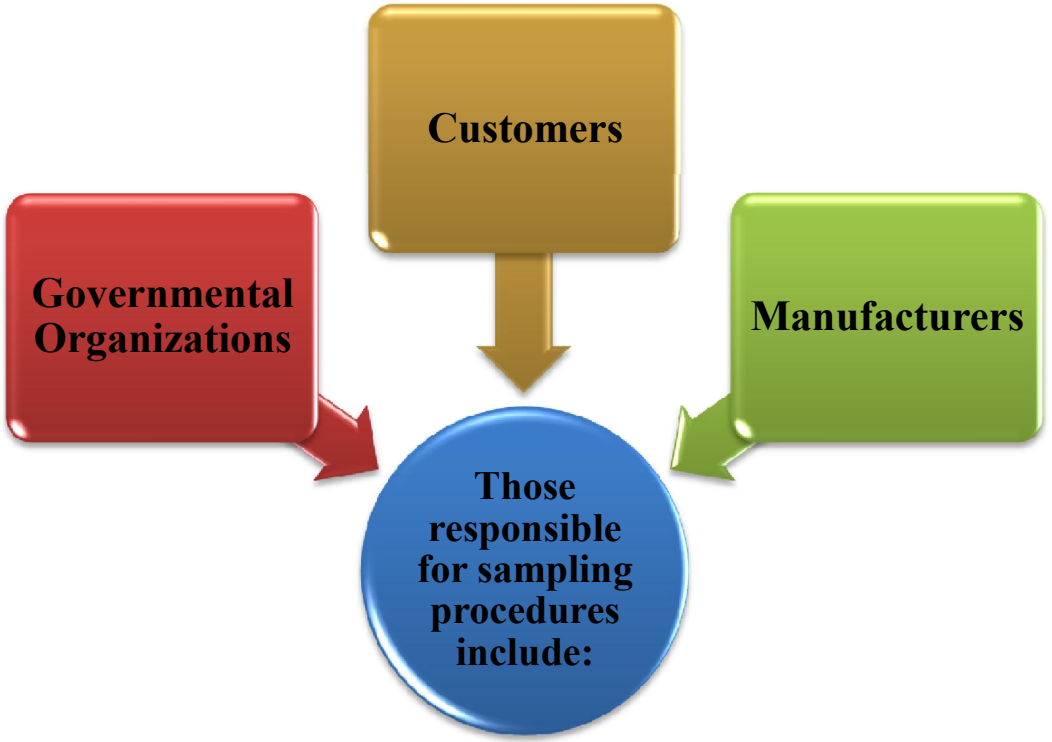
•Where possible, sampling should be performed in an area designed for and dedicated to this purpose, although this will not be possible where samples are required to be taken from a production line (e.g. in-process control samples). The area in which the sample was taken should be recorded in the sampling record.

•Sampling from large containers of starting material or bulk products can present difficulties. Whenever possible, this work should be carried out in a separate, closed cubicle within the warehouse, to reduce the risk of contamination (e.g. by dust) of either the sample or the materials remaining in the container, or of cross-contamination.

6. Responsibilities for sampling

such as drug control authorities (including inspectorates); quality control laboratories; customs and police authorities responsible for the clearance of drug products held in quarantine after manufacture or importation, and for the detection of pharmaceutical products that have deteriorated or have been contaminated, adulterated or counterfeited.

such as governmental or nongovernmental agencies involved in the acquisition of drug products.



in the context of good manufacturing practices (GMP)

The samplers need to :

- **be adequately trained in the practical aspects of sampling,**
- **qualified to perform the sampling operation,**
- **should have sufficient knowledge of pharmaceutical substances to allow them to execute the work effectively and safely,**
- **The sampler should remain alert to any signs of contamination, deterioration or tampering**

7. Health and safety

The sampler should :

•read the relevant health and safety information (e.g. the safety data sheet for a pharmaceutical product and related materials) before sampling the material. The information should include necessary safety precautions and requirements for both the operator and the environment.

•wear appropriate protective clothing for the task. If specific safety precautions are required, such as the use of respiratory equipment, the sampler should be properly trained in its use.

•have safe access to and egress from the place where the sample is taken, and the places where the samples are taken for storage. The sample storage areas should have adequate light and ventilation and should be arranged to satisfy the requirements for safety as well as any special ones arising from the characteristics of the material being sampled.

Care should be taken to guard against collapse of stacked containers or solids in bulk.

8.Sampling process

1. Preparation for sampling

For the sampling of products, the responsible person should have at his or her disposal all the tools needed to open the containers

knives

pliers

saws

hammers

wrenches

vacuum cleaner

sealing tape

self-adhesive labels

•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. Adequate washing facilities should be provided in, or in close proximity to, the sampling area, otherwise samplers will need to bring separate clean sets of implements for sampling each product.

•The cleaning procedure used for all sampling tools and implements should be documented and recorded. The adequacy of the cleaning procedure for the material from which the sampling tool is made should be demonstrated. The use of disposable sampling materials has distinct advantages.

2. Sampling operation and precautions

- **Sampling procedure should include the details of the health and safety aspects of sampling.**
- **Sampling procedure should ensure that representative samples are taken in sufficient quantity for testing in accordance with specifications.**
- **Samples should never be returned to the bulk.**
- **The sampling process should be appropriately supervised and documented (see Appendix 2 for an example of a sample collection form).**
- **The sampling procedure should be such that non-uniformity of the material can be detected.**
- **During the sampling procedure, attention should be paid to any signs of nonconformity of the material (differences in shape, size or colour of particles in crystalline, granular or powdered solid substances; moist crusts on hygroscopic substances; deposits of solid pharmaceutical product 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).**
- **Homogeneous portions of the material or bulk such as those mentioned above should be sampled and tested separately from the rest of the material that has a normal appearance.**

➢**Pooling of the samples from the different portions should be avoided, because this can mask contamination, low potency or other quality problems.**

➢**Labelling of samples should provide appropriate details, including the batch number and, if known, the container number from which the sample was taken, the amount taken and for what purpose. Labels should be applied at the time of sampling. The container used to store the sample should also be properly labelled with appropriate details such as sample type, name of material, identification code, batch/lot number, code, quantity, date of sampling, storage conditions, handling precautions and container number.**

3. Storage and retention

•The container used to store a sample :

- **should not interact with the sampled material (inert) nor allow contamination.**
- **should also protect the sample from light, air and moisture, as required by the storage directions for the pharmaceutical product or related material sampled.**

•Liquid samples should be transported in suitable bottles closed by screw tops with inert liners that provide a good vapour-proof (moisture-proof) seal for the contents.

•Suitable screw-top jars in exceptional cases only should be used for solid or semi-solid pharmaceutical products.

•Light-sensitive materials should be protected by using amber glass containers or by wrapping colourless glass containers in foil or dark coloured paper. Headspace should be kept to a minimum to minimize any possible degradation. Any special procedures, for example, nitrogen gassing, should be discussed with the consignee of the material and carried out as appropriate.

• Solid dosage forms such as tablets or granules should be protected during transit, either by totally filling the container with the product or by filling any residual space with a suitable material. All samples should be packaged adequately and transported in such a way as to avoid breakage and contamination during transport.

• Security and adequate storage conditions should be ensured for the rooms in which samples are stored.

• Samples should be stored in accordance with the storage conditions as specified for the respective active pharmaceutical ingredient (API), excipient or drug product.

9.Sampling plans for starting materials, packaging materials and finished products

• Quality of pharmaceutical products majorly depends upon the sampling of the excipients and the API. Proper sampling can give us confidence in our analysis. In other words, sampling is a starting process but it has its importance.

• The number of containers to be samples is an interesting part of the raw material sampling because if we receive 5000 containers of an excipient then it shall be very difficult to sample all containers and it is difficult too to analyze the thousands of samples. In such cased, sampling plans are used to reduce the sampling and analysis of a large number of containers.

•Generally, in pharmaceuticals, $1 + \sqrt{N}$ formula is used to determine the number of containers to be sampled. Where N is the number of containers received. This formula is used to reduce the sampling of a large number of containers of the excipient.

1 Sampling PLAN for Starting Materials

WHO suggests 3 formulae of sampling for pharmaceutical ingredients :

'n' plan
- **Material is uniform**
- **Supplied from a recognized source**
- **Drawn from any part of the container (usually from the top layer)**
- **The formula :**
  - **$n = 1 + \sqrt{N}$**
  - **N is the number of sampling units in the consignment.**
  - **The value of n is obtained by simple rounding**

'p' plan
- **Material is uniform**
- **Supplied from a recognized source**
- **The main purpose is to test for identity**
- **The formula :**
  - **$p = 0.4\sqrt{N}$**
  - **N is the number of sampling units in the consignment.**
  - **p are obtained by rounding up to the next highest integer**

r' plan
- **Material is suspected to be non-uniform**
- **Received from a source that is not well known**
- **The formula :**
  - **$r = 1.5\sqrt{N}$**
  - **N is the number of sampling units in the consignment.**
  - **r are obtained by rounding up to the next highest integer.**

Values of n, p or r for the N (number of containers received) 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***

samples taken from 7 containers selected at random. The appearance and identity of each of these 7 samples is checked. If the results are concordant, the 7 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***

samples taken from each container . The appearance and identity of each of these samples is checked. If the results are concordant, the samples are appropriately combined to form 3 final, composite samples to be 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***

samples 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.

References

1. Good practices for national pharmaceutical control laboratories. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report. Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902), Annex 3.
2. World Health Organization. *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Good manufacturing practices and inspection*. Vol. 2. World Health Organization, 2007.
3. Guidelines on packaging for pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report. Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902), Annex 9.