OVERVIEW OF RM PRODUCTION

RM Production – An overview

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6.1 General

- ✓ The production and distribution of an RM require careful planning prior to undertaking any actual activity in the project.
- ✓ The following slides provide
- brief overview of the steps involved in the production of a reference material
- description of the main issues involved in planning each step

6.2 Summary of project design

Production of an RM involves the following steps:

a) definition of the RM, i.e. the matrix, the properties to be characterized and their desired levels, the intended use of the material, and for CRMs, the target uncertainty;
b) design of a procedure for the sourcing of the material;
c) design of a reference material manufacturing and/or preparation procedure;
d) selection of measurement procedures appropriate for **characterization**, **homogeneity** and **stability** studies;
e) consideration of metrological traceability for each measured property, particularly for CRMs, for which a statement of metrological traceability is required;
f) assessment of homogeneity;

6.2 Summary of project design

Production of an RM involves the following steps:

g) assessment of stability;
h) assessment of commutability (if required);
i) characterization of the reference material;
j) combination of the results from homogeneity studies, stability studies, and, for CRMs, evaluation of the measurement uncertainties of certified values;
k) preparation of a certificate or product information sheet and, if appropriate, a report on the production and/or certification;
l) specification of storage and transportation conditions;
m) post-production monitoring of stability.

6.3 Acquisition of starting material

The **first task in an RM production project** is the acquisition of a **sufficient amount of starting material(s) with the desired properties**. The **amount of material** needed is determined by the following:

a) **No. of units of the RM needed for distribution over the expected life of the RM;**
b) **No. of units needed for homogeneity study;**
c) **No. of units needed for stability study;**
d) **No. of units needed for the characterization of the candidate RM;**
e) **No. of units required for monitoring stability over the expected lifetime of the material;**

6.3 Acquisition of starting material

f) the planned **size of each RM unit**, which has to be sufficient for at least one measurement;
g) the need for one or more **feasibility studies**

Optionally, **additional units to cover contingencies** such as, for example,

- ✓ **follow-up studies** to respond to customer queries,
- ✓ **future recertification** required by a significant change in the storage conditions, or
- ✓ **extension of the number of certified properties**.

It may be prudent to limit the No.of units produced for less stable materials to avoid wastage due to unavoidable degradation over time.

6.4 Feasibility studies

Feasibility studies are short studies intended to address concerns about the feasibility of producing and characterizing a sufficiently homogeneous and stable RM.

Questions such as the best way of preparing the RM or ensuring sufficient stability of the material can be answered by small-scale feasibility studies.

Where characterization is expected to be performed through the use of an interlaboratory study, a feasibility study can identify possible sources of error and enable participants involved in the characterization to optimize their equipment and procedures.

6.5 Reference material processing

Processing can involve a range of processes, including, for example:

— synthesis, manufacture or formulation of a synthetic reference material;

— drying, lyophilisation, milling, and/or filtration for natural materials;

— addition of stabilizing agents;

— homogenization prior to packaging.

The particular procedures used depend on the particular material and usually require expert guidance.

6.6 Homogeneity assessment

Homogeneity is an important requirement for all RMs and includes **both within- and between-unit homogeneity**.

Between-unit homogeneity is important to ensure that each RM unit carries the same value for each property;

Within-unit homogeneity is important where subsamples can be taken for measurement by users of the material.

6.7 Stability assessment

RMs should be sufficiently stable for their intended use, so that the end user can rely on the assigned value at any point within the period of validity of the certificate.

It is important to consider stability under long-term storage conditions, under transport conditions and, where applicable, the storage conditions at the RM user's laboratory.

This can include consideration of stability after opening, if re-use is permitted.

6.8 Choice of measurement procedures

In a reference material production project, each step that requires measurements may use different measurement procedures;

Characterization generally requires **minimally biased measurement procedures with low uncertainty**;

Homogeneity studies primarily require the **best available repeatability**; and

Classical stability studies typically require measurement procedures that show **good precision over time within the same laboratory.**

6.9 Metrological traceability

Metrological traceability is key to ensuring the comparability of measurement results over time and between locations,

This includes the measurement results used to characterize reference materials.

By definition, CRMs are accompanied by a statement of metrological traceability for each certified property value.

The proper choice of the stated references to which metrological traceability of the property values is established is essential for CRMs, because CRMs are primarily used to make measurement results traceable.

6.10 Characterization and uncertainty evaluation

Characterization refers to the **determination of the property values of the relevant properties of an RM**, as part of the production process.

For CRMs, certified values are accompanied by **a statement of measurement uncertainty**

6.11 Commutability assessment

Commutability is particularly important where different measurement procedures can respond very differently to different types of test materials.

Commutability assessment is not required for all RMs but is required for some important classes of RM. (e.g) **Clinical RMs**

6.12 Transport issues

RMs should be sufficiently stable for their intended use, so that the end user can rely on the assigned value at any point within the period of validity of the certificate.

It is important to consider stability under long-term storage conditions, under transport conditions and, where applicable, the storage conditions at the RM user's laboratory.

This can include consideration of stability after opening, if re-use is permitted.

6.13 Value assignment

Value assignment is the **process of combining the results from the homogeneity and stability assessment with the results from the characterization studies** to determine the assigned values and their uncertainties.

6.14 Stability monitoring

RMs are **stored for extended periods** at the **RM producer's premises** or by **distributors**.

Since **stability assessment** cannot usually anticipate all changes that may occur, it is usually necessary, **as a part of managing the risks associated with possible instability**, to monitor the property values of materials held for extended periods.

6.15 RMs produced in repeated batches

Need for experimental study of homogeneity, stability and commutability can be reduced where the material is produced in a repeat production run following an established procedure.

Reliance on prior experience is reasonable so long as:

a) the process for producing batches of the RM has not changed in any way that might adversely affect the end use;

b) the materials used in production of the RM have not changed in any way that might adversely affect the end use;

6.15 RMs produced in repeated batches

c) materials previously produced by the same process have shown no failures attributable to the production process, either during routine monitoring or by users; and

d) the requirements for the material are reviewed regularly, taking account of the intended use of the material at the time of the review, to ensure that the production process remains fit for purpose.

Consistent performance of the production process should be checked, for example by comparing the property values of samples from successive batches under repeatability conditions.