

Extracts from:

Particle Standards: Their Development and Application

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Abstract

With the increase in the importance of dispersed materials (powders, aerosols, emulsions etc.) to trade, there is an increasing awareness of the need to verify that instruments which measure particle properties, particularly size, are operating within defined limits of accuracy. As a minimum, this process requires some form of verification with reference to standard particles whose properties are known in relation ultimately to the international standards of mass and length (so-called traceability chain). In some cases, a formal calibration to establish instrument response in terms of size, shape or concentration may be required. This article reviews the particle standards that are available to establish the performance of measurement equipment, placing most emphasis on particle size, as this is the variable that is generally of most importance to industry. However, secondary properties, such as shape, density and refractive index, influence the response of many types of particle size analyser. Attempts to provide standard materials that may enable independent assessment to be made of the effect of some of these variables on instrument performance are therefore also considered.

1. Introduction

1.1 Background

There is an increasing awareness that instruments used to measure the properties of dispersed systems (powders, aerosols, particles suspended in liquid etc.) cannot by themselves provide absolute values. Quality systems, such as the ISO 9000 series [1] require that the performance of instrumentation used in the measurement of properties deemed critical to the process for which the materials under investigation are being used, be verified on a regular basis as part of a method validation process, or standard operating procedure (SOP). The intention behind this requirement is to enable measurements made on a particular product at one location to be reproducible within well-defined limits anywhere else. Standard or reference materials (RMs) that are particle-based have an important part to play in this process.

1.2 Concept of Particle Size

The definition of 3-dimensional particle size itself requires clarification before proceeding to look at particle standards. The concept of particle diameter has unambiguous physical meaning only for spherical particles. It is not possible to define a single diameter that describes the geometric size of particles that are irregular-shaped, which comprise that vast majority of cases where measurements are sought. There are many techniques that can be used to measure particle size; some are more suited to liquid-based particle systems [2] (coarse particle suspensions and colloids) and others are applicable to gas-based systems [3] (aerosols). Each technique measures a particular dimension that is dependent on the measurement principle (**Table 1**). Hawksley has postulated that there are only three fundamental diameters [4]:

- volume equivalent diameter (D_v): the diameter of a sphere having the same volume as the particle being studied
- surface equivalent diameter (D_a): the diameter of a non-porous sphere having the same surface area as the particle being studied
- drag or Stokes diameter (D_{st}): the diameter of a sphere having the same resistance to motion as the particle in question, in fluid of the same viscosity

More recently, Scarlett [5] has presented a view that D_v is the most basic parameter to choose as the calibrating size, because it is directly proportional to the quantity of matter in the particle, regardless of shape. D_a has limited use, except in applications where surface properties (e.g. catalysis) are under consideration. D_{st} is not strictly a fundamental diameter, but one of a series of equivalent sphere diameters (including aerodynamic and mobility diameters) that relate to the interaction of a particle of any shape with the fluid within which it is contained. D_{st} is measured directly by several widely used techniques that employ gravitational sedimentation as the size-separating principle, where Stokes Law applies, and:

$$U_{ts} = \frac{[\rho_b - \rho_{fl}]}{18\eta} D_{st}^2 g \quad [1]$$

where ρ_p is the particle density and U_{ts} is the particle terminal settling velocity, ρ_b and ρ_f are the particle density immersed in the fluid and fluid density respectively, η is fluid viscosity and g , acceleration due to gravity. D_v and D_{st} are related through the expression [3]:

$$D_{st} = D_v \left[\frac{\rho_p}{\chi \rho_p} \right]^{1/2} \quad [2]$$

where χ is a correction that adjusts for the effect of 3-dimensional particle shape on sedimentation behaviour (dynamic shape factor). χ is unity for spheres, and always exceeds this value for irregular-shaped particles. It may also have more than one value for certain shapes (e.g. spheroids), depending upon their orientation with respect to their motion in the suspending fluid [6].

Particle size analysis techniques that operate on other measurement principles measure one of several different equivalent sphere diameters (**Table 1**), each of which can ultimately be related to D_v , though not necessarily in the form of a simple relationship, such as that given by equation [2]. It follows that the response of particle size analysis equipment to irregular particles with few exceptions is modified by shape (as well as in some cases by bulk properties such as density, porosity etc.). This behaviour becomes especially important when it becomes necessary to compare data from instruments that operate on different principles, a not uncommon situation. The question to be posed is 'can particle standards provide meaningful reference values to enable such comparisons to be made accurately?' The answer depends on the properties of the standards themselves, and the approach taken to verify analyser performance (section 1.3). Size-based standard particles are the most widely used RMs, and several options are available for their use. Reference particles which have specified non-spherical shapes (so-called 'particle shape standards' are considered separately from particles used in connection with particle sizing (Section 4.1), as their function in performance verification is fundamentally different.

Table 1 Particle Size Measured by Selected Analyser Principles

Technique	Operating Principle	Weighting of Size Distribution	Remarks [†]
impactors, impingers, gas-and hydro-cyclones	inertia	mass	size analysis by fractionation in several stages - measures D_{ae}
inertial spectrometers, spiral duct centrifuge	inertia	mass	size-separated particles are retained as a continuous deposit - measures D_{ae}
Sedimentometers	gravity (Stokesian flow)	mass	various techniques to weigh size-separated particles - measures D_{st}
TOF analysers	inertia (ultra-Stokesian flow)	number	TOF of individual size-separated particles measured - measures modified D_{ae}
laser (phase) Doppler systems	light scattering (phase angle)	number	Doppler 'burst' from individual particles passing through measurement zone
laser diffractometers	light scattering (Lorenz-Mie theory)	volume (mass)	'ensemble' scattering of whole particle population in measurement zone
electrical sensing zone (ESZ)	electrical resistance change	number	individual particles sized by passage through micro-orifice - measures D_v
electrical mobility analysers	particle mobility	number	mobility of individual particles having known charge in an applied electric field
optical particle counters	angular light scattering	number	individual particles sized in terms of light scattering intensity
microscopy/image analysis	direct observation	number	individual particles sized in terms of projected area diameter (equivalent to D_v for spheres)
sieve analysis	Penetration through mesh aperture	mass	fractions weighed (near-mesh technique provides link to microscopy-measured size)

[†] diameters (D_x) are defined in the text

1.3 Verification of Sizing Accuracy

There are two distinctly different approaches that can be taken to verify the accuracy of measurements based on particle size, on which this article is primarily focused. In one approach, particle standards produced from bulk powders, whose size distributions and related properties (e.g. density) have been corroborated by independent laboratories, are used as so-called 'certified reference materials' (CRMs). The particles may be spherical or of irregular shape, but their range of size will be chosen to encompass the measurement range of the instrument being evaluated. This process is termed performance verification. The attractiveness of this process to industry is obvious; it is usually rapid to carry out, as only a single RM is normally required for the purpose, and analysers operating on different measurement principles can be readily compared.

Table 2 International Standards[†] Relating to Particle Size Analysis as of Jan 1, 2000

Standard	Description	Date
ISO 2591-1	Test Sieving – Part 1: Methods using test sieves of woven wire cloth and perforated metal plate	1988
ISO 3310-1	Test Sieves – Technical requirements and testing – Part 1: Test sieves of metal of metal wire cloth	1990
ISO 3310-2	Test Sieves – Technical requirements and testing – Part 2: Test sieves of metal of perforated metal plate	1999
ISO 3310-3	Test Sieves – Technical requirements and testing – Part 2: Test sieves of metal of electroformed sheets	1990
ISO 13320-1	Particle size analysis – Laser diffraction methods – Part 1: General principles	1999
ISO 13321	Particle size analysis – Photon correlation spectroscopy	1996
ISO 13317-2	Determination of particle size distribution by gravitational liquid sedimentation methods – Part 2: Fixed pipette method	in process FDIS
ISO 13319	Particle size analysis – Electrical sensing zone method	2000
ISO 13722	Particle size analysis – Image analysis methods	in process
ISO 13762	Particle size analysis – Small angle x-ray scattering method	in process
ISO 13323	Particle size analysis – Single particle light interaction methods	in process

[†] FDIS = final draft international standards

[†] from International Standards Organization, Geneva, Switzerland

Performance verification should be distinguished from instrument calibration, which is the other approach for which particle standards are widely used. The calibration process in its most generic form, involves measurement of analyser response and associated bias conversion factor, when presented with particles having known size properties by an independent procedure that is traceable ultimately to the international standard of length. The various documented international (**Table 2**) and national (**Table 3**) standards that relate to many of the particle size analysis methods in widespread use generally call for the use of standard particles as part of the calibration or performance verification process, particularly in instances where the instrument response is not a straightforward monotonic function of particle size.

Table 3 Selected National Standards Relating to Particle Size Analysis

Standard	Description	Date
BS 3406 [†]	Determination of particle size distribution: <ul style="list-style-type: none"> Part 1: Guide to powder sampling Part 2: Gravitational liquid sedimentation methods Part 4: Optical microscope methods Part 5: Electrical sensing zone method Part 6: Centrifugal liquid sedimentation methods Part 7: Single particle light interaction methods Part 8: Photon correlation spectroscopy Part 9: Filter blockage method (mesh obscuration) 	1986 1984 1993 1983 1985 1988 1997 (ISO 13321:1996) 1997
ASTM [‡] F 328-98	Standard practice for determining counting and sizing accuracy of an airborne particle counter using near-monodisperse spherical particulate material	1998
ASTM [‡] F 660-83	Standard practice for comparing particle size in the use of alternative types of particle counters	1983 (rev. 1993)
ASTM [‡] F 649-80	Standard practice for secondary calibration of airborne particle counter using comparison procedure	1980 (rev. 1992)
ASTM [‡] F 658-87	Standard practice for determining size calibration, resolution and counting accuracy of a liquid-borne particle counter using near monodisperse spherical particulate material	1987 (rev. 1992)
JIS B 9921 [¶]	Light scattering automatic particle counter	1989
JIS B 9925 [¶]	Light scattering automatic particle counter for liquid	1991
DIN 66165 [#]	Particle size analysis – Sieve analysis: General principles	1987: parts 1 and 2
DIN 66111 [#]	Particle size analysis – Sedimentation analysis: General principles – pipette method	1989
DIN 66115 [#]		1983

[†] available from British Standards Institute, Milton Keynes, UK – www.bsi.org.uk

[‡] available from American Society for Testing and Materials, Philadelphia, USA – www.astm.org

[¶] available from Japanese Standards Association, Tokyo, Japan – www.jsa.org.jp

[#] available from Deutsches Institut für Normung e. V., Berlin, Germany – www.din.de

Even techniques, such as laser diffractometry (low-angle laser light scattering (LALLS)), which provide volume-weighted size distribution data for spherical particles by rigorous solution of Lorenz-Mie equations [7], so that formal calibration is not strictly necessary, should ideally be validated on a regular basis with particle size-based RMs [8], or at least by the use of a suitable reticle [9]. The purpose of such measurements is as a check on the continued stability of the complete measurement system, including the software. The precise requirements for such RMs should be spherical with maximum light absorption to avoid anomalous responses due to light reflection and refraction, and for examining liquid-based suspensions at least, the particle density should be close to that of the dispersion fluid [8]. Their size distribution should also be preferably uni-modal and log-normal. Rothele and Witt [8] have gone as far as to provide indicative size distributions for this class of analyser with the following size distribution properties based on D_v :

- CRM1: range 0.1 - 10 μm : D^{10} 0.126 μm , D^{50} 1.0 μm ; D^{90} 7.94 μm
- CRM2: range 1.0 - 100 μm : D^{10} 1.26 μm , D^{50} 10 μm , D^{90} 79.4 μm
- CRM3: range 10 - 1000 μm : D^{10} 12.6 μm , D^{50} 100.0 μm , D^{90} 794 μm

where D^{10} , D^{50} and D^{90} are the 10th, 50th (median) and 90th percentiles by volume (mass). Such CRMs have yet to be developed, although some of those planned by the European Community Bureau of Reference (BCR) will come close to meeting these criteria (Section 2.3).

The calibration process can be considerably more time consuming than performance verification, as it is necessary to utilize more than one RM to gauge the sensitivity of the response function to change in particle size. It is important that the properties of the RMs likely to be used for calibration purposes (particularly their shape, but also other properties that relate to the instrument response e.g. density in the case of techniques that measure Stokes or aerodynamic diameter) are well specified. In general, the most useful RMs for this activity will therefore be formulated from spherical, rather than irregular-shaped particles.

1.4 RM Hierarchy

It is useful to consider the hierarchy of particle size standards as having the form of an equilateral triangle (**Figure 1**), in which the international standard of length as the fundamental unit pertaining to size, forms the apex. Immediately beneath are the limited range of certified or standard reference material (CRMs or SRMs) produced by governmental agencies, usually in partnership with industry and academia. CRMs/SRMs have been subjected to rigorous inter-laboratory evaluation by independent methods that are directly traceable to international standards, and are normally supplied with a data report in which their specification is defined. These standards are available in limited amounts and the process of certification, being labor intensive, results in their high cost.

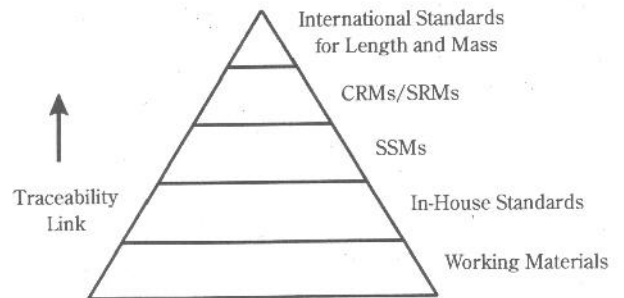


Fig. 1 Calibration hierarchy in terms of particle size standards

A compromise between the rigor of a formal certification process and the need for standards in appropriate quantities at reasonable cost is therefore necessary, resulting in the growth of secondary standard materials (SSMs). These calibrants are available from many sources, making them particularly useful for processes where frequent calibration is necessary or with techniques, such as sieve analysis, where relatively large quantities of calibrant is needed to achieve acceptable precision in the size analysis process. There is often less information available on the properties of SSMs, other than size distribution, more often than not measured by a single technique. At the lowest level in the hierarchy are so-called tertiary standards. These particles are prepared in-situ for calibration purposes, frequently by aerosol generation methods. The twin advantages of tertiary standards are their low relative cost (although the equipment used to create the aerosol can be expensive), and the convenience in being able to both control and vary particle size within fairly wide limits. In some cases, it may be possible to control other properties, such as shape, density and refractive index, each of which may modify the response of the equipment under calibration. Since the process is essentially local to the laboratory undertaking the calibration, inter-laboratory data are by definition unavailable. Ultimately, the traceability of the size measurements is dependent upon the calibration of the size analysis equipment that is used to verify correct operation of the particle generation equipment, even in instances such as the vibrating orifice monodisperse aerosol generator (VOMAG), where the modal particle size can be predicted directly from the operating variables of the system [10] (Section 4.3).

2. CRMs/SRMs:

2.1 The Certification Process

The approach taken by the two organizations that have been responsible for almost all the particle size-based CRMs/SRMs produced to date is radically different. At the US National Institute for Standards and Technology (NIST-formally the National Bureau of Standards), their own laboratory has been responsible for the production of ranges of SRMs with limited assistance from outside bodies. In the case of the SRMs based on uniform-sized particles (**Table 4**) [11-12, 14-17], the basic approach has been to certify by means of a so-called 'first principle' technique that is directly traceable to the international length standard, supported by one other sizing technique. Certifying techniques chosen for each of the SRMs based on uniform-sized polymer latex particles were as follows:

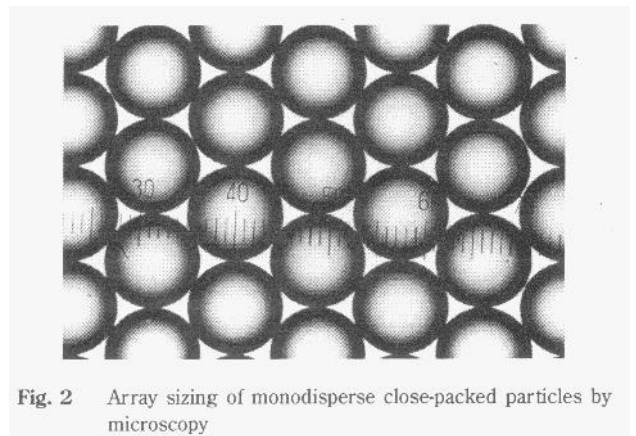


Fig. 2 Array sizing of monodisperse close-packed particles by microscopy

- optical microscopy of close-packed arrays of the larger spherical particles (SRMs having nominal D_v of 3, 10 and $30\mu\text{m}$) [11, 12, 14] (**Figure 2**)
- Mie angular light scattering intensity patterns, measured to size the SRM having nominal D_v of $1\mu\text{m}$ [15]
- transmission electron microscopy, to size the SRM having nominal D_v of $0.3\mu\text{m}$ [16] – difficulties associated with the establishment of an accurate edge defining each particle boundary and distortion at the image periphery were overcome by including $1\mu\text{m}$ diameter spheres from the previously calibrated SRM
- electrical mobility of particles having a known charge to size the SRM having nominal D_v of $0.1\mu\text{m}$ [17].

Table 4 Selected National Standards Relating to Particle Size Analysis

Standard	Source	Nominal D_v (μm)	Certification Method	Reference
SRM 1961	NIST	$29.64 \pm 0.06^\dagger$	optical microscopy – array sizing	Hartman <i>et al.</i> [11]
SRM 1960	NIST	$9.89 \pm 0.04^\dagger$	optical microscopy – array sizing	Lettieri <i>et al.</i> [12]
CRM 167	BCR	$9.475 \pm 0.018^\ddagger$	optical microscopy – array sizing	Thom <i>et al.</i> [13]
CRM 166	BCR	$4.821 \pm 0.019^\ddagger$	optical microscopy – array sizing	Thom <i>et al.</i> [13]
SRM 1962	NIST	$2.978 \pm 0.007^\dagger$	optical microscopy – array sizing	Hartman <i>et al.</i> [14]
CRM 165	BCR	$2.223 \pm 0.013^\ddagger$	optical microscopy – array sizing	Thom <i>et al.</i> [13]
SRM 1690	NIST	$0.895 \pm 0.008^\dagger$	angular intensity light scattering	Mulholland <i>et al.</i> [15]
SRM 1691	NIST	$0.269 \pm 0.007^\dagger$	transmission electron microscopy	Lettieri and Hembree [16]
SRM 1693	NIST	$0.101 \pm 0.002^\dagger$	electrical mobility	Kinney <i>et al.</i> [17]

[†] based on total uncertainty (certification by single laboratory)

[‡] uncertainty based on 95% confidence interval (consensus certification by several independent laboratories)

NIST SRMs are each supplied in ca. 5cm^3 aqueous suspension at a mass concentration of about 0.5% w/v solids

BCR CRMs are each supplied in 2cm^3 aqueous suspension: CRM 165 contains 0.02% w/v solids, CRM 166 contains 0.2% w/v solids and CRM 167

In addition to the certifying techniques, quasi-elastic light scattering (QELS), in which the decay of coherence of the scattered light from the particles suspended in water, was used as the second method with the SRM having a nominal D_v of $0.3\mu\text{m}$. Resonance light scattering, in which sharp Mie resonances were observed in the plots of scattering light intensity versus size, was used with the SRM having nominal D_v of $10\mu\text{m}$. Metrology electron microscopy was utilized to size the SRMs having nominal D_v of 3, 10 and $30\mu\text{m}$. In this secondary technique, the focused beam of a scanning electron microscope (SEM) was held stationary whilst a single sphere (or row of spheres) was moved beneath the beam by means of a scanning stage. An interferometer was used to measure stage travel, whilst the SEM indicated where the leading and trailing edge of each particle passed by the beam.

The size distribution data provided for these SRMs accurate though they are, represent the outcome of each certifying method, but are limited to measurements made within the laboratories at that single organization. In contrast, the certification process undertaken at the BCR has been by consensus measurements between several independent laboratories, also using techniques directly traceable to the international length standard. The BCR has no internal laboratory, but operates by contracts with outside organizations, almost always, but not necessarily within the European Union. The procedure is no less rigorous than that utilized by NIST, in that the certifying procedure (undertaken at each participating laboratory) is a 'first principle' method. However, there is added strength to the process by requiring corroboration of results from independent sources before certification takes place. In the case of the three sizes of uniform CRMs produced to date (**Table 4**), the certifying method has been optical microscopy of close-packed particle arrays, similar to that used by NIST with their larger sized SRMs [13]. Supporting measurements of these CRMs were also made by an individual participating laboratory using electrical sensing zone (ESZ) method (to estimate the dispersion of particle size about the modal value – distribution skewness and kurtosis), and also by TEM (3-participants).

Similar considerations apply with the range of polydisperse CRMs also certified by the BCR (**Table 5**) [18-19] each based on a bulk sample of powder derived from materials in common use (e.g. quartz sand, gravel). However, the certifying techniques had to be quite different from those employed with the uniform-sized CRMs. Array sizing by optical microscopy would not work, since the particles were irregular in shape as well as varying substantially in size. Alternative methods were therefore chosen (gravitational sedimentation in liquid suspension under Stokesian flow conditions for the CRMs containing particles with D_v finer than ca. $100\mu\text{m}$ and sieve analysis for those comprising larger particles). The certified size was therefore an equivalent sphere (Stokes) diameter (D_{st}) in cases where sedimentation in a liquid suspension was used. In the instances where sieve analysis was the certifying technique, the near-mesh procedure, in which particles held firmly in the sieve mesh are brushed out for microscopy-based analysis, was used to establish D_v for particles close in size to the mean aperture size of each sieve. The link between D_{st} and D_v is relatively straightforward [equation 2], although the immersed particle density (ρ_b) had to be determined as accurately as possible in the dispersant medium (0.1% w/v sodium pyrophosphate in aqueous solution [19]).

Table 5 Polydisperse CRMs/SRMs

Code	Source	Nominal Range Based on D_v (μm)	Size Property	Material	Density [†] ($\text{kg/m}^3 \times 10^3$)	Mass per Unit (g)	Reference
CRM 132	BCR	1400 – 5000	D_v	quartz gravel [†]	-	700	BCR
CRM 131	BCR	480 – 1800	D_v	quartz sand [†]	-	450	BCR
CRM 130	BCR	50 – 220	D_v	quartz sand [†]	-	200	BCR
CRM 068	BCR	160 – 630	D_v	quartz sand [†]	2.647	100	Wilson <i>et al.</i> [19]
CRM 069	BCR	14 – 90	D_{st}	quartz sand [†]	2.645	10	Wilson <i>et al.</i> [19]
CRM 067	BCR	2.4 – 32.0	D_{st}	quartz powder [†]	2.646	10	Wilson <i>et al.</i> [19]
CRM 070	BCR	1.2 – 20	D_{st}	quartz powder [†]	2.642	10	Wilson <i>et al.</i> [19]
CRM 066	BCR	0.35 – 3.50	D_{st}	quartz powder [†]	2.619	10	Wilson <i>et al.</i> [19]
SRM 1019b	NIST	750 – 2450	D_v	glass beads	-	200	http://oip.nist.gov/srmcatalog/tables
SRM 1018b	NIST	220 – 750	D_v	glass beads	-	87	http://oip.nist.gov/srmcatalog/tables
SRM 1017b	NIST	100 – 400	D_v	glass beads	-	70	http://oip.nist.gov/srmcatalog/tables
SRM 1004a	NIST	40 – 170	D_v	glass beads	2.45	70	http://oip.nist.gov/srmcatalog/tables
SRM 1003b	NIST	6 – 60	D_v	glass beads	2.445	25	http://oip.nist.gov/srmcatalog/tables

D_v = volume equivalent diameter

D_{st} = Stokes diameter

[†] irregular shaped particles

[†] density values are uncertified – provided to relate D_v to D_{st} through equation [2] with $\chi = 1.00$

2.2 Spherical or Irregular-Shaped Particles for SRMs/CRMs

Two equally valid, but distinctly different options exist when utilizing SRMs/CRMs to evaluate equipment in terms of particle size, and these options apply equally to other RMs.

In one approach that is becoming increasingly popular, standard particles that are spherical and have well-defined density as well as other relevant properties, such as refractive index, may be used. In the case of CRMs/SRMs of this type, the particles have been processed to control the primary properties of concern with the intention of being primarily used as calibrants. The CRMs/SRMs that have been prepared from polymer latex sources (**Table 4**), as well as being highly uniform in size (monodisperse), have well-defined, though not certified particle density ($1.05 \times 10^3 \text{ kg/m}^3$ for polystyrene) and refractive index ($m = 1.59 + 0i$ (polystyrene)). However, they are relatively expensive and are available only in small quantities, and in limited sizes (Section 1.4).

RMs may also be used to relate measurements as part of performance verification to check the collective reliability of procedure, operator and instrument (arguably the true purpose of a so-called 'reference material' [20]), rather than as calibrants *per se*. The 8-polydisperse CRMs from the BCR (Section 2.1) are available in several overlapping size ranges, in many cases encompassing about half an order of magnitude in size per CRM, and are supplied in amounts varying from 10g (CRMs 66, 67, 69 and 70) to as much as 700g (CRM 132). Although ρ_b for many of these CRMs was established by pycnometry, the individual particles are ill-defined. The four SRMs from NIST in this category all comprise spherical glass microspheres, having relatively narrow but still polydisperse unimodal size distributions.

The use of spherical SRMs/CRMs as particle standards implies that the theoretical behaviour of a sphere of the material in question is known, and that for the purpose of instrument calibration a check is being made between the presumed behaviour and the actual response of the equipment on test. It follows that if a particular instrument has been calibrated using spherical particles, any irregular particle that gives the same response as a spherical particle with that instrument, is presumed to have the same equivalent size (equivalent sphere diameter (Section 1.2)). Scarlett *et al.* have argued that in cases where the response of a particular instrument (e.g. one that operates by the ESZ principle) is proportional to the volume of each particle entering the measurement zone, calibration with spheres of known volume is no different in principle to calibration with irregular particles of known volume [20]. However, in instances where the relationship between the response function of the instrument and size is complex (especially with techniques such as laser diffractometry, that involve some form of deconvolution), true calibration may only be achievable with irregular-shaped RMs in fact, the particles which are themselves to be measured. To judge from experience where systematic comparisons of the performance of laser diffractometers from different manufacturers have been carried out using polydisperse BCR CRMs, the process still leaves much to be desired, with deviations as large as $\pm 70\%$ in reported size compared with certified size observed in some instances, albeit with excellent reproducibility [21-23]. It is interesting to note that in one study, significant deviations were also observed with methods based on sedimentation/centrifugation of particles in liquid suspension, attributed to a variety of causes, including software error and dilution corrections [22]. The variability between techniques of similar principle has been attributed to a combination of the following factors [23]:

- poor sampling (from the 10g bottles of powder supplied by the BCR)
- inadequate dispersion (both with surfactant and by ultrasonic methods)

- non-prescriptive analytical procedures, including statistical interpretation of data
- in the case of laser diffractometers, differences in interpretation of light scattering from the angular quartz particles (including ill-defined and variable refractive index)

The development of SOPs that describe good sample handling and analytical practices would alleviate the impact of the first three factors, but the fourth factor reflects a more fundamental limitation in the CRMs themselves.

2.3 The Planned Certification of Spherical Polydisperse CRMs

Studies of the sort already described [19-21] illustrate that the performance verification of many types of particle size analysers with polydisperse, irregular shaped particles is a valid procedure, notwithstanding SOP-related issues that are best defined in written procedures, such as those already published and in development through ISO (**Table 2**). However, it is increasingly recognised that it is important that the RM be homogeneous, but also that different samples have equivalent secondary properties within the range of particle size that is present. Such homogeneity is, in fact, essential if agreement is to be achieved, even between instruments operating on the same principle. Furthermore, it should be possible to reconcile measurements by instruments that operate on different principles on the basis of the equivalent sphere diameter, once RMs having consistent properties have been created. In response to these demands, the BCR since the late 1980s, has been pursuing the development of a new range of CRMs comprising polydisperse, spherical particles having both homogeneous and well-defined secondary properties. However, it can be argued that current demand cannot be met with the quantities of powder that were originally envisaged even if certification of these CRMs eventually takes place.

The original specification was to provide a series of CRMs, each comprising a narrow width, uni-modal and near log-normal size distribution occupying an order of magnitude in size [24]. The overall size range between 0.1 and 650µm volume equivalent diameter was to have been encompassed by these CRMs having overlapping size ranges. On a volume (mass) weighted basis, between 5% and 95% of the spherical particles in each CRM would be within the upper and lower nominal size boundaries and the modal size would be well-defined. Most size fractions were to be produced with a uniform, measured: (a) transparent – non absorbing, (b) colored – absorbing.

The development of the CRMs based on sub-micron particles were, to the author’s best knowledge, not pursued beyond the initial materials sourcing stage. However, the need for these CRMs could be even more urgent now than in the early 1990’s, as many techniques are being developed or extended in capability to size sub-micron particles without the necessary means to verify performance satisfactorily.

The International Fine Particle Research Institute (IFPRI) was responsible for coordinating the production of the bulk powders to manufacture the 8-CRMs comprising particles larger than 1µm, and these materials (**Table 6**) were delivered to the BCR by the mid 1990s. They are currently sub-divided and awaiting certification by traceable techniques in accordance with the principles defined by the BCR [25]. The technical document supporting the current Call for Proposals defines the following methodology for consensus certification [26]:

- 100 – 100µm and 150 – 650µm: sieve analysis (near mesh technique)
- 3 – 30µm, 10 – 100µm and 150 – 650µm: optical microscopy
- 1 – 10µm; 3 – 30µm and 10 – 100µm: ESZ analysis

density measurements by helium or water pycnometry

Table 6 Planned BCR Polydisperse, Spherical CRMs

Nominal Size Range Based on D_v (µm)	Appearance	Material
1 – 10	transparent, colorless	barium titanate glass
1 – 10	opaque, light absorbing	glassy carbon
3 – 30	transparent, colorless	barium titanate glass
3 – 30	opaque, light absorbing	glassy carbon
10 – 100	transparent, colorless	barium titanate glass
10 – 100	opaque, light absorbing	glassy carbon
150 – 650	transparent, colorless	barium titanate glass
150 – 650	opaque, light absorbing	glassy carbon

Materials supplied by the International Fine Particle Research Institute (IFPRI)

In addition, each CRM is required to be characterized by non-directly traceable size analysis procedures (laser diffractometry and sedimentation methods not involving direct gravimetric assay). Finally, additional properties of importance (refractive index, porosity (if significant) and surface area (BET-method) as well as stability of the particle size distribution are to be established with their tolerances wherever possible.

It is encouraging to note that, in a study in preparation for the main certification program, inter-laboratory agreement by each of the certifying techniques proposed for the new CRMs was within ±20% of the consensus mean between 10% and 90% of each number – or volume (mass)-weighted size distribution [27]. Several RMs based on glass particles that ‘mirrored’ the size distributions of the proposed CRMs were size by several

independent laboratories. Great care was taken to ensure homogeneity of important particle properties (e.g. sphericity, density and refractive index) during manufacture of the bulk powder. Furthermore, the size distribution of the sub-divided samples of 'mirror' standards from the bulk powder sources was accomplished in the minimum number of operations by custom-made spinning riffles. It is understood that similar rigor has been applied to the CRMs themselves.

The addition of methods to characterize the proposed CRMs with widely used techniques to the certification methods will add to their value as tools for comparing analysers of different kinds, as a significant database will be available that is directly applicable to instrumentation in actual laboratory use. However, caution will still be required in the interpretation of data from this material. For instance, Scarlett *et al.* have observed that in cases where proprietary deconvolution techniques are used to transform measured data into size distribution (e.g. laser diffractometry), compatibility between instruments operating on the same principle may not be achievable even with spherical CRMs [20]. Access to proprietary software is a commercially sensitive issue, and until international agreement can be achieved on standards for such software, each basic instrument and its attendant software must be separately specified and tested, regardless of the type of size-based CRM that is being used.

3. Monodisperse or Polydisperse Standards

A useful distinction can be made between particle standards in which the size distribution, which is almost always unimodal, is either uniform (monodisperse) or comprises a significant range of particle sizes (polydisperse). If, as a first approximation, the size distribution is represented as a log-normal function, the degree of dispersity is given by the geometric standard deviation (σ_g). A perfectly monodisperse standard would have σ_g of unity. However, a practical and widely accepted definition of monodispersity is given by $\sigma_g < 1.2$ [28]. Many CRMs/SRMs are monodisperse by this definition (**Table 4**). In addition, there are several sources of manufactured SSMs (**Table 7**), as well as a number of aerosol-based methods that can be readily implemented in the laboratory to custom-produce monodisperse particles for routine work (**Table 8**) [29-35].

Table 7 Selected Sources of Secondary Standard Materials (SSMs)

SSM Type	Indicative Size Range Available (μm)	Dispersity	Source
soda-lime glass (monosphere)	20 – 200	monodisperse	Whitehouse Scientific, Cheshire, UK www.WhitehouseScientific.com
soda-lime glass intermediate/broad/wide range	1 – 5000	Polydisperse	Whitehouse Scientific, Cheshire, UK www.WhitehouseScientific.com
polymer latex/silica/glass	0.020 – 1000	monodisperse [†]	Duke Scientific Corp., Palo Alto, CA, USA www.dukescientific.com
polymer latex (particle counter SSMs)	0.1 ($10^9/\text{ml}$) – 80 ($3 \times 10^4/\text{ml}$)	monodisperse	Duke Scientific Corp., Palo Alto, CA, USA www.dukescientific.com
polymer latex	0.05 – 10	monodisperse	Polysciences Inc., PA, USA www.polysciences.com
polymer latex/silica	0.1 – 100	monodisperse /polydisperse	Bangs Laboratories, IN, USA www.bangslabs.com
polymer latex	0.038 – 91	monodisperse [†]	Seradyn Inc., IN, USA www.seradyn.com
polymer latex (premium grade)	0.5 – 25	monodisperse	Dyno Particle a/s, Norway www.dyno.no
polymer latex	0.042 – 3.1	monodisperse	Japan Synthetic Rubber Co., Japan www.jsr.co.jp
polymer latex (surfactant-free)	0.014 – 6.0	monodisperse	Interfacial Dynamics Corp., OR, USA www.teleport.com

[†] larger sizes ($D_v > ca. 50\mu\text{m}$) are more polydisperse

Regardless of the choice or availability of spherical or irregular-shaped RMs, the decision whether to calibrate or verify particle size analyser performance verification is all that is required. However, the presentation of the sample to the analyser is of critical importance, if size-related bias is to be avoided. Precautions are therefore required in sample preparation [2] (especially if a sub-sample is being extracted from the bulk RM for the test), as well as in how the RM is introduced to the measurement zone of the analyser. The latter is particularly an issue with the calibration of equipment in which a sample of the particle stream is measured, where consideration must be given to both inlet sampling bias and size-related internal loss [2, 3, 36]. For these reasons, the use of monodisperse particle standards has become widespread, despite the limited availability of particle sizes, at least for CRMs/SRMs. In most cases, SSMs (**Table 7**) or custom-made calibrants (**Table 8**) are satisfactory alternatives for routine calibration activities.

Table 8 Production of Custom Monodisperse Standard Particles by Aerosol Generation Procedures[†]

Method	Size Range (µm)	Materials	References
liquid atomisation – vibrating orifice	1 – 50	soluble species	Berglund and Liu [10] Vanderpool <i>et al.</i> [29]
liquid atomisation – spinning top/disk	2 – 50	soluble species	Walton and Prewett [30] Cheah and Davies [31]
heterogeneous vapor condensation	0.1 – 10	low-volatile substances	Sinclair and LaMer [32] Prodi [33]
electrostatic classification (EC)	0.01 – 1.0	soluble species (nebulization as dilute aerosol prior to EC)	Liu and Pui [34]

[†] A detailed appraisal of all methods has been given by Mitchell [35]

Certain techniques, most notably laser diffraction, provide size measurements of the whole population of particles simultaneously in the measurement zone (so-called ensemble light scattering (**Table 1**)). The performance of these instruments is most conveniently validated when a range of different particle sizes is present at the same instant, so that the use of polydisperse standards (with appropriate precaution to ensure representative delivery to the measurement zone) is more appropriate. Ideally, the size distributions of such standards should each be unimodal, and well-defined by at least one independently traceable technique between 10% and 90% of the number, or mass of particulate contained in the standard. The standards should also be available in quantities appropriate for repeated use with the technique being validated. Polydisperse glass microspheres, such as the so-called 'broad-range' RMs supplied by Whitehouse Scientific Ltd. (**Table 7**), most of which were developed to mirror the size distribution properties of the proposed spherical, polydisperse BCR CRMs (Section 2.3), meet this specification.

References

- 1) International Standards Organization (ISO). Quality Management and Quality Assurance Standards: ISO 9001-1 (1994); ISO 9000-2; ISO 9000-3 (1997); ISO 9000-4 (1993). ISO, Geneva, Switzerland (1993-1997).
- 2) Allen, T. Particle Size Management. Fourth Edition Wiley, NY., USA (1990).
- 3) Hinds, W.C. Aerosol Technology. 2nd Edition Wiley, NY., USA (1999).
- 4) Hawksley, P.G.W. The Physics of Particle Size Measurement: Part 1 – Fluid Dynamics and the Stokes Diameter. *Br. Coal Util. Res. Assoc. Mon. Bull.*, 15 (4), 105, (1951).
- 5) Scarlett, B. Measurement of Particle Size and Shape, Some Reflections on the BCR Reference Material Programme. *Part. Charact.*, 2, 1-6, (1985).
- 6) Oseen, C.W. Latest Methods and Results in Hydrodynamics. Akademische Verlag, Leipzig, Germany, (1927).
- 7) International Standards Organization (ISO). Particle Size Analysis: Laser Diffraction Methods, Part 1: General Principles. ISO 13320-1, (1999).
- 8) Rothele, S. and Witt, W. Standards in Laser Diffraction. Pp. 625-642 in *Proc. PARTEC, 5th European Symp. Particle Characterisation*, Nurnberg, Germany, 1992.
- 9) Muhlenweg, H. and Hirleman, E.D. Reticles as Standards in Laser Diffraction Spectroscopy. *Part. Part. Syst. Charact.*, 16, 47-53, (1999)
- 10) Berglund, R.N and Liu, B.Y.H. Generation of monodisperse aerosol standards. *Environ. Sci. Technol.*, 7, 147-153, (1973).
- 11) Hartman, A.W., Doiron, T.D. and Hembree, G.C. Certification of NIST SRM 1961: 30µm Diameter Polystyrene Spheres. *J. Res. Natl. Inst. Stand. Technol.*, 96, 551-563, (1991)
- 12) Lettieri, T.R., Hartman, A.W., Hembree, G.C. and Marx E. Certification of SRM 1960: Nominal 10µm Diameter Polystyrene Spheres ('Space Beads'). *J. Res. Natl. Inst. Stand. Technol.*, 96, 669-691, (1991).
- 13) Thom, R., Marchandise, H. and Colinet, E. The Certification of Monodisperse Latex Spheres in Aqueous Suspensions with Nominal Diameter 2.0µm, 4.8µm and 9.6µm. Commission of the European Communities (Bureau of Community Reference) Report EUR-9662-EN, Brussels, Belgium, (1985).
- 14) Hartman, A.W., Doiron, T.D. and Fu, J. Certification of NIST SRM 1962: 3µm Diameter Polystyrene Spheres. *J. Res. Natl. Inst. Stand. Technol.*, 97, 253-265, (1992).
- 15) Mulholland, G.W., Hartman, A.W., Hembree, G.C., Marx, E. and Lettieri, T.R. Development of a One-Micrometer Diameter Particle Size Standard Reference Material. *J. Res. Natl. Bur. Stds.* 90, 3-26, (1985).
- 16) Lettieri, T.R. and Hembree, G.C. Dimensional Calibration of the NBS 0.3µm Diameter Particle Sizing Standard. *J. Coll. Interface Sci.*, 127(2), 566-572, (1989).
- 17) Kinney, P.D., Pui, D.Y.H., Mulholland, G.W. and Bryner, N.P. Use of the Electrostatic Classification Method to Size 0.1µm SRM Particles – A Feasibility Study. *J. Res. Natl. Inst. Stand. Technol.*, 96, 147-176, (1991).
- 18) BCR, Reference Materials of Defined Particle Size, Bureau of Community Reference, Brussels, Belgium, (1992).
- 19) Wilson, R., Leschonski, K., Alex, W., Allen, T., Koglin, B. and Scarlett, B. Bureau of Community Reference Certification Report on Reference Materials of Defined Particle Size, Quartz: BCR No. 66-70, Commission of the European communities (Bureau of Community Reference) Report EUR 6825 EN, Brussels, Belgium, 1980.
- 20) Scarlett, B., Merkus, H.G. and Meesters, G.M.H. European Progress on Calibration and Standardization for Particle Sizing. Pp. 9-18 in *Liquid Particle Size Measurement Techniques: 2nd Volume*, ASTM STP 1083, eds. E.D. Hirleman, W.D. Bachalo and P.E. Felton, American Society for Testing and Materials, Philadelphia, USA, (1990).

- 21) Harfield, J.G., Simmons, A.W., Wenman, R.A. and Wharton, R.A. A Study of the BCR Reference Materials. P. 349-357 in *Particle Size Analysis-85*, ed. P.J. Lloyd, John Wiley and Sons, Chichester, UK, (1985).
- 22) Allen, T. and Davies, R. Evaluation of Instruments for Particle Size Analysis. Pp. 17-46 in Proc. 4th Eur. Symp. Part. Charact. (PARTEC), ed. K. Leschonski, NMA NurnbergMesse- und Ausstellungsgesellschaft mbH, Nurnberg, Germany, (1989).
- 23) Merkus, H.G., Bischof, O., Drescher, S. and Scarlett, B. Precision and Accuracy in Particle Sizing: Round-Robin Results from Sedimentation, Laser Diffraction and Electrical Sensing Zone Using BCR 67 and 69. in Proc. 6th Eur. Symp. Part. Charct. (PARTEC), ed. K. Leschonski, NMA NurnbergMesse- und Ausstellungsgesellschaft mbH, Nurnberg, Germany, (1995).
- 24) Mitchell, J.P. Certification and Characterization of a New Range of Community Bureau of Reference Polydisperse, Spherical Certified Reference Materials, *Anal. Proc.*, 29, 508-509, 1992.
- 25) Standards, Measurement and Testing (SMT) Programme of the European Union (formerly BCR), Guidelines for the Production and Certification of BCR Reference Materials: Part A – Recommendations to Proposers of Reference Materials Projects. BCR/01/97-Part A, (1997), SMT Programme Research DG-CII/3, Brussels, Belgium.
- 26) Standards, Measurement and Testing (SMT) Programme of the European Union (formerly BCR), 1994-98. Topic 29: Certification of Polydisperse Particulate Reference Materials, now Topic II-21 (Support to the Development of CRMs), in *Measurements and Testing Newsletter*, 7 (2), (1999), Measurements and Testing Generic Activity, SMT Programme Research DG-CII/3, Brussels, Belgium.
- 27) Rideal, G.R., Dodds, J.A., Pons, M-N., Leschonski, K., Lloyd, P.J. and Merkus, H.G. The Development of New Reference Standards for Particle Sizing Instrument Calibration. Paper 50 in *Proc. World Congress on Particle Technology 3*, UK Inst. Chem. Engrs., Brighton, UK, (1998).
- 28) Fuchs, N.A. and Sutugin, A.G. Generation and Use of Monodisperse Aerosols. Pp. 1-30 in *Aerosol Science*, ed. C.N. Davies, Academic Press, NY., USA, (1996).
- 29) Vanderpool, R.W., and Rubow, K.L. Generation of Large, Solid Monodisperse Calibration Aerosols. *Aerosol Sci. Technol.*, 9, 65-69, (1988).
- 30) Walton, W.H. and Prewett, W.C. The Production of Sprays and Mists of Uniform Drop Size by Means of Spinning Disc Like Sprayers. *Proc. Phys. Soc.*, 62, 3441-350, (1949).
- 31) Cheah, P.K.P. and Davies, C.N. The Spinning-Top Aerosol Generator – Improving the Performance. *J. Aerosol Sci.*, 15 (6), 741-751, (1984).
- 32) Sinclair, D. and LaMer, V.K. Light Scattering as a Measure of Size in Aerosols. *Chem. Rev.*, 44, 245-267, (1949).
- 33) Prodi, V. A Condensation Aerosol Generator for Solid, Monodisperse Particles. Pp. 169-181 in *Assessment of Airborne Particles*, eds. T.T. Mercer, P.E. Morrow and W. Stober. C.C. Thomas, Springfield, IL, USA, 1972.
- 34) Liu, B.Y.H. and Pui, D.Y.H. A Sub-Micron Standard and the Primary, Absolute Calibration of the Condensation Nucleus Counter. *J. Coll. Interface Sci.*, 47, 155-171, (1974).
- 35) Mitchell, J.P. Aerosol Generation and Instrument Calibration. pp. 31-79 in *Physical and Chemical Properties of Aerosols*, ed. I. Colbeck, Blackie Academic and Professional, London, (1998).

Author's short biography

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Jolyon Mitchell is currently Scientific Director of Trudell Medical International, with responsibility for all aspects of *in vitro* aerosol testing. During the past 5 years, he has built up the laboratory to the point at which more than 50 publications have been produced for the open literature, many of which have appeared in peer-reviewed journals. He is Chair of Task Group 1 (In Vitro Methods) of the Inhalant Drug Delivery Systems Sub-Committee of the Canadian Standards Association. This committee is currently developing a standard for testing Spacers and Holding Chambers. He is a member of the American Association of Pharmaceutical Scientists (Inhalation Technology Focus Group) and a Member of Executive Committee developing the Next Generation Impactor for the Pharmaceutical Industry. He is about to join the Editorial Advisory Board of Journal of Aerosol Medicine.

Since graduating from the University of Salford in the United Kingdom with a doctorate in physical chemistry in 1976, he has had approaching 20 years experience in the measurement and control of aerosols, initially as an experimentalist and more recently as coordinator of major projects involved with standards and calibration of aerosol measuring equipment. He joined the UK Atomic Energy Authority in 1980 to undertake research into the release and subsequent behaviour of aerosols that might be released from severe nuclear reactor accidents. This work involved developing several measurement devices and tools for their calibration, and subsequently evolved into initiative to apply the principles of valid analytical measurement to the assessment of aerosols. He developed an interest in medical aerosols as a result of working with colleagues to develop better measurement techniques and immigrated to Canada in 1994 to join Trudell Medical Group.

He has published more than 120 articles in the open literature, of which about 40 are in peer-reviewed journals. He has also contributed to two major books on aerosol science, writing chapters concerned with aerosol measurement techniques and calibration of aerosol measurement equipment.