

Annex 4

WHO guidelines for sampling of pharmaceutical products and related materials

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1. Introduction

These guidelines are primarily intended for use by governmental organizations, such as drug regulatory authorities (including inspectorates), quality control laboratories and customs and police officials, but some of the general principles may also be appropriate for application by procurement agencies, manufacturers and customers.

These guidelines should be useful when surveying the national markets for the quality of drug products in accordance with national drug quality surveillance programmes for marketed products, whether registered for sale or compounded in pharmacies.

The choice of a sampling plan should always take into consideration the specific objectives of the sampling and the risks and consequences associated with inherent decision errors. The bibliography at the end of this Annex should be consulted when justifying a sampling plan for a given purpose.

1.1 General considerations

Sampling comprises the operations designed to select a portion of a pharmaceutical product (for definition, see glossary) 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. The procedure should be described in writing.

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.

1.2 Glossary

The definitions given below apply to the terms as used in these guidelines. They may have different meanings in other contexts.

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.

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.

Final sample

Sample ready for the application of the test procedure.

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.

Original sample

Sample collected directly from the material.

Pharmaceutical product

Any material¹ 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.

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

¹ "Material" is used in the document for "pharmaceutical products and related materials".

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.

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.

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.

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*.

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.

1.3 **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.

1.4 **Classes and types of pharmaceutical products and related materials**

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

- starting materials for use in the manufacture of finished pharmaceutical products;
- intermediates in the manufacturing process (e.g. bulk granule);
- pharmaceutical products (in-process as well as before and after packaging);
- primary and secondary packaging materials; and
- cleaning and sanitizing agents, compressed gases and other processing agents.

1.5 **Sampling facilities**

Sampling facilities should be designed to:

- prevent contamination of the opened container, the materials and the operator;
- prevent cross-contamination by other materials, products and the environment; and
- protect the individual who samples (sampler) during the sampling procedure.

Where possible, sampling should be performed in an area or booth 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 and a sequential log should be kept of all materials sampled in each area.

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.

Some materials should be sampled in special or dedicated environments (e.g. when sampling articles for which contamination with dirt

or particles from the environment should be avoided, such as aerosol valves, hormones and penicillins).

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.

1.6 Responsibilities for sampling

Those responsible for sampling procedures include:

- *governmental organizations*, 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;
- *customers* such as governmental or nongovernmental agencies involved in the acquisition of drug products; and
- *manufacturers* 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, and should have sufficient knowledge of pharmaceutical substances to allow them to execute the work effectively and safely. Given that the sampling technique itself can introduce bias, it is important that personnel carrying out the sampling should be suitably trained in the techniques and procedures used. The training should be documented in the individual's training records. Sampling records should clearly indicate the date of sampling, the sampled container and the identity of the person who sampled the batch.

A conscientious approach, with meticulous attention to detail and cleanliness, is essential. The sampler should remain alert to any signs of contamination, deterioration or tampering. Any suspicious signs should be recorded in detail in the sampling record.

If a governmental agency needs to sample a sterile or bulk pharmaceutical product at the manufacturing site, it may be best to have the manufacturer's personnel collect the sample, using their own procedures. The regulatory inspector would observe the procedure in such a way as not to increase the chance of contamination (e.g. for sterile pharmaceutical products, the inspector would observe through

a glass window outside the aseptic sampling area) and to preclude the possibility of the inspector inadvertently contaminating the remaining bulk pharmaceutical product through poor procedures, for example.

1.7 Health and safety

It is the responsibility of the sampler to 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.

The sampler should 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.

The sampler should 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.

2. Sampling process

2.1 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 (e.g. packages, barrels and others). Tools may include knives, pliers, saws, hammers, wrenches, implements to remove dust (preferably a vacuum cleaner), and material to reclose the packages (such as sealing tape), as well as self-adhesive labels to indicate that some of the contents have been removed from a package or container. Containers due to be sampled should be cleaned prior to sampling if necessary.

Sampling of uniform starting materials does not require complicated tools. 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.

The tools for sampling non-uniform materials are more complicated and more difficult to clean. For example, a sampling tube with a shutter at the lower end may be used to sample liquids in drums or other large containers and a slotted tube with a pointed end may be used to sample solids. It is important to follow the manufacturer's instructions for the use of sampling devices.

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.

Examples of sampling tools suitable for each type of material are given in Appendix 1.

2.2 **Sampling operation and precautions**

There should be a written procedure describing the sampling operation. This should include details of the health and safety aspects of sampling. It should ensure that representative samples are taken in sufficient quantity for testing in accordance with specifications. Closures and labels should preferably be such that unauthorized opening can be detected. 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.

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 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.

For finished drug products, the sampling procedure should take account of the official and non-official tests required for the individual dosage form (e.g. tablets or parenteral preparations). Non-official tests could include testing for adulteration and counterfeiting.

The sampling procedure should also take account of past experience with the pharmaceutical product or related material and with the supplier, and of the number of sampling units in the consignment.

Examples of steps for sampling are given in Appendix 3.

When a container is sampled outside the control of the consignee of the product, the following precautions should be taken. If the tamper-proof seal is broken to obtain a sample, then the consignee of the product should be informed and the container resealed with an appropriate tamper-proof seal, and the consignee of the product informed of its type and its identification. If a bag has been punctured to take a sample, then the sampling hole should be appropriately closed and identified as a sampling hole made by an authorized sampler. Sampled containers should be identified, as they may no longer contain the quantity of product stated on the label. In accordance with national legislation there may be exceptions, e.g. during ongoing investigations of cases related to counterfeit pharmaceutical products.

2.3 Storage and retention

The container used to store a sample should not interact with the sampled material nor allow contamination. It should also protect the sample from light, air and moisture, as required by the storage directions for the pharmaceutical product or related material sampled. As a general rule the container should be sealed and preferably tamper-evident.

Samples of loose materials, whether solid or liquid, should be placed in one or more clean containers. 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. The container should be inert. 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 containers should be sealed and labelled, and all samples should be packaged adequately and transported in such a way as to avoid breakage and contamination during transport.

For all containers that come apart (e.g. screw-capped jars or metal tins with separate lids) precautions should be taken to avoid any mix-up when they are opened for examination, such as by labelling all parts of each container whenever possible.

If one sample is divided into several sample containers, they should be transported in a suitably sealed box, which should be labelled with the identity of the product, the consignment from which the sample was drawn, the size of the sample, the date and place of sampling, and the name of the inspector.

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. Packaging materials similar to those in which the bulk is supplied should be used for long-term storage.

Examples of types of containers used to store samples of starting materials and bulk products are given in Appendix 4.

3. **Regulatory issues**

When sampling for regulatory purposes, additional samples for regulatory testing and verification purposes should be provided (e.g. for duplicate testing and parallel testing by different regulatory

laboratories and by the consignee of the product). The consignee of the product should be informed that samples have been taken, and should the consignee wish to conduct his/her own testing of the sample taken for regulatory purposes, regulatory authorities should provide a sample to the consignee of the goods.

Sampling of products for prequalification purposes may follow similar procedures.

3.1 **Pharmaceutical inspections**

Pharmaceutical inspectors may take samples from retail or hospital pharmacies (including samples of preparations manufactured in bulk on the premises), or from industry and wholesalers for a variety of reasons, such as:

- routine monitoring and control;
- following the suspicion or discovery of products that show signs of possible deterioration, contamination, adulteration or counterfeiting; and
- when a particular product is suspected of being either ineffective or responsible for adverse clinical reactions.

For deteriorated dosage forms, the sample should consist of one or more retail containers of the product that shows visual signs of deterioration.

When a complaint has been received about a drug product, the sample should include the original container and, if possible, one or more unopened containers containing the same product and bearing the same batch number. There should be good communication between the regulatory authority and the consignee of the goods concerning the findings and any necessary corrective action.

3.2 **Surveillance programmes**

National drug regulatory authorities are responsible for monitoring the quality of all drug products marketed in their country and as defined by legislation. The extent to which routine surveillance should be undertaken, as opposed to assessment of suspect products, will depend upon factors such as:

- the capacity of the national quality control laboratory;
- the extent to which the quality of the product has been assessed prior to registration;
- the extent to which the requirements for GMP are implemented; and
- the number of products that are imported from abroad.

A systematic programme of drug quality surveillance should be in place which may include sampling of marketed products, whether registered for sale or compounded in pharmacies, as deemed necessary. Each product should be assessed regularly (e.g. every 2–3 years) for inclusion in the surveillance programme, but particular attention should be accorded to products that are of prime importance to public health programmes or that are potentially dangerous, unstable or difficult to formulate properly.

The responsible laboratory should draw up the sampling programme, if necessary under the guidance of the drug regulatory authority, on a yearly or half-yearly basis. This programme should not only list the products to be sampled during a given period, but should also specify the sampling procedures and the size of the samples to be collected, taking into account the need for retention samples. The programme should state to what extent each brand of a given product will be sampled and which local authority or inspector will be responsible for each sampling operation. It should indicate to which laboratory (if more than one exists) each sample should be sent. Such a programme enables the facilities of each laboratory to be used to best advantage.

4. Sampling on receipt (for acceptance)

4.1 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, including coning and quartering and the treatment of fines. Details of appropriate procedures may be found in the relevant International Organization for Standardization (ISO) documents (see Bibliography). These procedures are not further described in these guidelines.

4.2 **Intermediates in the manufacturing process and bulk pharmaceutical products**

Pharmaceutical intermediates and products supplied in bulk may need to be examined. These include liquids and semi-solid pharmaceutical products, powdered solids or granulates transported in large containers and intended either for further processing or for direct packaging into final market containers, and unit dosage forms (tablets, capsules) supplied in bulk which are intended for repackaging into smaller containers.

There is a risk of segregation of bulk materials during transportation and this should be taken into account when drawing up the sampling plan.

Products of this kind may be assumed to be uniform where the transportation process has been validated, provided that they:

- are labelled with the name of the manufacturer and a single batch number;
- have been produced in accordance with GMP; and
- are supplied with a certificate, issued in the country of origin, according to the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce.

In these circumstances the collection of a single sample, sufficient for the intended analyses, is adequate.

4.3 **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. A single consignment of a product from a single manufacturer and labelled with a single batch number may be assumed to be uniform.

The minimum size of the samples will be determined by the requirements of the analytical procedure that will be used to test the product. Tests of unit dosage forms for uniformity of weight, volume or content can require a considerable number of units, as can tests

for sterility. Depending upon the type of material, the size of the consignment and the way in which the material is packed, a unit to be sampled may be regarded as the transport container, e.g. 20 packs shrink-wrapped or boxed together, rather than an individual container. The required number of unit dosage forms is then withdrawn from any individual container in the selected transit container.

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 favourable 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.

Note: When sampling finished products, packaging materials may be retained for testing.

4.4 **Packaging materials (primary and secondary)**

There is a potential for mixing up printed packaging materials during the sampling operations and, therefore, only one material should be handled at a time. Also, samples of packaging materials should never be returned to the consignment.

Adequate protection (e.g. collapsible metal tubes) and identification should be provided for the sample to avoid mixing or damage.

Primary packaging materials should be adequately protected during the sampling operation to avoid environmental contamination. The final use of the packaging should be taken into consideration and appropriate sampling protection afforded (e.g. in the sampling of parenteral ampoules). There are several reasons why a consignment of packaging materials may not necessarily be considered homogeneous; for example:

- Materials were manufactured on different days or machines.
- Materials were manufactured on one machine, but on different stations (e.g. 16 printing dye stations or 12 moulding stations).

- Packaging was manufactured with different source materials (e.g. polyethylene from two different sources).
- A change of quality occurred during the process (e.g. container-wall thickness, colour variation, text legibility or change of printing plate).

It is, therefore, important at least to take random samples (e.g. from across the consignment), and to consider focused sampling, taking into account some of the above points.

5. **Sampling plans for starting materials, packaging materials and finished products**

As stated in the introduction, these guidelines are intended primarily for drug regulatory authorities and procurement agencies. The following sampling plans are, therefore, not necessarily appropriate for manufacturers, although the guiding principles may be useful. The choice of the sampling plan should always take into consideration the specific objectives of the sampling and the risks and consequences associated with inherent decision errors. It should be noted that sampling plans are not recommended for sampling of starting materials for identification tests (see *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2, Updated edition. Good manufacturing practices and inspection*. Geneva, World Health Organization, 2004; and *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report*. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929, Annex 2).

Ideally each sampling unit should be examined to ensure that it is intact and also checked for possible damage to the container. The contents should be inspected for uniformity and appropriately tested for identity. Uniformity should be tested on selected layer samples at different points in the material without previous intermixing. However, in cases when this ideal procedure is not possible or justified by the purpose of sampling, a number of sampling units should be randomly selected for sampling. It is not prudent to open all containers of products, which are liable to deteriorate under the influence of moisture or oxygen when held in a transit warehouse. However, materials in damaged containers or those found to be non-uniform should either be rejected or individually sampled for a complete quality control. Unlabelled sampling units should be rejected.

Table 1
Values of n , p or r for the N sampling units^a

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

^a An example of how these plans work is given in Appendix 5.

For random sampling, whenever possible each sampling unit should be consecutively numbered and the required number of random sampling units selected using tables of random numbers.

The number of units to be sampled depends on different assumptions and three possible plans are shown in Table 1. For more comprehensive, statistically-based sampling schemes, see Bibliography.

It is important to recognize that the “ n -plan” is not statistically based and should be used only as a guiding principle.

5.1 Starting materials

When sampling starting materials proper consideration has to be given to deciding on a sampling plan. The following are examples of sampling plans that could be used.

5.1.1 The n plan

The “ n plan” should be used with great caution and only when the material to be sampled is considered uniform and is supplied from a recognized source. Samples can be withdrawn from any part of the container (usually from the top layer). The n plan is based on the formula $n = 1 + \sqrt{N}$, where N is the number of sampling units in the consignment. The value of n is obtained by simple rounding. 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.

Note: The n plan is not recommended for use by control laboratories of manufacturers who are required to analyse and release or reject each received consignment of the starting materials used to produce a drug product.

5.1.2 **The p plan**

The “ p plan” may be used when the material is uniform, is received from a recognized source and the main purpose is to test for identity. The p plan is based on the formula $p = 0.4 \sqrt{N}$, where N is the number of sampling units. The figures for p are obtained by rounding up to the next highest integer. According to this plan, samples are taken from each of the N sampling units of the consignment and placed in separate sample containers. These original samples are transferred to the control laboratory, visually inspected and tested for identity (a simplified method may be used). If the results are concordant, p final samples are formed by appropriate pooling of the original samples.

5.1.3 **The r plan**

The “ r plan” may be used when the material is suspected to be non-uniform and/or is received from a source that is not well known. The r plan may also be used for herbal medicinal products used as starting materials. This plan is based on the formula $r = 1.5\sqrt{N}$, where N is the number of sampling units. The figures for r are obtained by rounding up to the next highest integer.

Samples are taken from each of the N sampling units of the consignment and placed in separate sample containers. These original 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.

5.2 **Packaging materials**

Sampling plans for packaging materials should be based on defined sampling standards, for example, British Standard BS 6001-1, ISO 2859 or ANSI/ASQCZ1.4-1993.

The objective is to ensure that there is a low probability of accepting material that does not comply with the predefined acceptance level.

5.3 Finished products

As for packaging materials, sampling plans for finished products should be based on defined sampling standards such as BS 6001-1, ISO 2859 or ANSI/ASQCZ 1.4-1993.

In some cases it may be sufficient to limit examination of finished goods to visual inspection only. If physical and chemical testing is required, however, the sampling units should consist of whole packs. Individual packs should not be broken open for the purposes of sampling.

An example of the steps to be considered when sampling finished products is given in Appendix 3, based on the sampling plans given in ISO 2859-1.

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Appendix 1

Types of sampling tools

Scoops

Small containers of solid materials may be adequately sampled using a spatula or scoop. The samples are then blended to provide a representative sample of that container. Figure 1 shows the recommended designs of scoops, which should preferably be rounded.

Figure 1
Sampling scoops for solids



If the scoop used is too small for the sizes of particle being sampled, large particles will roll off and testing bias may be introduced. On the other hand, if the scoop is too big, an unnecessarily large sample will be obtained for a given number of increments.

A scoopful of sample should be taken in a single movement and transferred to the sample container. Avoid tapping the scoop to remove pharmaceutical product as this is likely to cause segregation of the sample.

Dip tubes

Dip tubes should be used for sampling liquid and topical products and should be made of an inert material, such as polypropylene or stainless steel. A typical dip tube is shown in Figure 2.

Figure 2
Typical dip tube



Weighted containers

For taking samples from large tanks and storage vessels, a container in a weighted carrier can be used. The container is designed such that it can be opened at the required depth. Marks on the cord used for lowering the container can be used to determine when the correct sampling depth has been reached. A typical weighted container is shown in Figure 3.

Thieves

Sample thieves should be used when taking samples from deep containers of solids. Typical thieves are shown in Figure 4.

The plug thief typically consists of a hollow tube with an inner rod that has a tip on the end to allow the thief to enter the powder bed in the closed position (see Figure 4.i). The geometry of this tip can

Figure 3
Typical weighted container

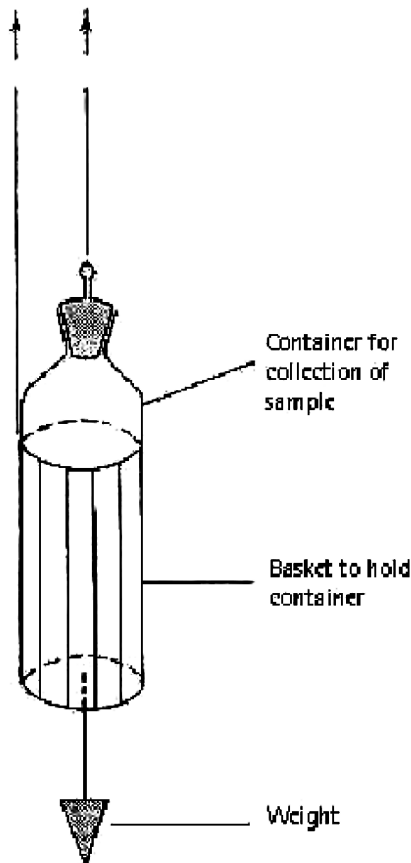
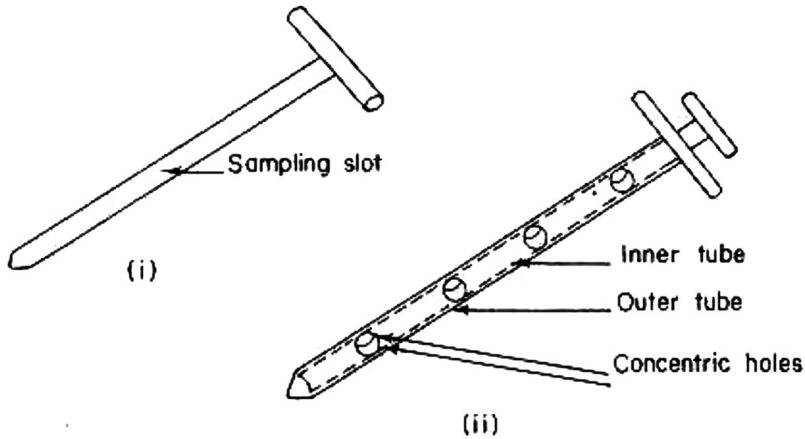


Figure 4
Typical sample thieves



influence the sample taken; pointed tips distort the powder bed less than blunt-tipped probes, thereby reducing sampling error. Some thieves have a locking device that allows the sample volume to be set to the required sample weight, thereby reducing the weight variation in the sample population.

A chamber thief generally consists of two concentric tubes (see Figure 4.ii); the inner tube is solid except for the chambers in which the sample is collected. The outer tube is hollow with openings that can be aligned with the chambers in the inner tube. A well-designed thief will have a sharp end to minimize disruption to the powder bed.

When it is inserted into a static powder blend a thief will distort the bed by carrying pharmaceutical product from the upper layers of the blend to the lower layers. The magnitude of this distortion can depend on whether the thief is inserted into the blend with a smooth, jerky or twisting action. Therefore, the correct sampling procedure should be defined and staff trained in using the appropriate technique. Thieves are also sometimes referred to as “double-tube spears”.

The angle at which the thief enters the powder bed can also influence sampling error. If a thief is inserted into the powder bed vertically, it can extract samples of different particle size from those that would be obtained using the same thief inserted at an acute angle. In addition the orientation of a chamber thief in relation to the powder bed (i.e. whether the chamber is at the top, the bottom or in the middle of the thief) may also influence the sampling error.

The material from which the thief is constructed, e.g. stainless steel or polypropylene, may also have an effect on sampling error due to static effects.

Sampling error can also be affected by bed depth, as the static pressure of the bulk blend forces the material into the sample chamber(s). This pressure is far greater at the bottom of a large container than it is in the middle or at the top. It is quite possible that the same thief could extract samples of different particle size from the top or bottom of a static powder blend.

Simple bag-sampling spears

Simple bag-sampling spears are the most commonly used instruments for taking samples from bags, because they are relatively cheap, simple and quick. Sampling spears generally have a maximum external diameter of about 12 mm, but can be up to 25 mm in diameter. To obtain a good cross-sectional sample, the spear should be 40–45 cm in length. The tapered type of sampling spear penetrates bags easily. Typical spears are shown in Figure 5.

Figure 5

Typical sampling spears

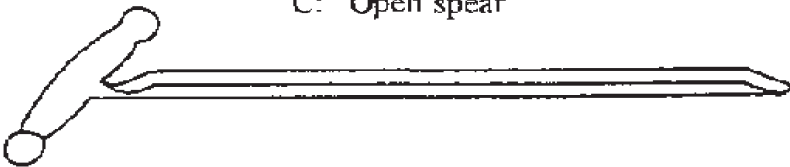
A: Closed spear for sampling large grains such as maize



B: Closed spear for sampling small grains such as wheat



C: Open spear



D: Double-tube spear



Appendix 2
Sample collection form^a

Serial number: _____

Name of location/place where sample was taken:

.....
.....
.....

Address (with telephone and fax number, if applicable):

.....
.....

Date of sampling:

Names of people who took samples:

1.
2.

Product name of the sample:

Name of (active) starting material (INN, generic or scientific name)

with dosage strength:

Dosage form (tablet, capsule, etc.):

Batch/lot number:

Date of manufacture:..... Expiry date:

Registration or licence number (if applicable):

Name of the manufacturer:

Number of sample unit taken (tablet, capsule, etc.: at least 20 but not more than 30 units):

.....

^a This sample collection form should always be kept with the sample collected. Proper sampling procedures should be followed.

Brief physical/visual description of sample:

.....
.....
.....
.....
.....

Signature of person(s) taking samples

Signature of representative of the establishment where sample(s) was taken (optional)

- 1.
- 2.

.....

Appendix 3

Steps to be considered for inclusion in a standard operating procedure

The steps for inclusion in a standard operating procedure described below are derived on a purely theoretical basis and are presented for information purposes only.

Bulk liquid products

The steps to be considered when sampling bulk liquid products are as follows.

1. Read and understand the precautions to be observed for the safe handling of the material.
2. Gather together the required sampling equipment (sampling tube or weighted sampling can, sample bottles and labels) and check that all the required items are clean.
3. Locate the batch.
4. Examine the container(s) for signs of contamination of the batch. Record any faults.
5. Examine the labels for obvious differences and signs of changes including obliterations and mislabelling. Record any faults.
6. Investigate and clarify the sources of and reasons for any faults before proceeding.
7. Choose a liquid-sampling tube of size and orifice suitable for the viscosity of the liquid being sampled.
8. Sample the liquid, suspension or emulsion (well stirred, if appropriate) by slowly pushing the open sampling tube vertically downwards through the liquid so that material is collected from each layer.
9. Seal the tube, withdraw it from the bulk liquid, and allow liquid adhering to the outside of the tube to drain. Transfer all the contents of the tube to a clean, labelled sample bottle.
10. Repeat steps 8 and 9 until sufficient samples for analytical and retention purposes have been obtained.
11. Seal the sample bottle.
12. Reseal the container from which the samples were taken and label as “sampled”.
13. Clean and dry the sampling tube, observing the relevant safety precautions.
14. Sample other required containers in the same manner following steps 8–12 above.

15. Clean the sampling tube using the recommended cleaning procedure.
16. Deliver the analytical samples to the laboratory and the reserve samples to the retention sample store. Report any aspects of the sampling that should be brought to the attention of the analyst or the inspector.
17. Check supplier certificate versus the specifications, if applicable.

Powdered starting material

The steps to be considered in sampling a powdered starting material are as follows.

1. Read and understand the precautions to be observed for the safe handling of the material.
2. Gather together the required sampling equipment (sampling spear, sample bottles and labels) and check that all items are clean.
3. Locate the consignment and count the number of containers. Record this number.
4. Examine all the containers for obvious differences and signs of damage. Record any faults.
5. Examine all the labels for obvious differences and signs of changes, including obliterations and mislabelling. Record any faults.
6. Segregate any damaged containers and those with suspected spoiled contents for separate examination. These should then be *referred* or *rejected* and dealt with accordingly.
7. Segregate any containers with different batch numbers and treat these separately.
8. Number the remaining containers.
9. Choose the appropriate sampling plan (n , p or r).
10. Choose the containers to be sampled in accordance with the requirements of the chosen plan (by the use of random number tables, by drawing lots or by the use of a random number generator if applicable).
11. Open the containers one at a time and inspect the contents. Record any differences.
12. Choose a suitable, clean sampling spear and plunge this (gates closed) into the powder so that the point of the spear reaches the bottom of the container.
13. Open the gates to allow the powder to enter the spear cavities, then reclose them.
14. Withdraw the spear from the container and transfer the spear contents to a labelled sample bottle.

15. Repeat steps 12–14 until sufficient material has been collected for analytical and retention requirements.
16. Seal the sample bottle.
17. Reseal the container from which the samples were withdrawn and label as “sampled”.
18. Wipe clean the sampling spear if required, observing the safety precautions, before sampling the other chosen containers.
19. Repeat steps 12–18 for each chosen container.
20. Clean the sampling spear using the recommended cleaning procedure.
21. Deliver the analytical samples to the laboratory and the reserve samples to the retention sample store. Report any aspects of the sampling that should be brought to the attention of the analyst or inspector.
22. Check the supplier certificate versus the specifications, if applicable.

Packaging materials

The steps to be considered in sampling packaging materials are as follows.

1. Check the consignment against any associated documentation.
2. Check transit containers for the following and report any deviations as necessary:
 - 2.1 correct identification;
 - 2.2 integrity of seal, if appropriate; and
 - 2.3 absence of physical damage.
3. Obtain the required sample from the required number of containers, bearing in mind the special considerations for sampling packaging materials noted in section 4.4 of this Annex.
4. Place the sample units into identified appropriate sample containers.
5. Identify the consignment containers that have been sampled.
6. Note any special situations found during the sampling process (e.g. rogue items or component damage). Report any such observations as necessary.
7. Remove all sampled material pallets or containers from the sampling area together with all documentation.
8. Check supplier certificate against the specifications, if applicable.

Finished products

The following steps should be considered when sampling finished products.

1. Determine the number of pallets per batch in the consignment.
2. Work out as per ISO 2859–1 table level II, the number of pallets to be checked visually.
 - 2.1 Check condition of pallet and packaging for integrity of outer packaging material.
 - 2.2 Check outside of goods on the pallets for general cleanliness.
 - 2.3 Check that the overall labelling of the pallets matches the packing list.
 - 2.4 Count, categorize and record the number of defects.
3. Count the total number of transport packs on the number of pallets present and verify the total against the packing list.
4. From the number of pallets work out the number of transport packs to be sampled using the ISO table.
 - 4.1 Check condition of boxes for integrity of packaging material.
 - 4.2 Check for cleanliness of boxes.
 - 4.3 Check the labelling of the boxes for damage.
 - 4.4 Check the boxes for overall damage.
 - 4.5 Check the labels for spelling mistakes.
 - 4.6 Check the labels for manufacturing and expiry dates.
 - 4.7 Count, categorize and record the number of defects.
5. From the number of boxes selected work out the number of unit packs to be examined visually using the ISO table.
 - 5.1 Check condition of the containers for integrity of packaging material.
 - 5.2 Check for cleanliness of containers.
 - 5.3 Check condition of containers for shape and colour.
 - 5.4 Check the labelling of containers for damage.
 - 5.5 Check the containers for overall damage.
 - 5.6 Check the labels for spelling mistakes.
 - 5.7 Check the labels for manufacturing and expiry dates.
 - 5.8 Count, categorize and record the number of defects.
6. From the number of containers selected, determine the number of containers to be taken for physical and chemical testing and for retention.
7. Check the supplier certificate against the specifications, if applicable.

Appendix 4

Examples of types of containers used to store samples of starting materials and bulk products

Figure 1

Bag for storage of samples

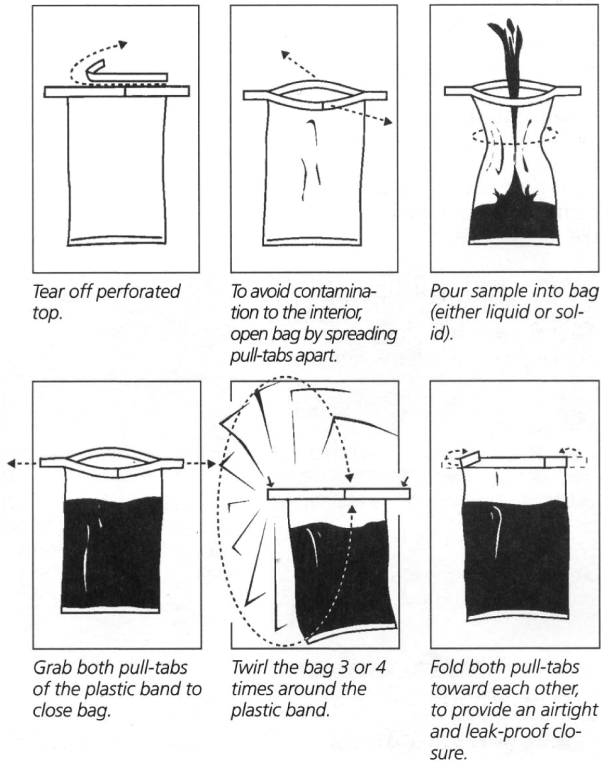


Figure 2
Screw-top containers



Appendix 5

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 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 three 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

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.