ECA Foundation
Fostering harmonisation of GMP/GDP regulations

Laboratory Data Management Guidance – Sampling and Sample Management –

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1 Introduction to AQCG & its Guidances

The AQCG aims at providing a networking platform for Analytical Chemists and Scientists and to facilitate an active discussion of the latest regulatory requirements as well as identifying and addressing technical issues and challenges. In addition, it supports a harmonised approach through providing discussion/position papers and generic guidances via expert working groups to foster an effective and efficient communication between industry, competent authorities and the pharmacopoeias.

1.1 Guides and Guidances

This guidance continues the sequence of these already published guidances which are available as pdf files for members of ECA

- ECA _AQCG_ SOP 01_OOS_v2.0 August 2012
- ECA _AQCWG_ SOP 02_OOE OOT_v1.2_July 2023
- ECA _AQCG_ SOP 03_APLM_v1.0_July 2018
- ECA-AQCG-AIQSV-Guide-November 2023-v1.0
- ECA_Data Integrity Guide_v3.0 December 2022

2 Importance of Sampling and Sample Management

It is important to understand that sampling is always an error generating process and that although the reported result may be dependent upon the analytical method, it will always be dependent upon the sampling process[i].

The sampling process includes the specific activities undertaken to select the sample from a batch or lot and the management of the chain of custody of that sample throughout the lifecycle journey from sampling, through testing to retention and ultimate disposal. A high level process flow is shown in Figure 1.

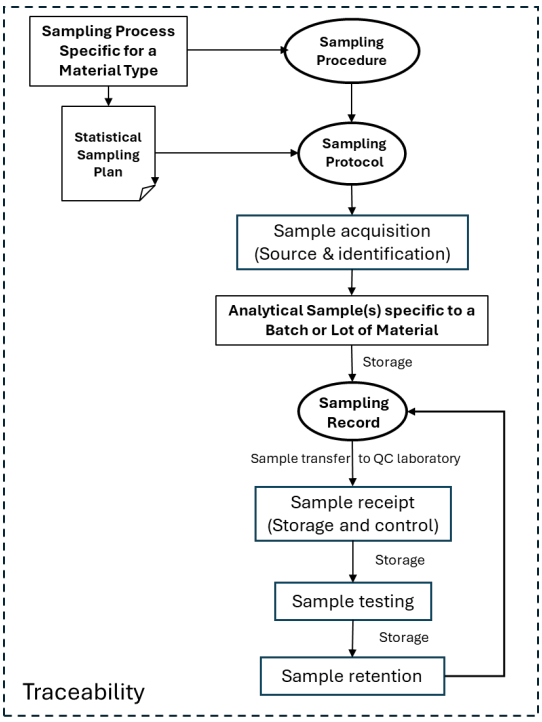

Figure 1 High level sampling and sample management process flow

2.1 Sampling

Inconsistent sampling processes can lead to errors, resulting in data integrity issues and potentially incorrect decisions about pharmaceutical quality.

If the sample provenance cannot be assured such that the sample is representative of the overall batch or lot of material or product any testing is useless. It is essential that sampling process steps and flows are consistent and traceable

2.2 Sample Management

Traceability is critical to demonstrate that the sample, as taken in accordance with the procedure is identified, protected and stored correctly prior to analysis. The sample record needs to contain all relevant data to confirm assurance that the sample tested has not been compromised prior to analysis in any way.

In particular, the storage and transportation of samples activities should be strictly controlled.

Ideally sampling should be performed in an area or booth designed for and dedicated to this purpose.

However, if this is not possible 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;
- protect the individual who samples (sampler) during the sampling procedure.

3 Regulatory Requirements for Sampling and Sample Management

The requirements for sampling and sample management are scattered across multiple sources as illustrated in **Figure 2**. Details are provided in the subsequent sections 3.1 to 3.6 and their subsections.

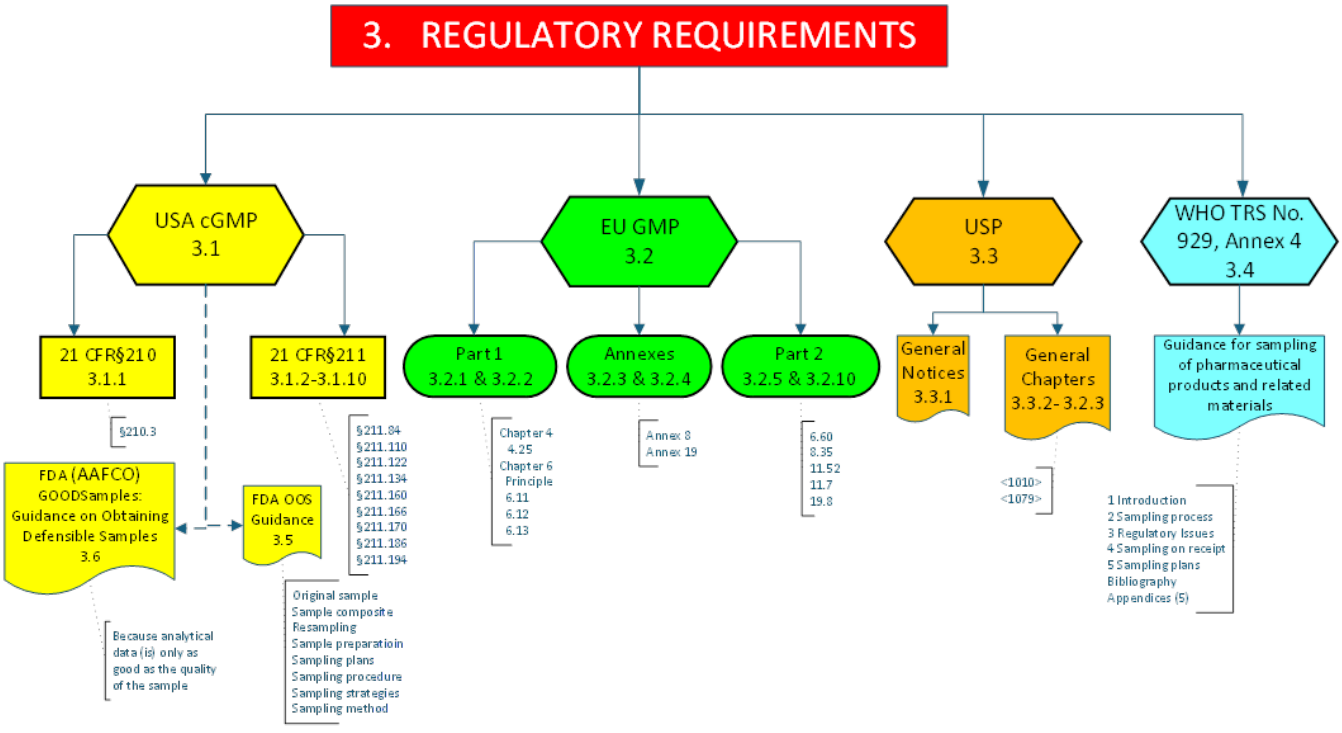

Figure 2 Overview of sources of requirements for sampling and sample management

3.1 USA cGMP (21 CFR §210ii & 21 CFR §211iii)

3.1.1 *21 CFR §210.3 Definitions*

Representative sample means a sample that consists of a number of units that are drawn based on rational criteria such as **random sampling** and intended to assure that the **sample** accurately portrays the material being sampled.

3.1.2 *21 CFR §211.84 Testing and approval or rejection of components, drug product containers, and closures.*

(a) **Representative samples** of each shipment of each lot shall be collected for testing or examination. The number of containers to be sampled, and **the amount of material to be taken from each container, shall be based upon appropriate criteria such as statistical criteria for component variability**, confidence levels, and degree of precision desired, the past quality history of the supplier, and the quantity needed for analysis and reserve where required by § 211.170.

(b) **Samples** shall be collected in accordance with the following procedures:

1) The containers of components selected shall be cleaned when necessary in a manner to prevent introduction of contaminants into the component.
2) The containers shall be opened, sampled, and resealed in a manner designed to prevent contamination of their contents and contamination of other components, drug product containers, or closures.
3) Sterile equipment and aseptic sampling techniques shall be used when necessary.
4) **If it is necessary to sample a component from the top, middle, and bottom of its container, such sample subdivisions shall not be composited for testing**.
5) **Sample containers** shall be identified so that the following information can be determined: name of the material sampled, the lot number, the container from which the sample was taken, the date on which the sample was taken, and the name of the person who collected the sample.
6) **Containers from which samples have been taken shall be marked to show that samples have been removed from them**.

3.1.3 *21 CFR §211.110 Sampling and testing of in-process materials and drug products.*[iv]

(a) To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on **appropriate samples of in-process materials** of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Such control procedures shall include, but are not limited to, the following, where appropriate:
(1) Tablet or capsule weight variation;
(2) Disintegration time;
(3) Adequacy of mixing to assure uniformity and homogeneity;
(4) Dissolution time and rate;
(5) Clarity, completeness, or pH of solutions.
(6) Bioburden testing.

3.1.4 *21 CFR §211.122 Materials examination and usage criteria.*

(a) There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, **sampling**, examination, and/or testing of labeling and packaging materials; such written procedures shall be followed. Labeling and packaging materials shall be **representatively sampled**, and examined or tested upon receipt and before use in packaging or labeling of a drug product.

3.1.5 *21 CFR §211.134 Drug product inspection.*

(a) Packaged and labeled products shall be examined during finishing operations to provide assurance that containers and packages in the lot have the correct label.
(b) A **representative sample** of units shall be collected at the completion of finishing operations and shall be visually examined for correct labeling.
(c) Results of these examinations shall be recorded in the batch production or control records.

3.1.6 *21 CFR §211.160 General requirements.*

(a) The establishment of any specifications, standards, **sampling plans**, test procedures, or other laboratory control mechanisms required by this subpart, including any change in such specifications, standards, **sampling plans**, test procedures, or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and **reviewed and approved by the quality control unit**. The requirements in this subpart shall be followed and shall be documented at the time of performance. Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified.
(b) Laboratory controls shall include the establishment of **scientifically sound** and appropriate specifications, standards, **sampling plans**, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include:

(1) Determination of conformity to applicable written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products. The specifications shall include a description of the sampling and testing procedures used. **Samples shall be representative and adequately identified**. Such procedures shall also require appropriate retesting of any component, drug product container, or closure that is subject to deterioration.
(2) Determination of conformance to written specifications and **a description of sampling and testing procedures for in-process materials**. **Such samples shall be representative and properly identified**.
(3) **Determination of conformance to written descriptions of sampling procedures and appropriate specifications for drug products. Such samples shall be representative and properly identified**.

3.1.7 *21 CFR §211.166 Stability testing*

The written program shall be followed and shall include:

(1) **Sample size** and test intervals based on statistical criteria for each attribute examined to assure valid estimates of stability;
(2) Storage conditions for **samples retained** for testing;

3.1.8 *21 CFR §211.170 Reserve samples.*

(a) An appropriately identified **reserve sample** that is representative of each lot in each shipment of each active ingredient shall be retained. The **reserve sample consists of at least twice the quantity necessary for all tests required** to determine whether the active ingredient meets its established specifications, except for sterility and pyrogen testing.

3.1.9 *21 CFR §211.186 Master production and control records*

(9) Complete manufacturing and control instructions, sampling and testing procedures, specifications, special notations, and precautions to be followed.

3.1.10 *21 CFR §211.194 Laboratory records*

(a) Laboratory records shall include complete data derived from all tests necessary to assure compliance with established specifications and standards, including examinations and assays, as follows:

(1) A description of the **sample** received for testing with **identification of source (that is, location from where sample was obtained), quantity, lot number or other distinctive code, date sample was taken, and date sample was received for testing**.

(3) A statement of the weight or measure of **sample used for each test**, where appropriate.

3.2 EU GMP[v]

3.2.1 *Part 1 Chapter 4 Documentation*

Sampling

4.25 There should be written procedures for **sampling**, which include the methods and equipment to be used, the amounts to be taken and any precautions to be observed to avoid contamination of the material or any deterioration in its quality.

3.2.2 *Part 1 Chapter 6 Quality Control*

Quality Control is concerned with **sampling**, specifications and testing as well as the organisation, documentation and release procedures which ensure that the necessary and relevant tests are carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory.

6.11 The **sample taking** should be done and recorded in accordance with approved written procedures that describe:

i. The method of sampling
ii. The equipment to be used
iii. The **amount of the sample** to be taken
iv. Instructions for any required sub-division of the **sample**
v. The type and condition of the **sample** container to be used
vi. The identification of containers sampled
vii. Any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials
viii. The storage conditions
ix. Instructions for the cleaning and storage of sampling equipment.

6.12 **Samples should be representative of the batch** of materials or products from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g. beginning or end of a process). The **sampling plan used should be appropriately justified and based on a risk management approach**.

6.13 **Sample** containers should bear a label indicating the contents, with the batch number, the date of sampling and the containers from which samples have been drawn. They should be managed in a manner to minimize the risk of mix-up and to protect the samples from adverse storage conditions.

3.2.3 *Annex 8 SAMPLING OF STARTING AND PACKAGING MATERIALS*

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

This training should include:

- **sampling** plans
- written **sampling** procedures
- the techniques and equipment for **sampling**
- the risks of cross-contamination
- the precautions to be taken with regard to unstable and/or sterile substances
- the importance of considering the visual appearance of materials, containers and labels
- the importance of recording any unexpected or unusual circumstances

Starting materials
The identity of a complete batch of starting materials can normally only be ensured if individual samples are taken from all the containers and an identity test performed on each sample.

The quality of a batch of starting materials may be assessed by taking and testing a **representative sample**. The **samples** taken for identity testing could be used for this purpose. **The 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 also be defined, taking into account the nature of the material, knowledge of the supplier and the homogeneity of the composite sample.

Packaging materials
The sampling plan for packaging materials should take account of at least the following;

- the quantity received
- the quality required
- the nature of the material (e.g. primary packaging materials and/or printed packaging materials)
- the production methods, and what is known of the Quality Assurance system of the packaging materials manufacturer based on audits.

The **number of samples** taken should be determined **statistically and specified in a sampling plan**.

3.2.4 *Annex 19 Reference and Retention Samples (also Annex 13 IMPs)*

This Annex to the Guide to Good Manufacturing Practice for Medicinal Products ("the GMP Guide") gives guidance on the taking and holding of reference samples of starting materials, packaging materials or finished products and retention samples of finished products.

2.1 **Samples** are retained to fulfil two purposes; firstly to provide a sample for analytical testing and secondly to provide a specimen of the fully finished product.

Samples may therefore fall into two categories

i. **Reference sample**: a sample of a batch of starting material, packaging material or finished product which is stored for the purpose of being analysed should the need arise during the shelf life of the batch concerned. Where stability permits, reference samples from critical intermediate stages (e.g. those requiring analytical testing and release) or intermediates, that are transported outside of the manufacturer's control, should be kept.
ii. **Retention sample:** a sample of a fully packaged unit from a batch of finished product. It is stored for identification purposes. For example, presentation, packaging, labelling, patient information leaflet, batch number, expiry date should the need arise during the shelf life of the batch concerned.

2.3 The reference and/or retention samples serve as a record of the batch of finished product or starting material and can be assessed in the event of, for example, a dosage form quality complaint, a query relating to compliance with the marketing authorisation, a labelling/packaging query or a pharmacovigilance report.

2.4 Records of **traceability of samples** should be maintained and be available for review by competent authorities.

3.2.5 *Part 2; 6.60 Laboratory Control Records*

A description of samples received for testing, including the material name or source, batch number or other distinctive code, **date sample was taken**, and, where appropriate, the quantity and **date the sample was received for testing**; -A statement of or reference to each test method used; -A statement of the weight or measure of **sample** used for each test as described by the method; data on or cross-reference to the preparation and testing of reference standards, reagents and standard solutions.

3.2.6 *Part 2; 7.33-7.35 Sampling and Testing of Incoming Production Materials*

7.33 **Samples should be representative of the batch of material** from which they are taken. **Sampling methods should specify the number of containers to be sampled, which part of the container to sample, and the amount of material to be taken from each container**. The number of containers to sample and the

sample size should be based upon a **sampling plan** that takes into consideration the criticality of the material, material variability, past quality history of the supplier, and the quantity needed for analysis.

7.34 **Sampling** should be conducted at defined locations and by procedures designed to prevent contamination of the material sampled and contamination of other materials.

7.35 **Containers from which samples are withdrawn** should be opened carefully and subsequently reclosed. They should be marked to indicate that a sample has been taken.

3.2.7 *Part 2; 7. 8.35 In-process Sampling and Controls*

In-process sampling should be conducted using procedures designed to prevent contamination of the **sampled** material and other intermediates or APIs. Procedures should be established to ensure the **integrity of samples** after collection.

3.2.8 *Part 2; 11.52 Stability Monitoring of APIs*

Stability samples should be stored in containers that simulate the market container. For example, if the API is marketed in bags within fiber drums, stability samples can be packaged in bags of the same material and in smaller-scale drums of similar or identical material composition to the market drums.

3.2.9 *Part 2; 11.7 Reserve/Retention Samples*

11.70 The packaging and holding of reserve samples is for the purpose of potential future evaluation of the quality of batches of API and not for future stability testing purposes.

3.2.10 *Part 2; 19.8 Laboratory Controls*

19.81 A system for retaining reserve samples of all batches should be in place. This system should ensure that a sufficient quantity of each reserve sample is retained for an appropriate length of time after approval, termination, or discontinuation of an application.

3.3 United States Pharmacopeia

3.3.1 *General Notices*

Sampling is not addressed in detail in the USP as the monographs are standards not specifications and apply to any tested sample (official article).

'Standards for an article recognized in the compendia (USP–NF) are expressed in the article's monograph, applicable general chapters, and General Notices. The standards in the relevant monograph, general chapter(s), and General Notices apply at all times in the life of the article from production to expiration.' 'Thus, any official article is expected to meet the compendial standards if tested, and any official article actually tested as directed in the relevant monograph must meet such standards to demonstrate compliance'…in all cases, statements about whether the compendial standard is met ***apply only to the units tested*** *'* [vi]

and hence

'Analytical results observed in the laboratory (or calculated from experimental measurements) are compared with stated acceptance criteria to determine whether the ***article*** *conforms to compendial requirements.'* [vii]

However, it does discuss sampling in two above 1000 General Chapters; <1010> and <1097>.

3.3.2 *General Chapter <1010> ANALYTICAL DATA—INTERPRETATION AND TREATMENT* [viii]

Effective **sampling** and randomization are important considerations in mitigating the impact of bias. Sampling is performed after the study has been designed and constitutes the selection of test articles within the structure of the design. How to attain such a sample depends entirely on the question that is to be answered by the data. When possible, use of a random process is considered the most appropriate way of selecting samples. The most

straightforward type of random sampling is called simple random sampling. However, sometimes this method of selecting a random sample is not desirable because it cannot guarantee equal representation across study factors. The design of a study to release manufactured lots might incorporate factors such as selected times, locations, or parallel manufacturing streams (e.g., multiple filling lines). In this case a stratified sample whereby units are randomly selected from within each factor can be utilized.

Regardless of the reason for taking a sample, **a sampling plan** should be established to provide details on how **the sample** is to be obtained to ensure that it is representative of the entirety of the population of interest.

3.3.3 *General Chapter <1097> BULK POWDER SAMPLING PROCEDURES*

The goals of this chapter are to provide guidance on bulk powder sampling procedures, identify important bulk powder sampling concepts, and collect a knowledge base of useful practices and considerations that can lead to the ideal physical sampling of bulk powder materials.

The primary difficulty in acquiring a representative sample is that the size of the sample for measurement, typically a few milligrams to grams, must be withdrawn from a large population on the order of hundreds to thousands of kilograms. The few milligrams analysed in a laboratory must be taken from a large population of particles in a warehouse in such a manner that the measurement sample is representative of all the particles in the lot.

A typical sampling strategy consists of two basic steps: (1) the primary or gross sample, followed by (2) the secondary sample, which reduces the primary sample to a size that is suitable for laboratory measurement. In short, the goal is to select from the lot a quantity of material suitable for measurement without significantly changing the attribute for which one is sampling.

In parallel with the sample size reduction, sample size calculations must be done in such a way that the sampling strategy has sufficient statistical power to determine whether the attributes of interest lie within the specification ranges with a reasonable degree of certainty. Each step must be done correctly, or the sampling strategy as a whole will not provide a sample that is representative of the original population.

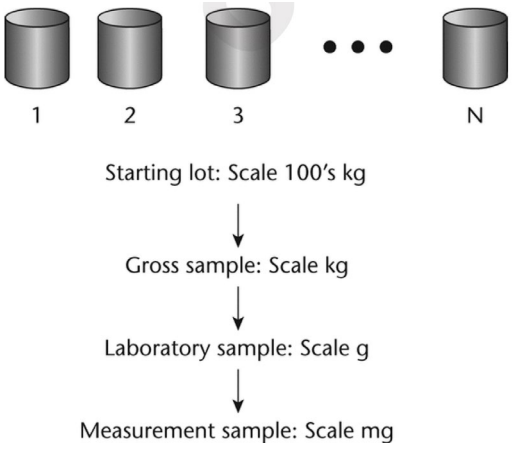

Figure 3 Sampling strategy that will help to minimize sampling errors

3.4 WHO Guidance for sampling of pharmaceutical products and related materials[ix]

1. Introduction
    - 1.1 General considerations
    - 1.2 Glossary
    - 1.3 Purpose of sampling
    - 1.4 Classes and types of pharmaceutical products and related materials
    - 1.5 Sampling facilities
    - 1.6 Responsibilities for sampling
    - 1.7 Health and safety

3.5 FDA Guidance Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production, May 2022[x]

Retesting and resampling are a critical aspects of this guidance.

*Part of the investigation may involve retesting of a portion of the **original sample**. The sample used for the **retesting** should be taken from the same homogeneous material that was originally collected from the lot, tested, and yielded the OOS results. For a liquid, it may be from the original unit liquid product or composite of the liquid product; for a solid, it may be an additional weighing from the same sample composite prepared for the original test.*

*While retesting refers to analysis of the original, **homogenous sample material**, **resampling** involves analyzing a specimen from any additional units collected as part of the original sampling procedure **or from a new sample collected from the batch, should that be necessary.***

See the ECA AQCG Guideline on OOS results for more details[xi].

3.6 GOODSamples: Guidance on Obtaining Defensible Samples [xii]

The FDA regulates food as well as drugs, In October 2015, the Sampling and Sample Handling Working Group of the Association of American Feed Control Officials (AAFCO) developed a guidance by a consortium, led by FDA, entitled GOODSamples: Guidance on Obtaining Defensible Samples. This 83 page guidance had the objective to "improve analytical data equivalency among state, federal and local agencies ... **Because analytical data is only as good as the quality of the sample**".

A subsequent document in 2018, GOOD Test Portions: Guidance On Obtaining Defensible Test Portions[xiii] (70 pages) was developed and contains detailed information on the TOS in respect of the error structure and sampling methodology for foodstuffs.

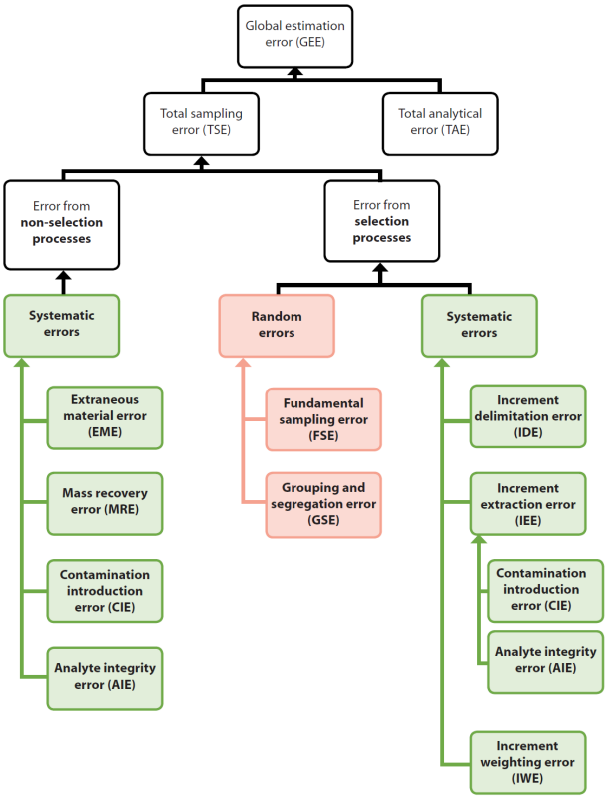

Figure 4 Categorization of errors contributing to total sampling error and relationship to global estimation error [from figure 4 of reference [xi].

4 Theory of Sampling

The theory of sampling (TOS) has been developed, primarily by Dr Pierre Gy, between 1950 and the early 2000s. In Gy theory, correct sampling is defined as a sampling scenario in which all particles have the same probability of being included in the sample. The theory was primarily developed for the mining industries and large scale sampling problems of large quantities of bulk materials as to how to generate a representative sample[xiv],[xv].

These two books are high level monographs and statistically very detailed. More recently, an introductory book has been published by Esbensen[xvi].

A more accessible and less statistical book on the sampling and weighing of bulk solids was published in 1985[xvii]. In addition, two older books may also be found useful [xviii],[xix]

The published literature is sparse with respect to pharmaceuticals and related materials. Representative sampling has been briefly addressed[xx] to understanding the differences between convenience, target, and self-selected samples. In addition, compositing of samples has also been discussed by Torbeck[xxi] because compositing samples is appropriate under certain circumstances but raises caveats on how and when it should be applied.

The best practical application of sampling practices is the WHO guidances for sampling of pharmaceutical products and related materials [ix]. However, more details regarding the sampling plan sections are given in Chapter 6.

5 Nomenclature of sampling

Consistent sampling and testing nomenclature are critical for data integrity and compliance with specifications and regulatory standards. Currently, there is a lack of agreement between the major sources of guidance both within the pharmaceutical industry and between other regulated sectors
The International Union of Pure and Applied Chemistry (IUPAC) made nomenclature recommendations for sampling in analytical chemistry in 1990[xxii]. This paper was referenced in the 2023 IUPAC Orange book[xxiii].

ASTM Standard Guide for Defining the Test Result of a Test Method, E2282-14(2019) has also produced a nomenclature guide[xxiv].

The similarities and differences between literature references have been discussed[xxv].

A recommendation of a proposed sampling nomenclature is shown in Table 1.

The four key documents for a particular material or product are;

1. Statistical Sampling Plan
2. Sampling Procedure
3. Sampling Protocol

and

4. Sampling Record

The relationship between these documents are shown in Figure 1 and some proposed terms and definitions listed in Table 1.

Table 1 Proposed terms and definitions

Term	Definition
Statistical Sampling Plan	• A predetermined procedure for the selection, withdrawal, preservation and preparation of the portions to be removed from a population as samples. • A sample is any portion of material selected from a larger quantity of material. The sample type is identified by specific qualifiers, e.g. random sample, with their own definitions • The intent is to minimize the difference between the properties as estimated from a sample and the actual properties of the lot, and to limit or control the uncertainty generated by the sampling operation on a statistical basis, all within practical constraints. • The end point is a representative sample for testing that can be expected to adequately reflect the properties of interest (Characteristics) of the parent population.
Characteristic	• A property or attribute of a material that is to be measured or observed. The ISO term is measurand.
Sampling Uncertainty (Homogeneity)	• That part of the error associated with using only a fraction of the material population to be sampled and extrapolating to the whole as distinct from analytical or testing error. It arises from a lack of homogeneity in the material population. • Sampling error may be determined by replication of sample increments and their multiple determinations or/and by reducing the particle size if appropriate. • Homogeneity is the degree to which a property, characteristic or attribute is uniformly distributed throughout a quantity of material. The degree of heterogeneity (the opposite of homogeneity) is the determining factor of sampling error.
Sampling Process (Definitions)	**Static sampling**: The composition of the parent material can be considered as permanent with respect to position in space and stable in time such that the only variable is the sampling position within the space occupied by the consignment, lot or batch.
	Dynamic sampling: If the parent material is almost always changing with respect to time (dynamic) and the removal of a portion of the parent material at any instant reflects only a state at that time and at a particular site e.g. In process control samples from a mixer.
	Sample increment: Each of the discrete, identifiable portions of material removed from a population which can be individually tested, or combined.
	Random sample: The sample so selected that any portion of the population has an equal (or known) chance of being chosen.
	Representative sample: A sample resulting from a sampling plan.
	Reference sample: A representative sample of a batch of starting material, packaging material or finished product which is stored for the purpose of being analysed should the need arise during the shelf life of the batch concerned.
	Retention sample: A sample of a fully packaged unit from a batch of finished product. It is stored for identification purposes. For example, presentation, packaging, labelling, patient information leaflet, batch number, expiry date should the need arise during the shelf life of the batch concerned.
	Stratified sample: A sample consisting of portions obtained from identified subparts (strata) of the parent population. Within each stratum, the samples are to be taken randomly.
	Sampling Procedure: The complete sampling operations to be performed on a defined material for a specific purpose.
	Sampling Protocol: A detailed written description of the sampling procedure to be carried out for a specific consignment, lot or batch.
Sampling Record	Documented evidence 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(s) and signature(s) of the sampler(s) in accordance with ALCOA++ principles. [Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring, Available and Traceable][xxvi].

6 The Sampling Process

The sampling process is comprised of two distinct phases: design and implementation[xxvii].

1. In the design phase, the application of statistical principles is expected to supply a statistical sampling plan to determine the acceptability of a lot, the magnitude of a property, or the quantity of a constituent, within a specified degree of variability with a stated degree of confidence, the document describes,
2. The implementation phase of sampling involves the physical realization of the statistically designated portions and the removal and preparation of them—an operation easier to state than to perform

6.1 Statistical Sampling Plans

A statistical sampling plan is a high-level master document containing all necessary definitions and structures to ensure that a representative sample from a given material population is available for testing in the laboratory. This is a critical document because sampling is always an error-generating process.
The suggested main terms and definitions are shown in Table 1.

The concept of sampling populations is straight forward, in theory, in that a representative sample is taken from the population and examined for compliance with acceptance criteria be they attributes (e.g. presence of defects) or variables (e.g. dimension within tolerance). On the basis of the finding the level of non-conformances in the representative sample, take a calculated risk of accepting or rejecting the batch (Population) using Acceptance Sampling.

There will always be a chance that;

- good material will be rejected; called the Producer's risk
- bad material will be accepted; called the Consumer's risk

6.2 Acceptance Sampling Plans

Acceptance sampling plans are available for attributes and variables. The most commonly used in the pharmaceutical industry is for attributes.

The mathematical model for sampling without replacement is the hypergeometric distribution whose cumulative distribution function (CDF) is given by

$$CDF = \sum_{0}^{x} \frac{\binom{X}{x}\binom{N-X}{n-x}}{\binom{N}{n}}$$

Where x is the number of occurrences of non-conformities found in the sample and n is the number of samples taken from the population. N is the batch size and X is the number of non-conformances in it. The () terms are the binomial coefficients.

What is required is an Operational Characteristic (OC) curve based upon a sample size, n, a defined acceptance criterion, (How many defects to accept), and the batch size.

This OC curve is a plot of the probability of accepting a batch containing a specified % non-conformance (Y axis), based upon the hypergeometric distribution, and the % non-conformances (X axis).

Fortunately, predetermined ISO standard sampling plans are available for use in laboratories for attributes[xxviii] and variables[xxix] which do not require the calculation of the CDF!

By way of a simple example to illustrate an OC curve, suppose, we have a batch size N of 1000 items, and decide to take a sample size (n) of 50 intending that we will accept the batch if we have one or less defects after examining n samples otherwise we will reject it.

We can therefore calculate the OC curve using the CDF function, using Excel, and interpret it.

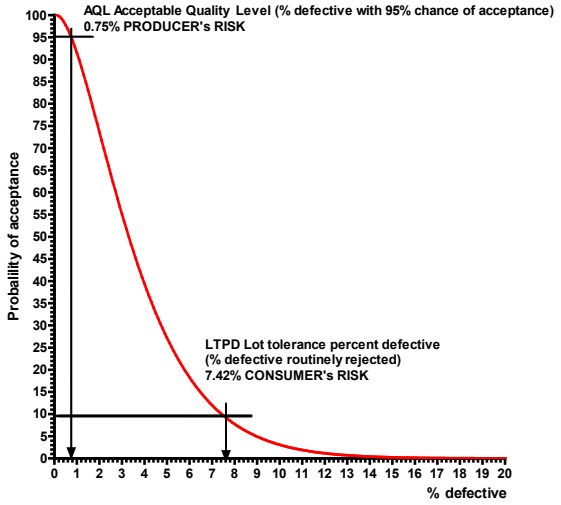

Figure 5 Example Operating Characteristic Curve

The AQL with a 95% chance of acceptance gives a producer's risk of rejection as 0.75%. However, the consumer's risk is 10 times higher! The LTPD is the percentage defective with a 10% chance of acceptance. This is the probability of falsely accepting a bad lot!

This guidance provides only a simplified overview of acceptance sampling. There is an excellent book which covers acceptance sampling in great detail[xxx].

In practice, we select a sampling plan based upon a batch size and an acceptance quality limit (AQL) based upon the risk associated with a defect or non-conformance using the sampling tables from ISO 2859-1 for attributes.

The risk-based strategy depends upon the risk level; Critical, Major or Minor (e.g. cosmetic defects). Let us assume one example for each risk level. The corresponding AQLs for the risk levels are 0.010%, 0.065% and 4.0% respectively. Let us also assume that the corresponding batch sizes are 300,000, 100,000 and 1000.

	General Inspection Level II for Normal		
	Minor	Major	Critical
AQL	4.0%	0.065%	0.010%
Batch size, N	1000	100000	300000
→ Code letter	J	N	P
Sample size, n	80	500	800
Where do these come from? → Accept on	7	1	0
→ Reject on	8	2	1

Figure 6 Example AQLs Sample Sizes & Acceptance Criteria

The sampling tables do not use exact sample sizes but sample size ranges as an approximation for any given inspection level. In this example, Level II (normal) has been selected which would be the usual practice.

The coloured sample size code letter for the batch size is shown in Figure 6.

Batch or Lot Size	General Inspection Level		
	I (reduced)	II **(normal)**	III (tightened)
2 to 8	A	A	B
9 to 15	A	B	C
16 to 25	B	C	D
26 to 50	C	D	E
51 to 90	C	E	F
91 to 150	D	F	G
151 to 280	E	G	H
281 to 500	F	H	J
501 to 1200	G	J	K
1201 to 3200	H	K	L
3201 to 10000	J	L	M
10001 to 35000	K	M	N
35001 to 150000	L	N	P
150001 to 500000	M	P	Q
500001 and over	N	Q	R

Figure 7 Allocation of sample size range code letter to Level II (normal)[xxxi]

The accept (Ac)/reject (Re) acceptance numbers depend on the sample size range code letter and the selected AQL. The representative sample sizes to be examined are linked to the sample size range code letter also.

Sample size code letter	Sample size	Acceptance Quality Limit, AQL, % nonconforming items for normal inspection																									
		0.010		0.015		0.025		0.040		0.065		0.10		0.15		0.25		0.40		0.65		1.0		1.5		2.5		4.0		6.5		10.0	
		Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re	Ac	Re
A	2	⇩		⇩		⇩		⇩		⇩		⇩		⇩		⇩		⇩		⇩		⇩		⇩		⇩		⇩		0	1	⇩	
B	3	⇩		⇩		⇩		⇩		⇩		⇩		⇩		⇩		⇩		⇩		⇩		⇩		⇩		0	1	⇩		⇩	
C	5	⇩		⇩		⇩		⇩		⇩		⇩		⇩		⇩		⇩		⇩		⇩		⇩		0	1	⇩		⇩		1	2
D	8	⇩		⇩		⇩		⇩		⇩		⇩		⇩		⇩		⇩		⇩		⇩		0	1	⇩		⇩		1	2	2	3
E	13	⇩		⇩		⇩		⇩		⇩		⇩		⇩		⇩		⇩		⇩		0	1	⇩		⇩		⇩		1	2	2	3	3	4
F	20	⇩		⇩		⇩		⇩		⇩		⇩		⇩		⇩		⇩		0	1	⇩		⇩		1	2	⇩		2	3	3	4	5	6
G	32	⇩		⇩		⇩		⇩		⇩		⇩		⇩		⇩		0	1	⇩		⇩		1	2	2	3	3	4	5	6	7	8
H	50	⇩		⇩		⇩		⇩		⇩		⇩		⇩		0	1	⇩		⇩		1	2	2	3	3	4	5	6	7	8	10	11
J	80	⇩		⇩		⇩		⇩		⇩		⇩		0	1	⇩		⇩		1	2	2	3	3	4	5	6	7	8	10	11	14	15
K	125	⇩		⇩		⇩		⇩		⇩		0	1	⇩		⇩		1	2	2	3	3	4	5	6	7	8	10	11	14	15	21	22
L	200	⇩		⇩		⇩		⇩		0	1	⇩		1	2	⇩		2	3	3	4	5	6	7	8	10	11	14	15	21	22	⇩	
M	315	⇩		⇩		⇩		0	1	⇩		1	2	2	3	3	4	5	6	7	8	10	11	14	15	21	22	⇩		⇩		⇩	
N	500	⇩		0	1	0	1	⇩		1	2	2	3	3	4	5	6	7	8	10	11	14	15	21	22	⇩		⇩		⇩		⇩	
P	800	0	1	⇩		⇩		1	2	2	3	3	4	5	6	7	8	10	11	14	15	21	22	⇩		⇩		⇩		⇩		⇩	
Q	1250	⇩		⇩		1	2	2	3	3	4	5	6	7	8	10	11	14	15	21	22	⇩		⇩		⇩		⇩		⇩		⇩	
R	2000	⇧		⇧		1	2	2	3	3	4	5	6	7	8	10	11	14	15	21	22	⇧		⇧		⇧		⇧		⇧		⇧	

Figure 8 The accept (Ac)/reject (Re) acceptance numbers for inspection Level II (normal) as a function of AQL[xxxii]

However, there is flexibility to switch between reduced and tightened inspection Levels (I & III) depending on the ongoing supplier performance. After 30 conforming lots or batches, a reduction of testing is warranted and reduced inspection level I is able to be implemented. However, if a lot fails then Level II is reinstated. If normal inspection (Level II) operation find that 2 of 5 inspections fail the Level III tightened inspection is implemented. If a total of 5 lots are rejected then inspection should be discontinued until the supplier rectifies the quality issue.

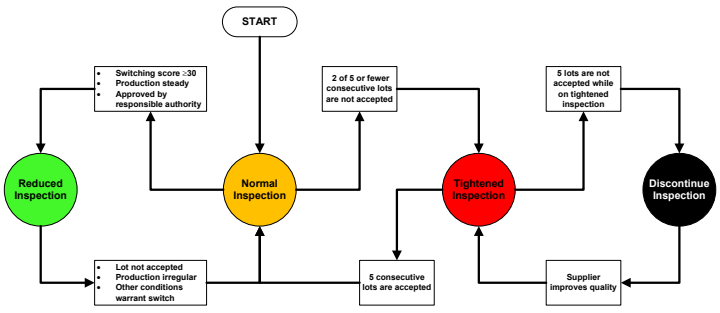

Figure 9 Quality performance; Switching rules[xxxiii]

6.3 WHO guidelines; three reduced sampling plans for starting materials [ix]

Pages 61 to 93 of this guideline discusses three reduced sampling plans for starting materials; the *n, p* and *r* plans. The use of any reduced sampling plan needs to be justified based upon data.

6.3.1 *The n plan*

The most commonly used plan is the **n plan**, more commonly called the 'Root N +1 reduced sampling plan'. The statistical aspects have been discussed by Torbeck in 2009[xxxiv]. The n plan '*assumes a uniform material from a recognized source where there is a high degree of confidence in the source*'. However, WHO makes a strong warning about the use of this plan.

*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.*

In 5.1.1, it continues;

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).

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**.

6.3.2 *The p plan*

In 5.1.2 it describes the p plan noting the caveat

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 *Root 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.

6.3.3 *The r plan*

In 5.1.3, it describes the r plan

The "r plan" may be used when the material is suspected to be nonuniform 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*Root 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.

Illustrative examples of these 3 plans are given in Figure 10.

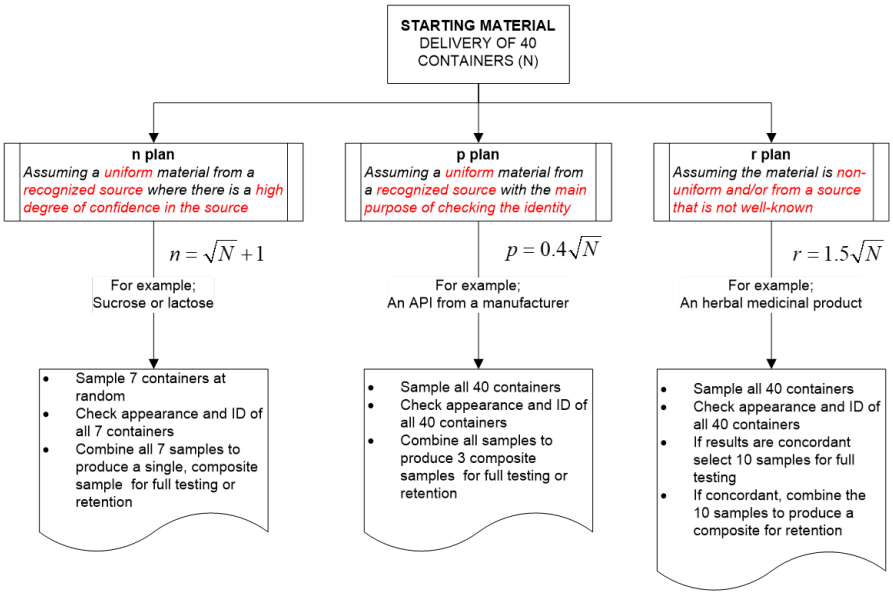

Figure 10 Examples of the WHO n, p & r plans for a consignment of 40 containers

7 Sampling Procedure & Protocol

The parent material (population) to be sampled is a consignment, batch or lot, uniquely identified, and is specified in the procedure and uniquely recorded as part of the procedure and the protocol.

The collection of one or more increments or units taken from a population as required by the material specific sampling procedure and the batch/material specific sampling protocol and suitably identified.

The overall sampling process is driven by the sampling protocol and the requirements of the statistical sampling plan (SSP) for a particular material. This protocol contains the complete sampling operations to be performed on a defined material for a specific purpose and is traceable to the SSP.

These increments may be combined (composited) to form a combined sample if specified in the protocol. A sufficient and representative amount sample for testing, of at least twice the amount required for testing, that can be expected to adequately reflect the characteristics of the parent population should be taken.

7.1 In-process sampling

Much of the sampling effort in companies is focused on materials received and finished products. The importance of a constant structured approach to in-process sampling is often overlooked.

Recently FDA have found it necessary to issue a specific draft guidance in this area [iv].

In section III. GENERAL CONSIDERATIONS FOR IN-PROCESS SAMPLING AND TESTING, it states;

'The determination of whether in-process controls, and tests, or examinations meet the regulatory requirements in § 211.110 primarily depends on the nature of the drug product (e.g., dosage form) and the type of process used by the manufacturer.'

And

'In addition to identifying which critical quality attributes and in-process material attributes to monitor, the manufacturer should ***define and justify where and when the proposed in-process controls****, and testing, or examinations that are used to monitor those attributes should occur.'*

And specifically

'The manufacturer should employ ***a scientifically sound and appropriate sampling*** *and testing* ***strategy*** *for* ***quality attributes at appropriate points in the process*** *that are adequate to ensure drug product quality. The manufacturer should* ***employ time-based sampling plans for quality attributes****, where appropriate.'*

'Although in-process controls, and tests, or examinations of in-process materials are required, ***sampling does not necessarily require steps for physically removing in-process materials to test their characteristics****. Innovative technologies allow in-line, at-line, or on-line measurements in place of physical sample removal for laboratory testing.'*

'In batch manufacturing of a solid oral drug product, blend uniformity should typically be assessed before in-process materials continue to the compression step. ***However, in continuous manufacturing, a manufacturer could conduct sampling and testing at an appropriate point in the process*** *(e.g., at the tablet press feed frame or after compression) to evaluate the adequacy of mixing to ensure batch uniformity and homogeneity.'*

8 Sampling Record

The sampling record is the documented evidence of the actual sampling operations carried out on a particular material for a defined purpose.

The sampling record should contain;

- a unique identifier for the parent material
- date, time and place of sampling
- reference to the sampling protocol used and, by inference, the SST
- a description of the containers, with labelling instructions, of the materials sampled
- the weights of all individual increments or units
- If compositing is undertaken, the analytical sample weight is recorded
- notes on possible abnormalities or deviations
- the name and signature of (all) the operator(s) involved.

Second person review should ensure traceability and compliance throughout this phase.

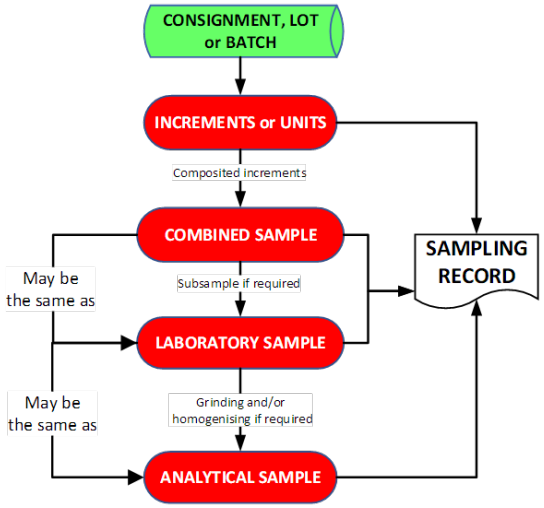

Figure 11 Proposed nomenclature and inputs to the sampling record

9 Additional Guidance sources on sampling

Eurachem and the Royal Society of Chemistry have resources which provide information on sampling and, in particular, measurement uncertainty as listed below.

Guides

- M. H. Ramsey, S. L. R. Ellison and P. Rostron (Eds.) Eurachem/EUROLAB/CITAC/Nordtest/AMC Guide: Measurement uncertainty arising from sampling: a guide to methods and approaches. (2nd ed., 2019). ISBN 978-0-948926-35-8 (www.eurachem.org)
- B. Magnusson, M. Krysell, E. Sahlin and T. Näykki, Uncertainty from sampling – A Nordtest Handbook, Nordtest Report TR 604 ed 2:2020 (www.nordtest.info)

Leaflets

- AMC Technical Briefs, RSC, (https://www.rsc.org/membership-and-community/connect-with-others/join-scientific-networks/subject-communities/analytical-science-community/amc/technical-briefs/):
  - AMC TB 96-2020, What's novel in the new Eurachem guide on uncertainty from sampling?
  - AMC TB 90-2019, The role of accreditation in ensuring sampling quality
  - AMC TB 71-2015, Sampling theory and sampling uncertainty
  - AMC TB 64-2014, Unbalanced robust ANOVA for the estimation of measurement uncertainty at reduced cost
  - AMC TB 58-2014, Estimating sampling uncertainty – how many duplicate samples are needed?
  - AMC TB 42-2009, The importance, for regulation, of uncertainty from sampling
  - AMC TB 40-2009, The duplicate method for the estimation of measurement uncertainty arising from sampling
  - AMC TB 20-2005, Analytical and sampling strategy, fitness for purpose, and computer games
  - AMC TB 16A-2004, What is uncertainty from sampling, and why is it important?

Articles and reports

- P.D. Rostron, T. Fearn, M. H. Ramsey, Comparing Uncertainties – Are they really different?, Accred. Qual. Assur., 2022, 27, 133–142, https://doi.org/10.1007/s00769-022-01501-2
- P. D. Rostron, T. Fearn, M. H. Ramsey, Confidence intervals for robust estimates of measurement uncertainty, Accred. Qual. Assur., 2020, 25, 101-119, https://https://doi.org/10.1007/s00769-019-01417-4
- W. Horwitz, Nomenclature for sampling in analytical chemistry, Pure Appl. Chem., 1990, 62, 1193-1208, http://dx.doi.org/10.1351/pac199062061193

10 Sampling is only part of the Analysis and Testing Process

Whilst this guidance is concerned with sampling and sample management, it forms only the first, albeit critical, part of the journey. The testing aspect is covered in another guidance document, ECA_AQCG_ SOP 03_APLM_v1.0_July 2018.

A high-level process flow is shown in Figure 11.

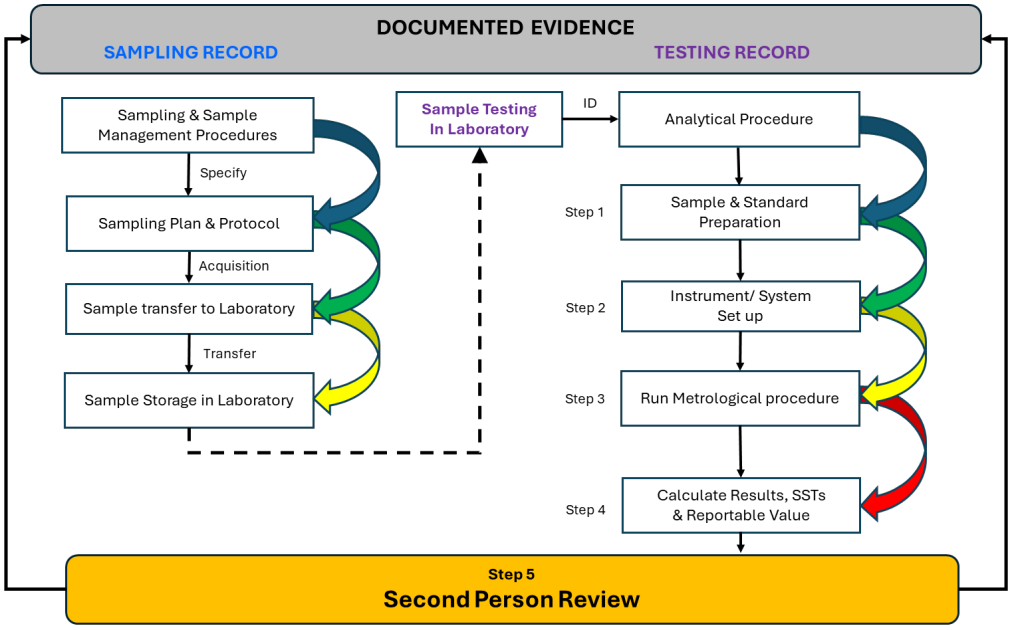

Figure 12 Traceability from sample to reportable value

11 References

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[ii] eCFR :: 21 CFR Part 210 -- Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General

[iii] eCFR :: 21 CFR Part 211 -- Current Good Manufacturing Practice for Finished Pharmaceuticals

[iv] FDA Consideration for complying with 21 CFR §211.110 Guidance for Industry January 2025

[v] EudraLex - Volume 4 - European Commission

[vi] USP-NF, General Notices and Requirements, 3.10. Applicability of Standards

[vii] USP-NF, General Notices and Requirements, 7.10. Interpretation of Requirements (of TEST RESULTS)

[viii] USP-NF, General Chapter <1010> ANALYTICAL DATA—INTERPRETATION AND TREATMENT

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[xxii] Horwitz W., IUPAC *Nomenclature for sampling in analytical chemistry recommendations*, **Pure and Applied Chemistry**, 62(6) 1183-1208 (1990)

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[xxiv] ASTM, *Standard Guide for Defining the Test Result of a Test Method*, E2282-14(2019)

[xxv] Burgess C., *Sampling and Testing Nomenclature for Pharmaceutical Analysis: A Review of Current Practices* **Pharmaceutical Technology** REGULATORY SOURCEBOOK, pages 23-33 (September 2021) Sampling and Testing Nomenclature for Pharmaceutical Analysis: A Review of Current Practices

[xxvi] ECA Guide on GMP, GCP and GDP Data Governance and Data Integrity, version 3, December 2022

[xxvii] Horwitz, W., *Nomenclature for sampling in analytical chemistry* (Recommendations), **Pure and Applied Chemistry**, 62(6) 1183–1208 (1990)

[xxviii] ISO 2859-1:1999 *Sampling procedures for inspection by attributes Part 1*: Sampling schemes indexed by acceptance quality limit (AQL) for lot-by-lot inspection,

[xxix] ISO 3951-1:2022 *Sampling procedures for inspection by variables Part 1*: Specification for single sampling plans indexed by acceptance quality limit (AQL) for lot-by-lot inspection for a single quality characteristic and a single AQL

[xxx] Taylor, Wayne A., *Guide to Acceptance Sampling,* Taylor Enterprises Inc,(1992) ISBN 9780963512208

[xxxi] Re drawn from Table 1 ISO 2859-1:1999

[xxxii] Re drawn from Table 2A ISO 2859-1:1999

[xxxiii] Re drawn from Figure 1 ISO 2859-1:1999

[xxxiv] Torbeck, L. D., *Statistical Solutions: Square Root of (N) + 1 Sampling Plan*, **Pharmaceutical Technology** 33 (10) (2009)