Joint Research Centre (JRC)

Reference materials: concepts, applications and examples

IRMM - Institute for Reference Materials and Measurements

Geel - Belgium

http://irmm.jrc.ec.europa.eu/

http://www.jrc.ec.europa.eu/

1960-2010 IRMM 50 Institute for Reference Materials and Measurements

ISO Guides (ISO REMCO 1976)

Number	Title	Published
Guide 30	Terms and definitions used in connection with reference materials and certified reference materials	1981, 1992, 2008 (Amd)
Guide 31	Reference materials - Contents of certificates and labels	1981, 2000
Guide 32	Calibration in analytical chemistry and use of certified reference materials	1997
Guide 33	Uses of certified reference materials	1989, 2000, in revision
Guide 34	General requirements for the competence of reference material producers	1996, 2000, Cor. 2003, 2009
Guide 35	General and statistical principles for certification	1985, 1989, 2006

ISO REMCO definition Reference Material (RM)

Material, sufficiently homogeneous and stable with respect to one or more specified properties, which has been established to be fit for its intended use in a measurement process.

Notes:
1) RM is a generic term.
2) Properties can be quantitative or qualitative, e.g. identity of substances or species.
3) Uses may include the calibration of a measurement system, assessment of a measurement procedure, assigning values to other materials, and quality control.
4) A RM can only be used for a single purpose in a given measurement. For instance, the same RM cannot be used for both calibration and validation of results in the same measurement procedure.
5) VIM has an analogous definition (ISO/IEC Guide 99:2007, 5.13), but restricts the term 'measurement' to apply to quantitative values and not to qualitative properties. However, Note 3 of ISO/IEC Guide 99:2007, 5.13 specifically includes the concept of qualitative attributes, called "nominal properties".

ISO Guide 30:1992/Amd.1:2008

ISO REMCO definition Certified Reference Material (CRM)

Reference material characterized by a metrologically valid procedure for one or more specified properties, accompanied by a certificate that provides the value of the specified property, its associated uncertainty, and a statement of metrological traceability.

Notes: **1) The concept of value includes qualitative attributes such as identity or sequence. Uncertainties for such attributes may be expressed as probabilities.**
2) Metrologically valid procedures for the production and certification of reference materials are given in, among others, ISO Guides 34 and 35.
3) ISO Guide 31 gives guidance on the contents of certificates.
4)VIM has an analoguous definition (ISO/IEC Guide 99:2007, 5.14).

ISO Guide 30:1992/Amd.1:2008

Type of materials

Non reference materials

Reference materials

- non-certified reference materials
- certified reference materials

Names used

Non-RMs:

test materials, study materials

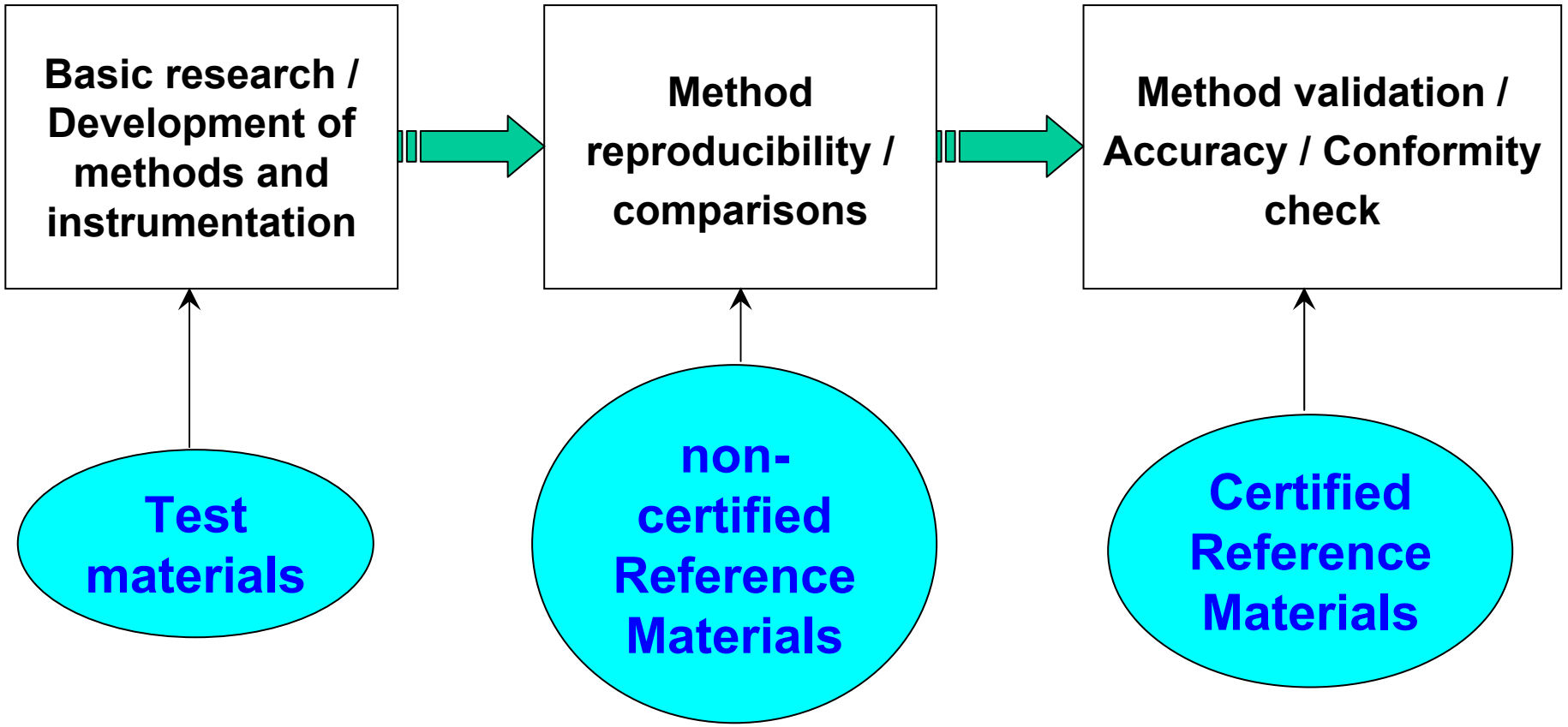
RMs:

test materials
in-house materials
quality control materials (QCM)
laboratory control materials (LCM)

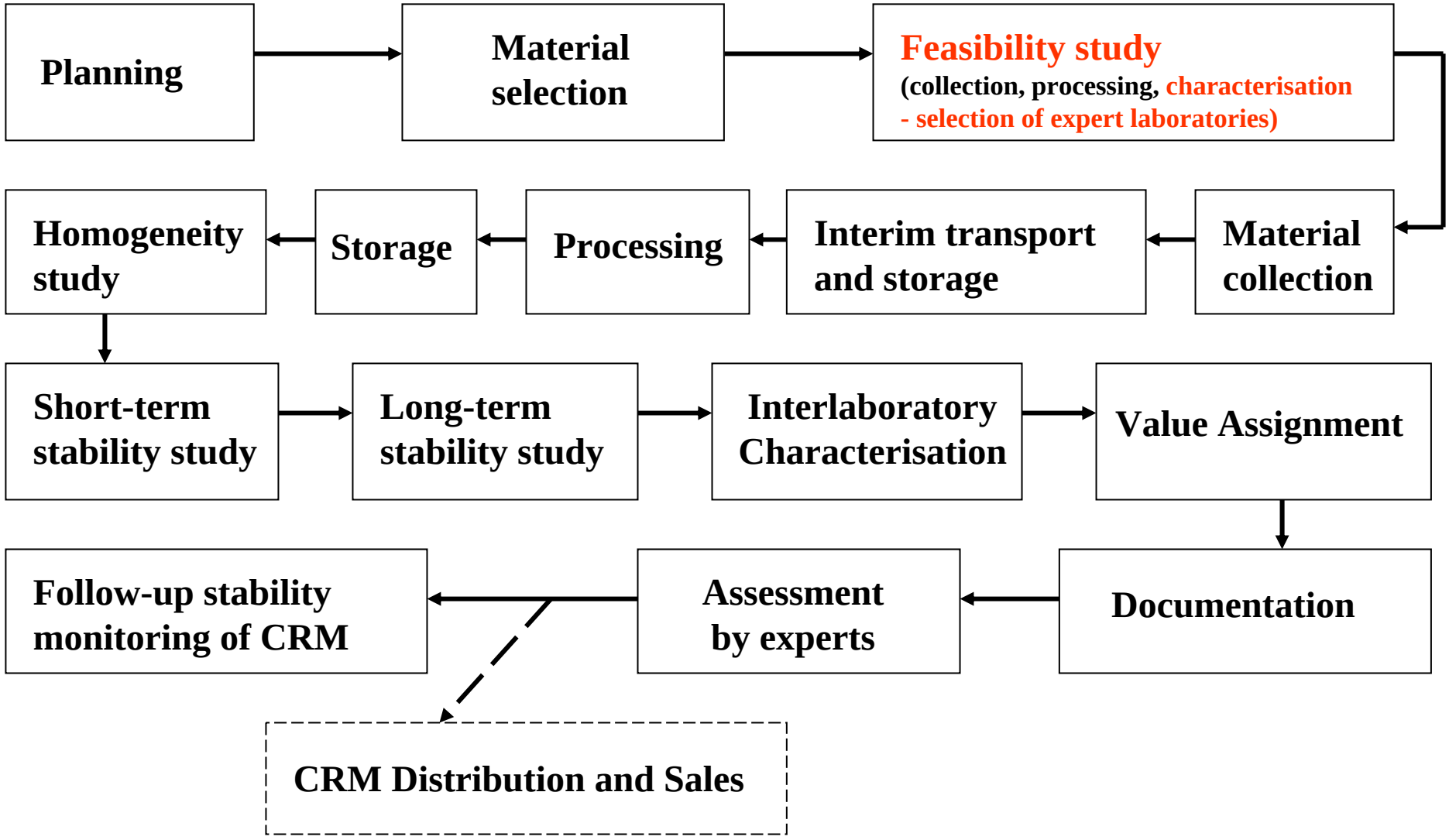
CRMs:

SRMs: NIST trademark for CRMs
BCR/IRMM/ERM labels: IRMM
BAM/ERM labels: BAM
LGC/ERM labels: LGC
…..
standards: documentary standard

"Sequence" of 'analytical' materials



General Procedure for CRM Production



Certified Reference Materials (CRMs)

ISO Guide 34 Competence of producers of Reference Materials

ISO Guides 30, 31 and 35

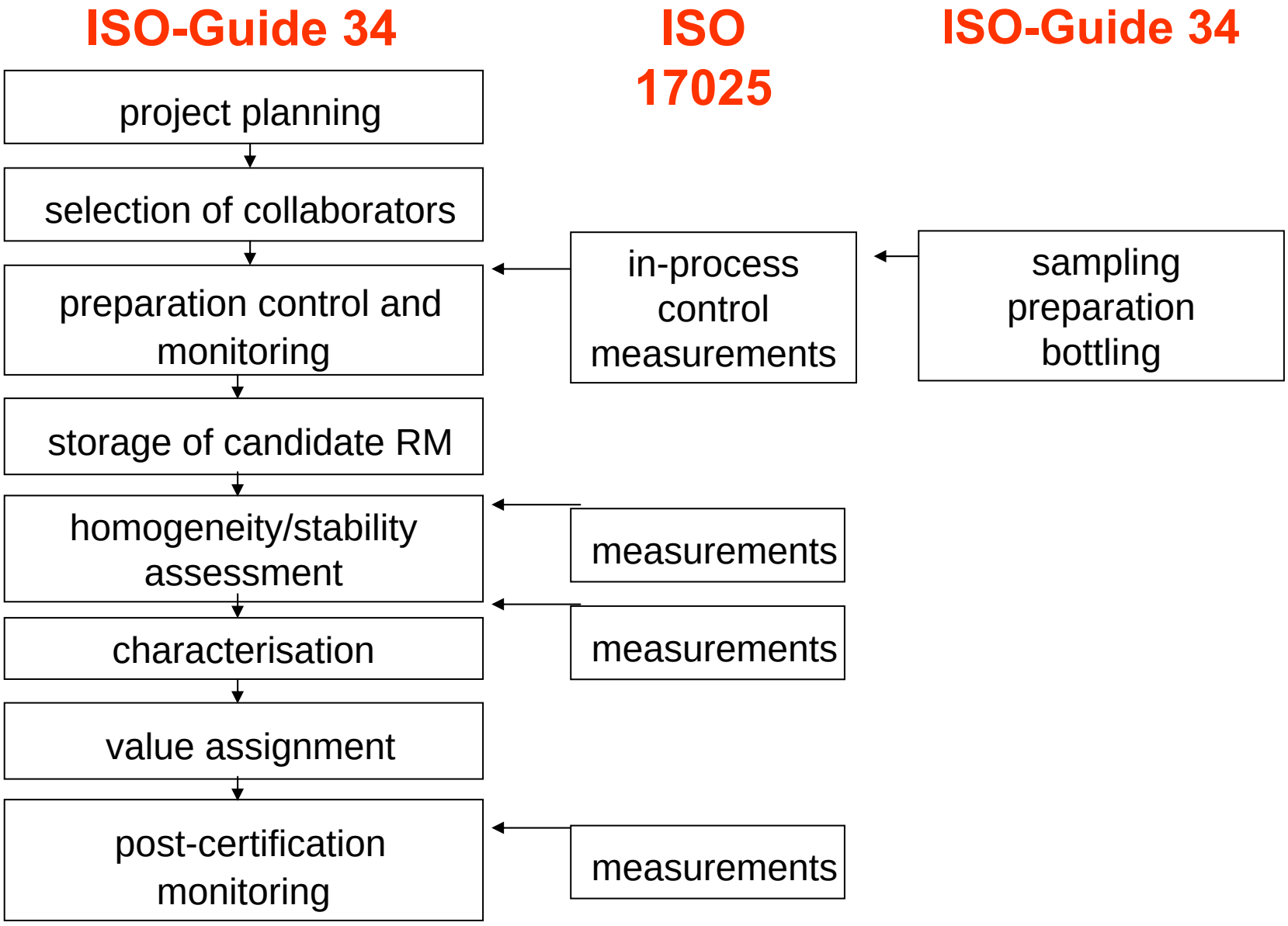
ISO/IEC Guide 98: Guide to the Expression of Uncertainty in Measurement (GUM) (1993, amended 1995)

ISO/IEC Guide 99: "International vocabulary of metrology – basic and general concepts and associated terms (VIM) (2007)

ISO/IEC 17025 General requirements for the competence of testing and calibration laboratories

ISO 15189 Medical laboratories – particular requirements for quality and competence

Applicability of standards



ISO/IEC Guide 98-3:

Guide to the Expression of Uncertainty in Measurement (GUM)

Expanded uncertainty:

$$U_{CRM} = k\sqrt{u_{char}^2 + u_{bb}^2 + u_{lts}^2 + u_{sts}^2}$$

Contributions to uncertainty:

Short-term stability u_{sts}
Long-term stability u_{lts}
Homogeneity u_{bb}
Characterisation u_{char}
Coverage factor k=2 corresponding to a level of confidence of about 95 %

Certified Reference Material
=
Material + Certificate

(=> certified value + certified uncertainty value + statement of metrological traceability)

CERTIFICATE OF ANALYSIS

ERM®- BE376

COMPOUND FEEDINGSTUFF		
	Mass fraction	
	Certified value[2] [µg/kg]	Uncertainty [3] [µg/kg]
Aflatoxin B_1[1]	12.9	1.8
Aflatoxin B_2[1]	0.68	0.10
Aflatoxin G_1[1]	5.2	0.8

1) As obtained, after extraction, by reversed phase chromatography with post column bromination and subsequent quantification by fluorescence detection.
2) Unweighted mean value of the means of accepted sets of data, each set being obtained in a different laboratory. The certified value and its uncertainty are traceable to the International System of Units (SI).
3) The certified uncertainty is the expanded uncertainty estimated in accordance with the Guide to the Expression of Uncertainty in Measurement (GUM) with a coverage factor k = 2, corresponding to a level of confidence of about 95 %

Vitamins

Proximates

Veterinary drugs

Mycotoxins

PCBs

Food CRMs

Enzymes

Prions

TSE QCMs

Clinical CRMs

Hormones

Microorganisms

Proteins

PAHs

Microbiol. CRMs

GMO CRMs

Hydrocarbons

DNA

Dioxins

Soil/ Sediment CRMs

Engin. Mat. CRMs

Size

Water CRMs

Elements

Isotopes

Ions

Metal species

Impact toughness

(Certified) Reference Materials for Particle Size Measurements at IRMM

Available materials

Reference materials for particle size or for particle size distributions are available which cover the size range from 35 nm to 5 mm.

Suspensions of latex spheres are available, the diameter of which has been established in an absolute way by microscopy and is hence traceable to the International System of Units.

Method specific size values (Stokes' diameter, equivalent volume diameter) were assigned to a series of quartz powder materials.

A colloidal silica quality control material with information values for particle sizes in the nanoscale range is available.

Latex materials certified for their particle size (low μm range)

Code	Material	Certified particle size
BCR-165	Suspension of latex particles (2 mL; 0.2 g/L solids)	(2.223 ± 0.013) μm
BCR-166	Suspension of latex particles (2 mL; 2 g/L solids)	(4.821 ± 0.019) μm
BCR-167	Suspension of latex particles (2 mL; 1.4 g/L solids)	(9.475 ± 0.018) μm

Suspension of silica nanoparticles

IRMM-304 is a **quality control material** consisting of silica nanoparticles suspended in an aqueous solution. Information values (not certified) are assigned for frequency analysis and cumulant method using dynamic light scattering according to ISO 22412 and ISO 13321, as well as centrifugal liquid sedimentation according to ISO 13318.

Assigned parameter	Particle diameter
Frequency analysis (ISO 22412), $\overline{x}_{DLS}$	(46 ± 2) nm
Cumulant method (ISO 22412), $\overline{x}_{DLS}$	(43 ± 3) nm
Disc sedimentation, modal Stokes particle diameter (ISO 13318)	(35 ± 1) nm

Quartz materials certified for their particle size distribution (μm to mm range)

Code	Material	Certified particle size distribution
BCR-066	Quartz powder (10 g)	Stokes' diameter ranging from 0.35 to 3.50 μm
BCR-070	Quartz powder (10 g)	Stokes' diameter ranging from 1.20 to 20 μm
BCR-067	Quartz powder (10 g)	Stokes' diameter ranging from 2.40 to 32 μm
BCR-069	Quartz powder (10 g)	Stokes' diameter ranging from 14 to 90 μm
BCR-130	Quartz powder (50 g)	Equivalent volume diameter ranging from 50 to 220 μm
BCR-068	Quartz sand (100 g)	Equivalent volume diameter ranging from160 to 630 μm
BCR-131	Quartz powder (200 g)	Equivalent volume diameter ranging from 480 to 1800 μm
BCR-132	Quartz Gravel (700 g)	Equivalent volume diameter ranging from 1400 to 5000 μm

Nanoparticle materials:

Test materials

IRMM: IRMM-304 (QCM) Silica nanoparticles in aqueous suspension (nominal 40 nm)

NIST: SRM1691 Polystyrene spheres (nominal 300 nm diameter)
SRM1963a Polystyrene spheres (nominal 100 nm)
SRM1964 Polystyrene spheres (nominal 60 nm)
RM-8011 – 8013 Au nanoparticles in aqueous suspension (nominal diameter 10/30/60 nm)

Others: e.g. Duke Scientific, BS-Partikel

BAM database: www.nano-refmat.bam.de

Nanoparticle test materials:

- JRC-IHCP repository of test materials (non-RMs)
- JRC-IRMM test material for ILC (RM)

Test material repository at JRC-IHCP (Institute for Health and Consumer Protection)

distributed for <u>toxicological testing</u>

- not systematically checked for homogeneity and stability (non-RMs)

- first step in standardisation: everybody uses the same material

Production of CRMs at IRMM:

Certified value based on measurement results of a laboratory intercomparison

IRMM accreditation according to ISO Guide 34 and
to ISO/IEC 17025 for measurements
=> expert laboratories using validated methods

Components of method validation

- Identification of measurand
- Selectivity
- LOD/LOQ
- Working range -linearity
- Repeatability
- Intermediate precision
- Robustness
- Trueness
- Uncertainty estimation

Problem:

no CRMs available to establish trueness of methods

=>full validation not possible

hen-egg problem

Alternative:

select qualified laboratories on the basis of results of ILC

Production of test material

colloidal silica aqueous suspension

homogeneity and stability fit for purpose (= RM)

Interlaboratory comparison

2 ampoules, 2 measurements per ampoule

No instructions for reporting

May-August 2009

Participants

42 laboratories agreed to participate

38 laboratories sent results:

USA/Canada	3
Asia	6
Australia	1
Europe	28

87 sets of samples à 2 ampoules/set dispatched
78 data sets received

Number of data sets per method

Method	Number of independent data sets
DLS (including FFF-DLS and PCCS)	26
CLS (including AUC and Photocentrifuge)	13
SAXS	4
Electron microscopy (SEM and TEM)	13
AFM	2
FFF-Nephelometry/MA(L)LS	2
HDC	3
ES-DMA-CPC	3
NTA	1
Zeta potential	10
Effective particle density	1
Total	78

2 step evaluation:

- **evaluation of reports**
- **evaluation of the results**

Reporting in coded form of

- **measured values**
- **z scores**

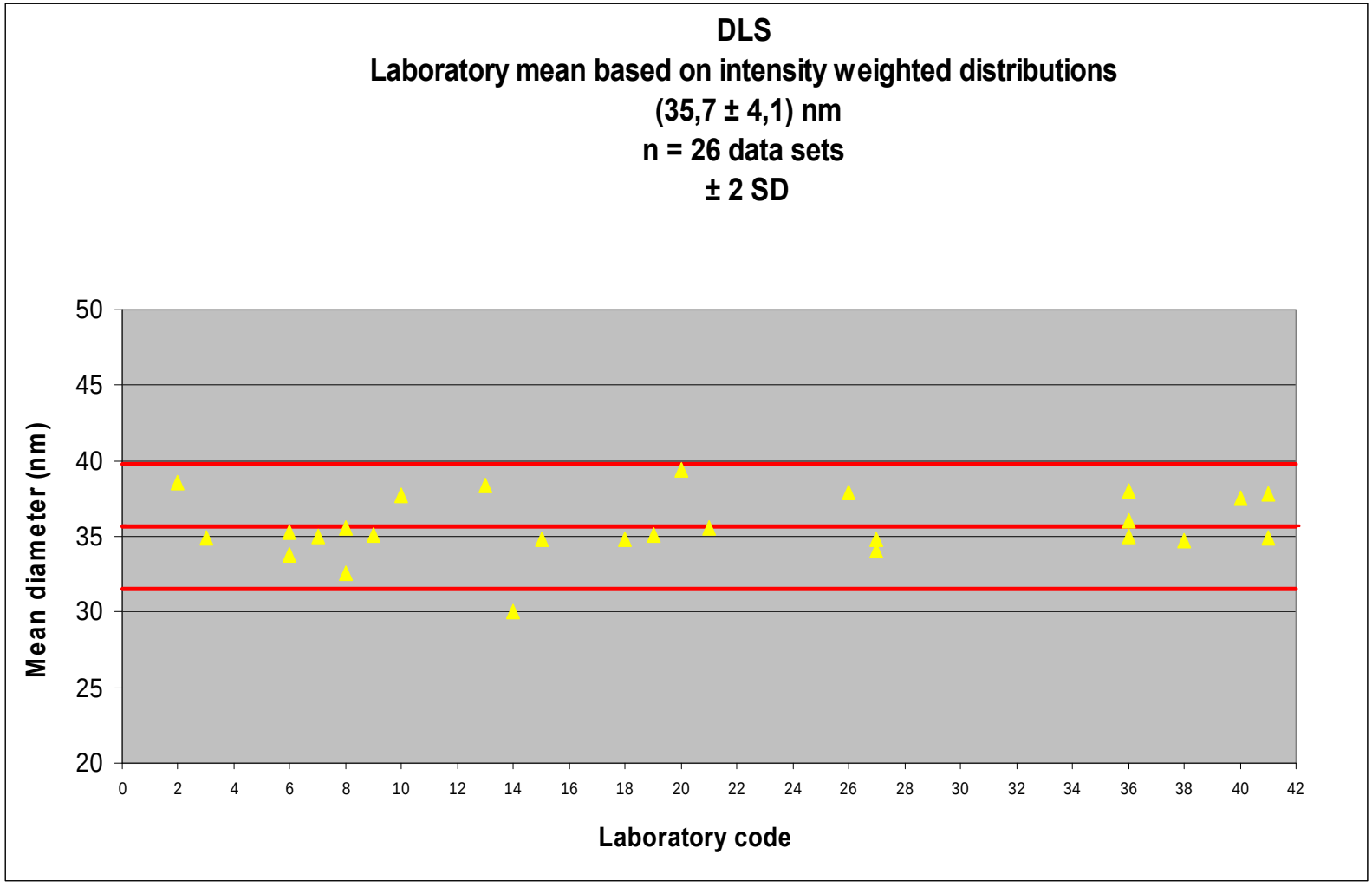
Z scores

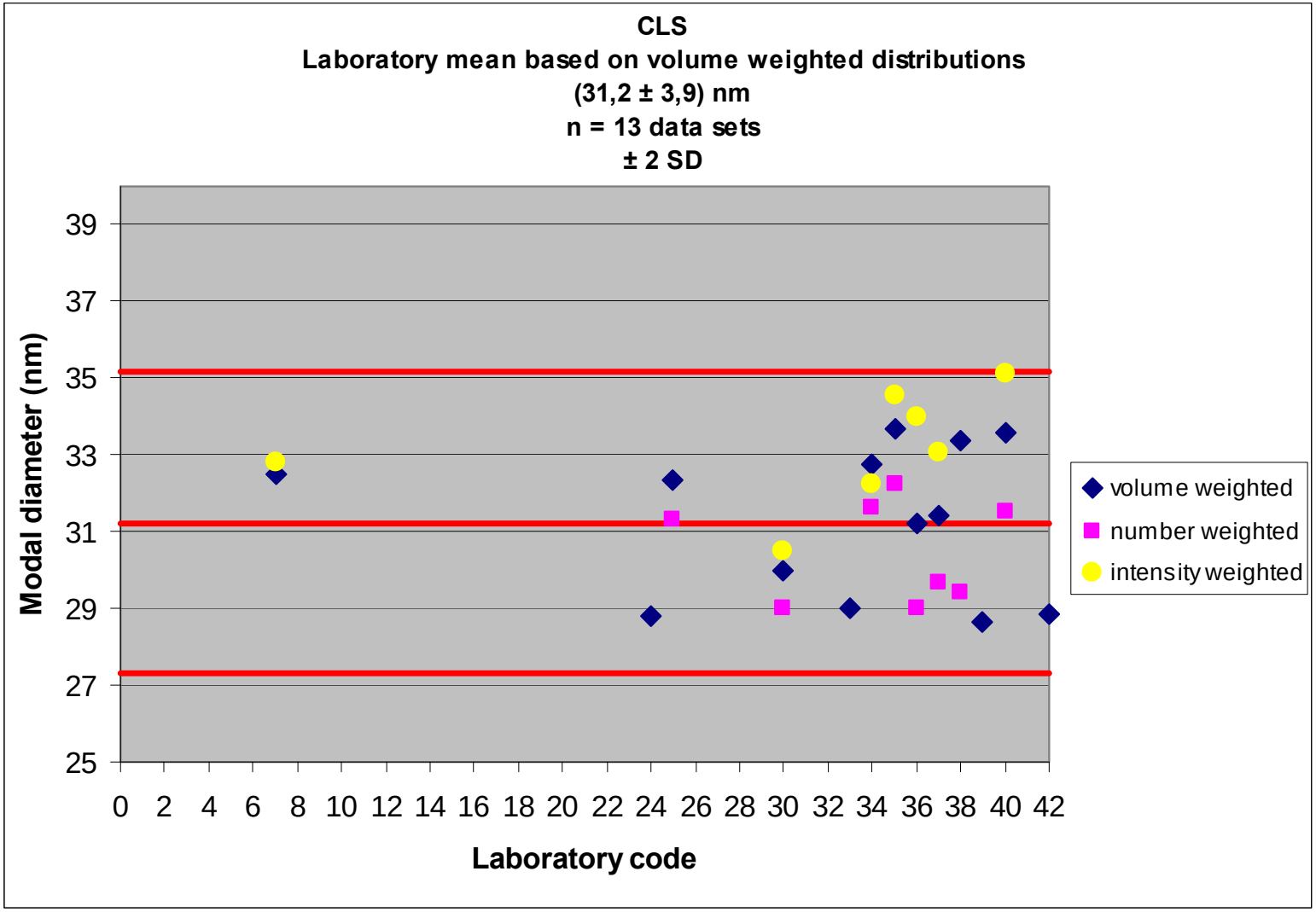
$$z = (x - X)/SD$$

x the result obtained by the participant for a specific method
X the mean of laboratory means (the "population") for the same method and
SD the standard deviation of the population

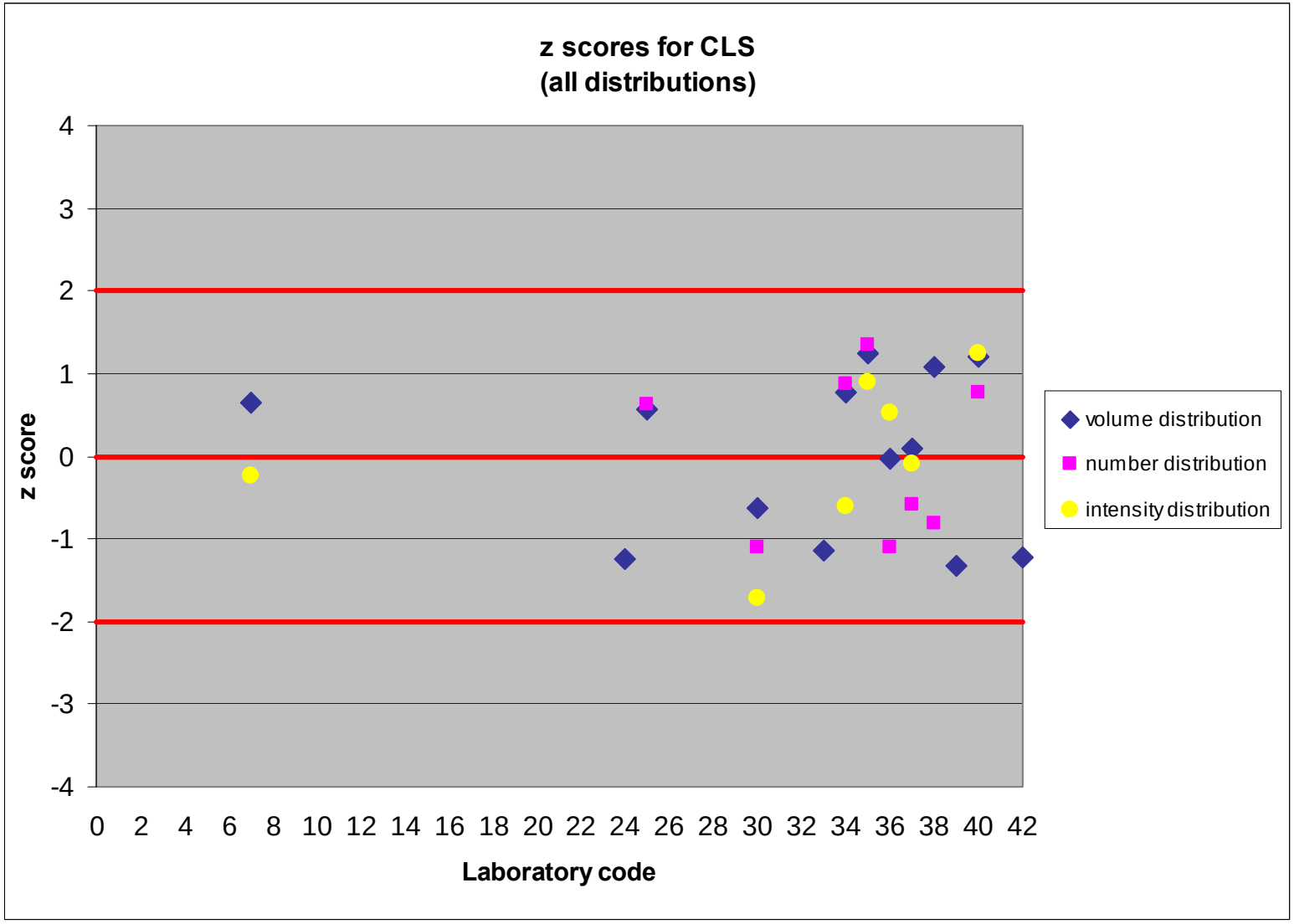
$\|z\| \leq 2$	satisfactory
$2 < \|z\| \leq 3$	questionable
$\|z\| > 3$	unsatisfactory

DLS

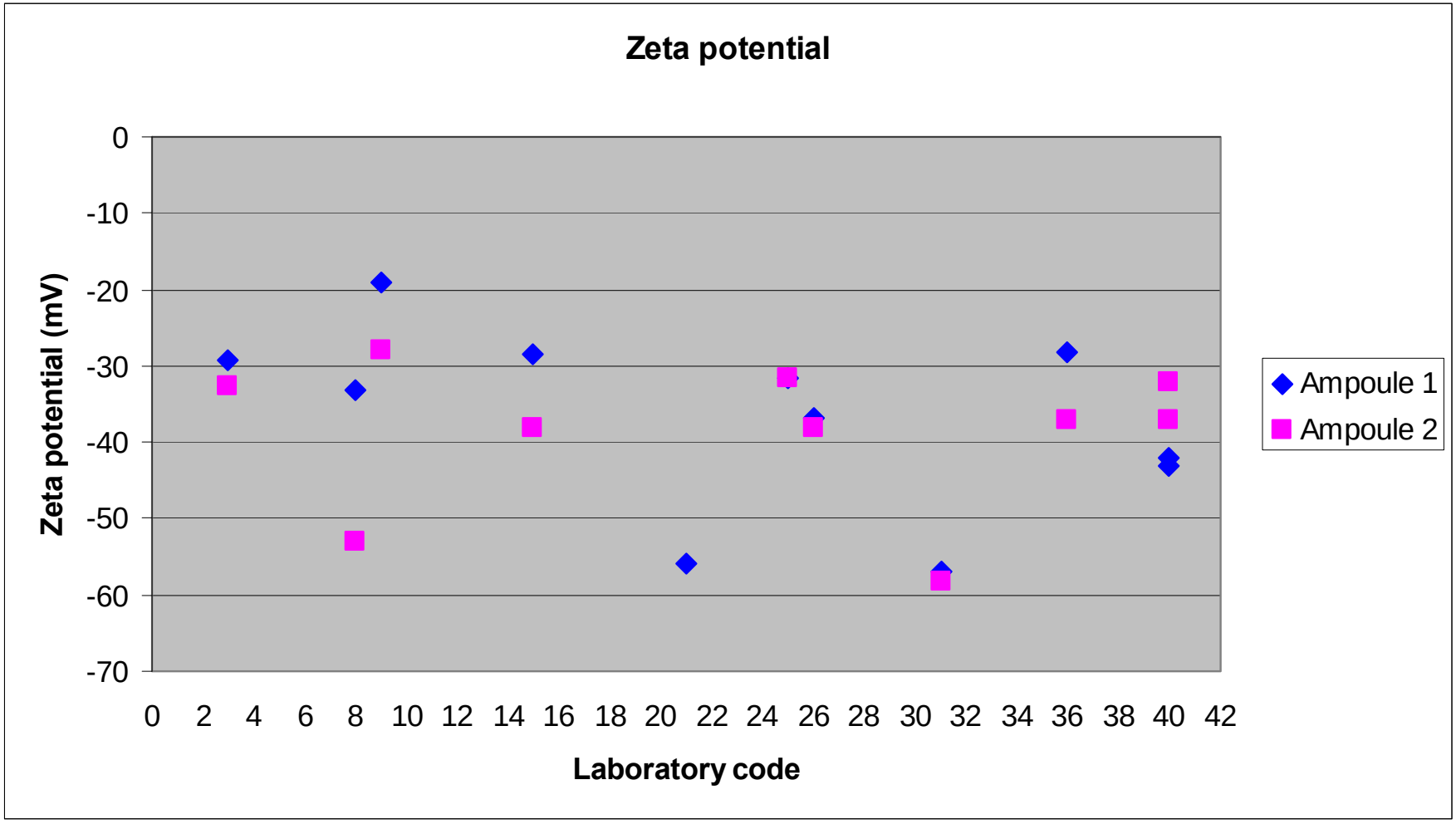

DLS
Laboratory mean based on intensity weighted distributions
(35,7 ± 4,1) nm
n = 26 data sets
± 2 SD
Mean diameter (nm)
50
45
40
35
30
25
20
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
38
40
42
Laboratory code


CLS
Laboratory mean based on volume weighted distributions
(31,2 ± 3,9) nm
n = 13 data sets
± 2 SD
Modal diameter (nm)
39
37
35
33
31
29
27
25
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42
Laboratory code
volume weighted
number weighted
intensity weighted

CLS


z scores for CLS
(all distributions)
z score
4
3
2
1
0
-1
-2
-3
-4
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42
Laboratory code
volume distribution
number distribution
intensity distribution

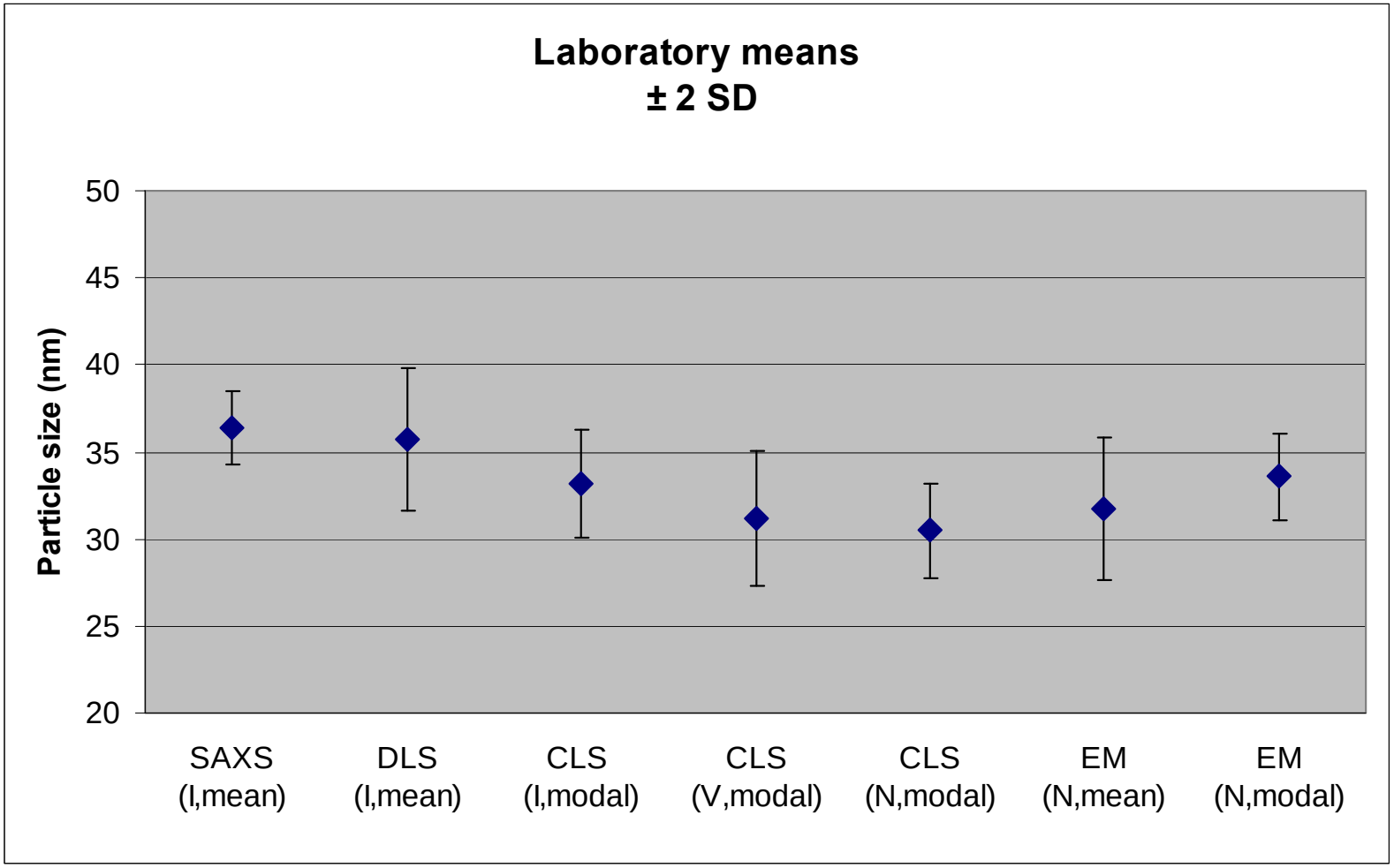
Zeta potential



Summary

Method	Type of distribution	Parameter	Laboratory mean (nm)	2 SD (nm)	Number of data sets	RSD (%)
SAXS	Intensity	Mean diameter	36.4	2.1	4	2.9
DLS	Intensity	Mean diameter	35.7	4.1	26	5.7
CLS	Intensity	Modal diameter	33.2	3.1	7	4.7
CLS	Volume	Modal diameter	31.2	3.9	13	6.3
CLS	Number	Modal diameter	30.5	2.7	8	4.4
EM	Number	Mean diameter	31.7	4.1	13	6.5
EM	Number	Modal diameter	33.6	2.5	9	3.7
			Laboratory mean (mV)	**2 SD (mV)**		
Zeta potential			-39	22	10	28

Summary


Laboratory means
± 2 SD
Particle size (nm)
50
45
40
35
30
25
20
SAXS (I,mean)
DLS (I,mean)
CLS (I,modal)
CLS (V,modal)
CLS (N,modal)
EM (N,mean)
EM (N,modal)

Summary

Z scores calculated for DLS, CLS and EM

± 2 |z| interval: 13 CLS results
13 EM results
25 DLS results
± 3 |z| interval: 1 DLS result (calculation error)

Qualified laboratories selected

=> Certification: 2 materials of silica nanoparticles in aqueous suspension

- **nominal 35 nm to 50 nm**
- **nominal 10 nm to 30 nm**

=> certified value for DLS, CLS, EM

=> indicative value for SAXS

=> additional information for Zeta potential

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Thank you for your attention!

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