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Guidance for the in-house preparation of quality control materials (QCMs)

Lignes directrices pour la préparation interne des matériaux de référence utilisés pour le contrôle qualité

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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For an explanation on the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the WTO principles in the Technical Barriers to Trade (TBT) see the following URL: Foreword - Supplementary information

The committee responsible for this document is ISO/REMCO, *Committee on reference materials* (which has the task to prepare guidance documents for the preparation, characterization, certification and use of reference materials (RMs) and the competence assessment of reference material producers.

Introduction

Reference materials (RMs) are widely used in measurement laboratories for a variety of purposes and it is important to recognize that the material most appropriate for a particular application should be used. Certified reference materials (CRMs), i.e. those which have property values and associated uncertainties assigned by metrologically valid procedures are primarily used for method validation and calibrations providing metrological traceability.

The preparation of reference materials for metrological quality control (i.e. control of the quality of measurements not products) is an important activity which provides materials suitable for the day-to-day demonstration that a particular (part of a) measurement system is under statistical control. Such materials do not require characterization by metrologically valid procedures, and can be prepared "in-house", i.e. by laboratory staff familiar with their behaviour, to fulfil specific quality control requirements.

Reference materials which are sufficiently homogeneous and stable are necessary for metrological quality control purposes, such as demonstrating a measurement system is under statistical control, performs as expected and provides reliable results; where the trueness of the measurement result is not critical. Different industries use various terminologies to describe such materials (e.g. in-house reference materials, quality control materials, check samples, etc.). For the purposes of this Guide, the term "Quality Control Materials" (QCMs) will be used to simplify repeated citation.

While CRMs are produced by established reference material producers and are commercially available, QCMs are often prepared by a laboratory for its own internal use. Frequently, QCMs are characterized only for a limited scope (a limited number of property values) and for specific laboratory applications.

The rationale for preparing quality control materials can be one or a combination of the following factors:

— to have an RM representing as closely as possible routine samples, suitable for quality control;

— to have a suitable day-to-day RM to complement a commercially available CRM;

— no suitable CRM exists;

— the application does not require a material having the full characteristics of a CRM (e.g. traceability and uncertainty for specified property values).

QCMs are RMs and as such the requirements of ISO Guide 34[1] for the production of RMs apply. However, if the material is only used in-house by the preparing laboratory, some requirements (e.g. for transport stability) can be relaxed. The preparation of a QCM is related to that of a CRM and those preparing QCMs may wish to consult ISO Guides 34[1] and 35[2] for further guidance. Where appropriate, this Guide will refer to relevant parts of these Guides.

It is recognized that the aim of many laboratories requiring QCMs is to minimize the time and effort needed to prepare the materials. To this end, many laboratories use samples of real products for which there is a body of analytical data available. A number of case studies are included as annexes of this guidance document to provide examples of how such data may be processed to confirm fitness for purpose of the materials.

Guidance for the in-house preparation of quality control materials (QCMs)

1 Scope

This Guide outlines the essential characteristics of reference materials for quality control (QC) purposes, and describes the processes by which they can be prepared by competent staff within the facility in which they will be used (i.e. where instability due to transportation conditions is avoided). The content of this Guide also applies to inherently stable materials, which can be transported to other locations without risk of any significant change in the property values of interest.

The primary audience for this Guide is laboratory staff who are required to prepare and use materials for specific in-house quality control applications. Preparation of QCMs, where transportation is a necessary component of the supply chain, such as laboratory sites at different locations or for proficiency testing schemes, should conform to the relevant requirements of ISO Guides 34[1] and 35.[2]

The description of the production of reference materials (RMs), as detailed in ISO Guide 34[1] and ISO Guide 35[2] is also applicable to the preparation of quality control materials (QCMs). However, the requirements for "in-house" QCMs are less demanding than those for a certified reference material (CRM). The preparation of QCMs should involve homogeneity and stability assessments, and a limited characterization of the material to provide an indication of its relevant property values and their variation, prior to use. This document provides the quality criteria that a material should fulfil to be considered fit-for-purpose for demonstrating a measurement system is under statistical control. Guidance on uses of such materials, for example setting up a QC chart, is adequately covered elsewhere [3],[4],[5],[6] and is not included in this Guide.

The layout and structure of this Guide provides general information on the preparation of QCMs in the main chapters, with specific case studies covering a range of sectors in the annexes. The case studies are not complete "process manuals" but are included to highlight some of the key considerations when preparing QCMs. The case studies vary in complexity and detail, including sector specific terminology, but provide a range of information for laboratory staff to draw from.

It is expected that those involved in QCM preparation will have some knowledge of the type of material to be prepared and be aware of any potential problems due to matrix effects, contamination, etc.

2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO Guide 30, *Reference materials — Selected terms and definitions*

ISO/IEC Guide 99, *International vocabulary of metrology — Basic and general concepts and associated terms (VIM)*

ISO 3534-1, *Statistics — Vocabulary and symbols — Part 1: General statistical terms and terms used in probability*

3 Terms and definitions

For the purposes of this document, the terms and definitions in ISO Guide 30[7] ISO/IEC Guide 99[8] and ISO 3534-1[9] and the following apply.

3.1
indicative value
value of a quantity or property, included in the certificate of a CRM or otherwise supplied, which is provided for information only (i.e. is not certified by the producer or the certifying body)

Note 1 to entry: Values assigned to quality control materials (QCMs) can only be indicative in that they have no metrological traceability. ISO Guide 30:1992[7] uses the term "uncertified value" to describe a value of a quantity provided for information only.

4 Quality control materials (QCMs)

The term "quality control material" or "QCM" has been devised for the purposes of this Guide solely to simplify repeated reference to materials used routinely to assess the precision of test procedures. It is not intended to define a new class of reference materials. Such materials are variously referred to in the open literature as "in-house reference materials", "quality control samples", "check samples", "set up samples", etc.

Where no suitable CRM exists, laboratories may use QCMs to provide an assessment of the repeatability / intermediate precision / reproducibility of a measurement result. QCMs cannot be used to establish metrological traceability or trueness of a measurement result.

QCMs should always comply with the basic requirements of any reference material, i.e. they should be sufficiently homogeneous and stable with respect to the properties of interest. The level of heterogeneity should be less than the expected standard deviation of the measurement process or an established criterion value against which the assessment of laboratory performance or the "normalization" of results is acceptable. The QCM should be stable for a period of time that is at least as long as that during which it is intended to be used.

5 Applications of quality control materials (QCMs)

The principal function of QCMs is to provide laboratories with an economical means of checking their routine test procedures for precision on a regular basis (e.g. daily, weekly or monthly).

While CRMs can in all cases replace QCMs, QCMs are not replacements for CRMs; they are complementary to them having a specific, limited purpose in the measurement process. CRMs produced according to the principles of ISO Guide 34[1] are essential to establish the concept of metrological traceability in a meaningful manner, and provide the highest standard with respect to reference materials. There is no requirement for QCMs to have metrologically traceable assigned values; consequently, QCMs cannot be used to establish metrological traceability or to estimate uncertainty. For method validation and uncertainty estimation, QCMs may be used to a limited extent (e.g. for establishment of a precision estimate as part of the total measurement uncertainty).

Uses of QCMs include (but are not limited to):

— preparation of QC charts – to demonstrate control of a measurement process within a laboratory or to confirm the effectiveness of a laboratory's quality control process or to demonstrate control of a measurement process over a period of time;

— comparison of results (e.g. from two or more series of related samples either in a short period of time or over an extended period of time when a measurement process is known to vary);

— method development – to establish consistency (for validation a certified reference material should be used);

— instrument performance checks;

— repeatability and reproducibility studies – repeated use over an extended period of time, instruments, operators, etc., to estimate long-term reproducibility or robustness of a measurement process or laboratory;

— as check samples – for example, to confirm the degree of equivalence of measurement results from two or more laboratories (e.g. provider and user), where the materials are inherently stable;

— operator variability;

— impact of any changes to the environmental conditions (e.g. temperature, humidity).

When confirming that a measurement process is under statistical control,[3],[4],[5],[6] the acceptability of laboratory performance is generally assessed by comparing either the standard deviation or the range of the individual results for the QCM against a pre-established criterion. If a lack of control of the measurement process is identified, the laboratory needs to take action. In the simplest case, this may require repeating the “suspect” measurements, perhaps following a re-calibration of instruments.

A more in-depth discussion of the uses of quality control materials can be found in ISO Guide 33.[10]

Regardless of the intended use, it is necessary to assess homogeneity and stability of a QCM.[11]

6 Steps in the in-house preparation of quality control materials (QCMs)

The fundamental purpose of QCMs is to detect change. In general, more pragmatic and less rigorous protocols can be used for stability and homogeneity steps to strike a balance between material development costs on the one hand and the intended use of the material on the other.

The production of any reference material requires a level of technical and organizational competence. It is acknowledged that in many cases “in-house” QCMs will be prepared by technically competent staff that is knowledgeable about the materials/processes being used.

The key steps involved in the in-house preparation of a typical QCM are summarized in the flow chart in Figure 1 and are described in more detail in References [12] and [13]. Materials can be sourced from, processed, sub-divided and packaged by third parties, where they have specialized equipment and/or expertise. Materials may even be products which are commercially available and meet the user’s specification (e.g. food products available in appropriately sized units from a single production batch).

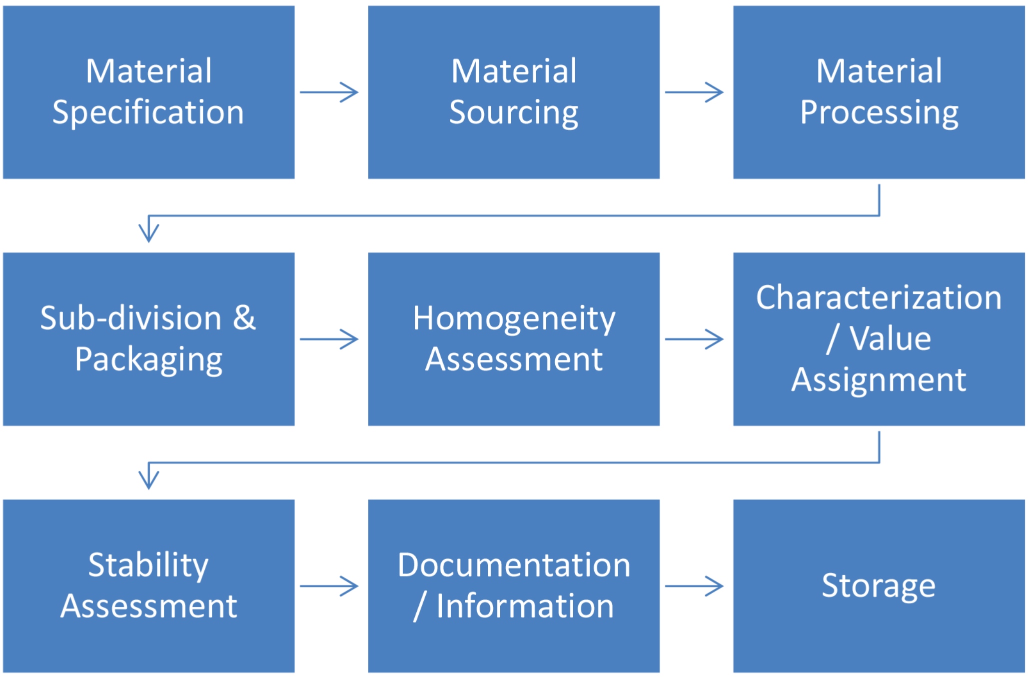

Figure 1 — Key steps in the preparation of a typical QCM

NOTE Any of these steps may be subcontracted to a technically competent subcontractor.

7 Material specification

The key criteria in the specification and selection of a QCM are for the material to be as close as possible to real samples and available in appropriate quantities.

7.1 Matrix type, matching and commutability

In general terms, the uncertainties associated with a measurement result arise from the two main stages of the measurement procedure:

— the preparation of a sample comprising digestion, extraction, clean-up, etc.;

— the measurement of the property in the prepared sample by a suitable technique.

The scope and applicability of a matrix reference material is an important consideration for both the production and use of all reference materials.

The matrix of the QCM should be the same or as similar as possible to the matrix of the routine test samples, so that a satisfactory result for the QCM is genuinely indicative of satisfactory results for the test samples. This matrix matching requires some knowledge of the analytical procedure used on the routine samples, so that a judgment can be made as to the degree of variation of the physical/chemical properties of the sample and test matrices that may cause them to respond differently to a particular measurement procedure. For example, a freeze-dried food matrix may behave differently during analysis to a similar foodstuff with higher moisture content.

Generally, QCMs are prepared for specific purposes and the materials' properties can be closely matched to the samples under analysis.

Commutability has particular significance in clinical chemistry and has been described elsewhere.[14]

In practice, the impetus for the preparation of a QCM may often be the fact that adequate matrix CRMs are not available and therefore the QCM producer is likely to use the specific matrix/property combination in question and matching is not an issue.

7.2 Properties and property values

As for any reference material, the QCM should be characterized for those properties that are of particular importance in the measurement of the routine test samples. The properties of the QCM should be as similar as possible to those expected in the test samples. This may require some preliminary screening measurements to be carried out on a number of candidate materials, to enable the most appropriate to be selected.

7.3 Unit size

Unit size is the amount of material that comprises a single bottled unit of the QCM. When preparing a QCM, the size of individual units should be based on the likely use, i.e. the amount of material required for the measurements concerned and whether the units are to contain sufficient material for a single analysis or for multiple measurements.

7.4 Total bulk amount of material

An estimate is required of the total bulk amount of candidate material that should be sourced. In principle, this may be estimated by considering

— the number of units per year required by the laboratory,

— the unit size,

— the preparation yield,

— the quantity of material that can readily be homogenized,

— the length of time the supply is to be maintained and the assumed stability of the material,

— the type and size of the required storage facility.

8 Preparation of quality control materials (QCMs)

8.1 Sourcing of bulk material

Sourcing and processing of bulk materials for QCM preparation may at first seem difficult especially in those cases where large quantities of material are required. However, there are a number of options that may be available including:

— excess sample material;

— accurate gravimetric formulation.

Processing the bulk material can have significant cost implications for the preparation of QCMs and simple, straightforward processing methods should be used to ensure cost-effective QCM preparation. The exact preparation procedures required for a particular QCM will depend on the nature of the matrix and the properties of interest.

In general, liquid matrix QCMs are much easier to produce than their solid counterparts. The main reason for this is that homogeneous liquids can easily be achieved even with fairly rudimentary equipment (e.g. large mixing containers equipped with paddle or magnetic stirrers). A liquid is easily spiked, filtered or mixed with additives and stabilizers. The corresponding processes for solid materials, milling, grinding, mixing and sieving are much more difficult to accomplish homogeneously, especially for quantities greater than 20 kg. These techniques require a significant investment in major capital equipment when large-scale preparation is envisaged.

During preparation of both liquid and solid materials it is important to prevent contamination by substances which can potentially interfere with the intended measurement process (e.g. a similar material or contamination of a blank material). Hence, all bottles, vials or flasks to be used for final containment must be carefully cleaned and dried before filling to remove possible contaminants.

When sourcing biological materials for example, for control of measurement procedures for medical laboratories, the following specific issues need to be considered:

— ethics of the retention and use of residual patients' samples for the preparation of QCMs;

— legal liabilities of retention and use of residual patients' samples purchased for the preparation of QCMs;

— medical laboratories creating QCMs need to have a high degree of confidence in the trueness of the material selected, to avoid use of misidentified organisms;

— materials sourced for QCM preparation should be screened for potential risks for health hazards, especially if the preparation includes the use of contaminated sharps or has the potential for aerosol formation.

8.2 Material processing

8.2.1 General

Once the bulk material has been sourced there are a number of processing stages which may need to be carried out to ensure the material has the appropriate homogeneity and stability for its intended purpose. Some of the more common processes are described in the following sub clauses.

8.2.2 Drying

Removal of water makes matrix materials far easier to handle and also improves both their short and long term stability. Drying of soils and similar matrices may be carried out at ambient or elevated temperature, depending on the properties of interest, since the more volatile components may be partly lost at higher temperatures. Water removal also reduces the likelihood of microbial growth formation, which is a particular problem with biological materials. Freeze-drying is a technique which is useful with temperature sensitive properties or matrices.

8.2.3 Milling and grinding

For solids, some form of crushing, milling, grinding and particle size reduction is often necessary to ensure uniform particle size and to improve homogeneity. For large bulk quantities, these processes are slow and may take several days to complete. Care should be taken not to introduce contamination from the apparatus during the grinding process. The health and safety aspects of grinding large quantities of particulate matter, which may have toxic components, should also be considered. Cryogenic grinding at −78 °C (solid CO_2) or −196 °C (liquid N_2) may be necessary for polymers, biological, oily/fatty and thermally labile materials.

8.2.4 Sieving

Sieving is often carried out after milling and grinding to improve material homogeneity. Particulate materials such as soils, ores, ashes and ground biological materials are passed through a standard sieve to remove large particles that are above a prescribed size.

Sieving however changes the matrix composition. If a large fraction is removed by sieving, the analyte concentration may change and the matrix may no longer reflect the composition of regular test samples.

8.2.5 Mixing and blending

Bulk solid material should be homogenized by thorough mixing, using for example a roll-mixer, shaker or end-over-end mixer. Such mixing is carried out after milling, grinding and sieving.

Blending of two or more materials with sufficiently similar matrix compositions and differing property values may enable the preparation of QCMs with a desired property values, a set of similar QCMs covering a range of property values, or the preparation of QCMs from an existing reference material.

In order to obtain homogeneous mixtures, the materials to be mixed should have similar densities and particle size distributions.

8.2.6 Filtration

Filtration of solutions before bottling removes any particulate and fibrous solids that would compromise the homogeneity of the bulk material. However, some liquids cannot be filtered due to i) viscosity, ii) potential loss of active ingredients by adsorption to the filter or iii) the introduction of contamination. Qualification of the filter is critical to avoiding loss of active ingredients.

Typically, liquids, waters and leachates are filtered through a 0,45 µm filter prior to bottling or ampouling.

8.2.7 Stabilization

Certain analytes are unstable in solution and as a consequence need to be stabilized at the bulk stage of the preparation procedure. Metals, for example, can precipitate out of neutral or alkaline solutions because of hydrolysis or oxidation and adjustment of the pH of the solution to below 2 counteracts this problem. Copper at a concentration of 1 $mg{\cdot}l^{-1}$ has been used to counteract algal growth in aqueous solutions. Different materials may require other approaches such as addition of antioxidants, preservatives, texture stabilizers, etc.

8.2.8 Sterilization

Prepared soils, sewage sludges and biological materials may contain persistent pathogens that are potentially harmful to humans. They may also contain spores that cause fungal moulds to develop on storage, which could initiate changes in either the composition of the bulk material or the individual units. Such organisms need to be destroyed before the final units are prepared and packaged.

Before sterilizing any candidate QCM, it is important to consider the impact of the proposed sterilization process on the material, particularly those which degrade at elevated temperatures.

Autoclaving is an inexpensive and convenient means of sterilization that can be used for materials that are temperature resistant, for example metals in sediments. Autoclaving can be done on the bulk material prior to final homogenization and unit preparation or on the final samples. However, it is important to ensure that the core of the material reaches 121 °C.

Irradiation can be used on the final packaged units (e.g. ampoules, bottles or pouches). Gamma irradiation is a convenient means of sterilization at ambient temperature so changes in matrix composition are less likely than with autoclaving. Dose values need to be determined such that they are effective in removing pathogens but do not adversely affect the material by, for example, raising the temperature to unacceptable levels (e.g. chocolate). However, gamma irradiation is beyond the means of most laboratories, requiring specialist sub-contractors.

8.3 Sub-division and packaging

8.3.1 General

Once the bulk material has been processed it will need to be sub-divided and packaged. The following sub clauses describe some of the key considerations for the sub-division process and choice of containers to ensure the QCM is sufficiently homogeneous and stable for its intended purpose.

8.3.2 Choice of containers

For QCMs to be produced cost-effectively one aspect that needs careful consideration is the choice of appropriate containers for the individual units. If unsuitable containers are used, a material may quickly degrade to the extent that time-consuming and expensive sourcing and preparation work on the bulk material may have to be repeated. The type of container used depends on the inherent stability of the material and the length of time it is required to remain stable. For particularly susceptible materials, two forms of containment (e.g. a vial within a polyethylene bag) can provide additional protection against degradation and contamination.

The following examples serve to illustrate the need for careful consideration of the container and its closure.

— Organic materials can either lose or pick up ***moisture*** if the container is not securely closed. Glass containers with screw-caps fitted with "polycone" inserts[1)] are preferable to simple screw caps. Sealed cans, foil pouches or septum-lined crimp-top vials offer more security.

— ***Oxygen sensitive materials*** should be prepared and sub sampled under an inert gas atmosphere (nitrogen or argon).

— For water samples containing low concentrations of metals (e.g. mg/kg or below), glass containers are not recommended because of possible adsorption of the metals onto the walls over time. High-density polyethylene (HDPE) bottles with screw-caps are more suitable for this application, but they themselves have the potential problem of loss of water by evaporation through the bottle walls. This can be minimized by storage in a refrigerator (rather than at ambient temperature) or by the use of fluorine-treated polyethylene bottles.

1) Polycone liners are cone-shaped polyethylene cap liners that provide a better seal than simple wadded cap closure.

— The possibility of contamination of the QCM by the ***leaching of impurities*** from the container should also be considered. For example, the iron content of canned foodstuff QCMs may be subject to unpredictable increases on a can-by-can basis, as iron leaches from the can wall into the food matrix. Bottles (whether glass or HDPE) containing aqueous acid solutions may also give rise to leaching problems. As a general rule, containers that might interact with the QCM should be carefully evaluated before use by suitable leaching trials.

— For relatively inert matrices, such as soils and other dried environmental or biological materials, screw-cap glass jars are usually satisfactory. Amber glass gives additional protection against degradation induced by light.

— QCMs comprising relatively volatile components susceptible to evaporation, such as some organic solvents, will normally require a septum-lined crimp-top, glass vial or flame-sealed glass ampoules. Vials and ampoules should preferably be amber to reduce the impact of light.

Some preliminary experimental work, including blank studies, may be required to identify the most suitable container type to use for a particular QCM.

The effect of repeated opening and closing of the sample containers may also be assessed if repeated use of the material is anticipated.

Tamper evident closures should be considered if the unit should only be used once.

8.3.3 Sub-division procedures

Once a homogeneous bulk material has been produced, the essential requirement of any sub-division process is that the homogeneity of the material is maintained. That is, the sub-division process itself, or the time taken to complete the sub-division of a bulk material, should not re-introduce heterogeneity into the material. This may conceivably occur in a number of ways.

Matrices comprised of mixtures of liquids of differing volatilities (e.g. ethanol in water) may undergo selective evaporation of one component during a prolonged sub-division run, causing a rising or falling trend in property value from the first to the last units produced. Effects of this sort may be minimized by protecting the bulk material from evaporation and by completing the sub-division in as short a time as is consistent with accurate dispensing.

All liquids and solutions should be stirred continuously while individual aliquots are being dispensed. Solutions should be filtered before dispensing commences if particulates are likely to be present to an extent that could affect the properties of interest.

Care should be taken with solid particulate matrices such as soils, sediments, industrial products, etc. to ensure that segregation of finer particles does not occur during sub-division. Special care should be taken when sampling bulk material from a large drum, to ensure that there is no vertical segregation. Riffling is a process for representatively subdividing free-flowing powdered materials so that each aliquot receives similar particulate fractions. When operated effectively, riffling minimizes flow segregation and produces units with low between-unit variation. Commercial riffling devices can be used to sub-divide such materials without introducing heterogeneity. Sampling and sub-division of particulate materials are described in more detail in ISO 14488:2007.[15]

In food matrices with a high fat content (e.g. mackerel paste), there may be a tendency for the fat to separate as a discrete phase. If such effects occur, the matrix should be stirred continuously during dispensing and/or additives included in the matrix to slow down the separation process.

As a general principle, sub-division of a bulk material should be completed as quickly as possible to minimize the opportunities for the matrix to revert to heterogeneity. Where appropriate, steps should be taken to maintain a homogeneous bulk material during the sub-division process. It may be necessary to discard the first and/or last portions dispensed from the bulk material, especially of complex matrices that are especially prone to segregation effects.

In the case of QCMs intended for trace analysis, special care must be taken not to introduce additional impurities (e.g. from the air, apparatus, laboratory vessels, etc.) during subdivision of the material as this could change the property value being measured.

9 Homogeneity

9.1 Overview

Homogeneity is a relative concept. The required level of homogeneity of a QCM is dependent on an understanding of the expected variation of the amount of sample used in the measurement process under investigation (see 7.3). In all cases, the level of inhomogeneity should result in a smaller effect on the measurement result than the expected variation of the measurement process or should be below an established criterion value.

Once a candidate QCM has been sub-divided into individual aliquots it is important to establish whether there are any variations in its property values between aliquots. For certain QCM matrices, such as true solutions which have been prepared by procedures such as filtration (to remove particulates) and thorough mixing, formal homogeneity testing is, in principle, not necessary. Such materials may be formally regarded as being inherently homogeneous. Nevertheless, because of the risk of contamination (e.g. introduced due to packaging) or imperfect subdivision, it is recommended to carry out a simple homogeneity study.

For more complex matrices such as foodstuffs, soils and solid matrices that are inherently heterogeneous, a formal experimental investigation of homogeneity is required. A sufficient number of units, representative of the entire batch of the QCM should be chosen and analysed for selected properties. [1] In certain instances, one property can be chosen to represent and quantify the homogeneity of several properties of a similar general type. This should be based on scientific evidence or on previous experience that certain properties exhibit similar behaviour [13] or are known to have a strong tendency to homogeneous distribution in the sample (e.g. some metals in alloys).

A statistical evaluation of the data and a test for sufficient homogeneity are carried out, which can be readily achieved using spreadsheet software (see 9.3). ISO Guide 35[2] details the requirements for the assessment of homogeneity and gives full details and examples of recommended approaches for the design of homogeneity studies and the statistical treatment of homogeneity data.

Homogeneity has two aspects, between-unit homogeneity and within-unit homogeneity. Between-unit homogeneity reflects the variation in the measurement results in each unit of the material. Within-unit homogeneity is reflected in the minimum size of subsample that is representative for the whole unit. It should be confirmed that sample sizes typically used in the day-to-day analysis are larger or at least equal to this size.

9.2 Analytical approach

A validated analytical method having a sufficient degree of repeatability should be selected for evaluation of the homogeneity. The selected units should be representative of the entire batch and the number of units is dictated by the total number of units produced.

Sampling guidelines [16] for the homogeneity testing of multi-unit batches recommend that for a stock comprising "*n*" individual units of material the number of units to be analysed for homogeneity should be three times the cubed root of "*n*". For a stock of 600 to 1 000 units this equates to between 27 and 30 units to be analysed in duplicate. This represents a considerable analytical effort which will be time-consuming and expensive. A study of the impact of reducing the number of units selected for homogeneity assessment of a QCM [2] concluded that in certain circumstances 10 units analysed in duplicate were sufficient. For the preparation of a QCM therefore, there may be scope for cost savings by reducing the number of units selected for homogeneity testing, although this should be assessed on a case by case basis.