ISO 33405:2024-05 (E)

Reference materials - Approaches for characterization and assessment of homogeneity and stability

Contents

Page

Foreword vi

Introduction vii

1 Scope 1

2 Normative references 1

3 Termsanddefinitions 1

4 Symbols 2

5 Conventions 3

6 Overview of reference material production 3
6.1 General 3
6.2 Summary of project design 3
6.3 Acquisition of starting material 5
6.4 Feasibility studies 6
6.5 Reference material processing 6
6.6 Homogeneity assessment 6
6.7 Stability assessment 6
6.8 Choice of measurement procedures 7
6.9 Metrological traceability 7
6.10 Characterization and uncertainty evaluation 7
6.11 Commutability assessment 7
6.12 Transport issues 7
6.13 Value assignment 8
6.14 Stability monitoring 8
6.15 Reference materials produced in repeated batches 8

7 Assessment of homogeneity 8
7.1 Preamble 8
7.2 Need for an experimental homogeneity study 9
7.3 Properties to be studied 10
7.4 Statistically valid sampling schemes 10
7.4.1 Minimum number of units for a homogeneity study 10
7.4.2 Use of statistical power analysis 12
7.4.3 Sampling strategies for a homogeneity study 12
7.5 Choice and conduct of the measurement procedure for a homogeneity study 13
7.5.1 Choice of measurement procedure 13
7.5.2 Conduct of measurements for homogeneity studies 13
7.6 Homogeneity study designs 15
7.6.1 Objective of a homogeneity study 15
7.6.2 The basic homogeneity study design - measurement in a single run 16
7.6.3 Randomized block design 17
7.6.4 Balanced nested design 17
7.6.5 Alternative strategies 17
7.7 Evaluating a homogeneity study 18
7.7.1 Initial inspection for measurement trends and outliers 18
7.7.2 Inspection for processing trends 19

7.7.3 Evaluation of the between-unit term - basic design 19
7.7.4 Evaluation of the between-unit term - randomized block design 20
7.7.5 Evaluation of the between-unit term - balanced nested design 21
7.7.6 Other homogeneity designs and alternative estimation methods 21
7.8 Insufficient repeatability of the measurement procedure 22
7.9 Within-unit homogeneity 22
7.9.1 Assessing the need for within-unit homogeneity study 22
7.9.2 Testing for significant within-unit heterogeneity 22
7.9.3 Assessing minimum sample size 24

7.10 Check for sufficient homogeneity 25
7.11 Uncertainty evaluation from homogeneity studies 26

8 Assessment and monitoring of stability 26
8.1 Preamble 26
8.2 Assessment of stability 27
8.2.1 Requirement for stability assessment 27
8.2.2 Types of (in)stability 27
8.2.3 General methods for assessment of stability 28
8.2.4 Need for experimental study of stability 28
8.3 Classification of stability studies 29
8.3.1 General 29
8.3.2 Classification according to conditions of measurement 29
8.3.3 Classification according to stability study duration and conditions 30
8.3.4 Classification by study objective 30
8.3.5 Designs for different storage and treatment conditions 31
8.4 General requirements for effective stability studies 32
8.4.1 Overview of requirements 32
8.4.2 Selection of RM units 32
8.4.3 Suitable measurement procedure(s) for stability studies 32
8.4.4 Appropriate experimental design 32
8.5 Evaluation of stability study results 33
8.5.1 General considerations for stability study data treatment 33
8.5.2 The basic stability study: multiple points in time at a single storage condition 34
8.5.3 Isochronous designs 36
8.5.4 Accelerated stability studies with multiple exposure conditions 38
8.5.5 Additional sources of random variation in stability studies 41
8.6 Action on finding a significant trend in a stability study 41
8.7 Uncertainty evaluation from stability studies 42
8.7.1 General considerations for uncertainty evaluation from stability studies 42
8.7.2 Sources of uncertainty in predicted change over time 42
8.7.3 Estimation of stability uncertainties in the absence of significant trends 43
8.7.4 Evaluation of stability uncertainties in the case of a known significant trend 43
8.8 Estimation of storage lifetime ("shelf life") from a stability study 44
8.9 Instructions for use related to management of stability 44
8.10 Stability monitoring 44
8.10.1 Requirements for monitoring 44
8.10.2 Choice of initial monitoring point and monitoring interval(s) 45
8.10.3 Experimental approaches and evaluation for stability monitoring 46

9 Characterization of the material 47
9.1 Preamble 47
9.2 Establishing metrological traceability 48
9.2.1 Principle 48
9.2.2 Metrological references 48
9.2.3 Types of measurands 49
9.2.4 Effect of sample preparation or pre-treatment 49
9.2.5 Verification of traceability 50
9.3 Characterization using a single reference measurement procedure (as defined in ISO/IEC Guide 99) in a single laboratory 50
9.3.1 Characterization by a reference measurement procedure without direct comparison with a CRM of the same kind 50

9.3.2 Characterization by value transfer from a reference material to a closely matched candidate reference material using a single measurement procedure performed by one laboratory 51
9.3.3 Selection of RM units for single-laboratory characterization 52
9.3.4 Formulation methods 52
9.4 Characterization of a non-operationally defined measurand using two or more methods of demonstrable accuracy in one or more competent laboratories 53
9.4.1 Concept 53

9.4.2 Study design 54
9.4.3 Evaluation 55
9.4.4 Single-laboratory multi-method studies 56
9.5 Characterization of an operationally defined measurand using a network of competent laboratories 56
9.5.1 Concept 56
9.5.2 Study setup 57
9.5.3 Evaluation 57
9.6 Purity 57
9.6.1 General 57
9.6.2 Direct determination of purity 57
9.6.3 Indirect determination of purity 58
9.7 Ordinal scales 59
9.8 Nominal properties including identity 59
9.9 Characterization of non-certified values 59

10 Evaluating measurement uncertainty 59
10.1 Basis for evaluating the uncertainty of a property value of a CRM 59
10.2 Basic model for a batch characterization 60
10.3 Uncertainty sources 61
10.4 Coverage intervals and factors 61

Annex A (informative) Design and evaluation of studies for the characterization of a method-independent measurand using two or more methods of demonstrable accuracy in one or more competent laboratories 62

Annex B (informative) Statistical approaches 73

Annex C (informative) Examples 84

Annex D (informative) Measurement uncertainty evaluation 94

Bibliography 95