SPOTLIGHT feature

Reagents, Reference Materials & Laboratory Chemicals

Compliance, CRMs and Accreditation in Spectroscopy – A Supplier's Perspective

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Since the 1970s, Instrument Qualification in testing laboratories has become an essential part of regulatory compliance. This brief history describes how regulators and commercial suppliers have met the demand for reliable reference materials to facilitate compliance

In the beginning

Any respectable analytical laboratory strives to achieve quality results, recognising that to do so, its instrumentation must be working correctly and be qualified by regular performance checks. Prior to the 1970s, most laboratories used home-made test solutions or proprietary test materials to perform these checks. Alternatively they relied on the instrument manufacturers' service organisation to calibrate their instruments as part of routine maintenance. Manufacturers like Optiglass (now Starna Scientific) supplied calibration standards such as rare earth glass filters for 'Wavelength', and neutral density filters and rare earth wavelength references primarily for 'Absorbance' to instrument manufacturers and some end users; whilst Starna supplied sealed liquid references such as potassium dichromate, lithium carbonate, holmium perchlorate and benzene vapour. In the meantime, the only available references with internationally recognised and certified calibration values were those from National Measurement Institutes (NMIs) such as the National Institute of Standards and Technology (NIST) in the United States, whose products were trademarked as Standard Reference Materials (SRMs).

Up until 1975 analytical results had been very much taken on trust, but then allegations were made, and subsequently proven against two major testing laboratories in the US, that results submitted during preclinical drug safety testing were seriously flawed and in some cases, had been deliberately falsified. This led to the publication, in 1976, and subsequent entry into US law of Good Laboratory Practice (GLP) [1], a code requiring non-clinical testing laboratories to implement formal quality control procedures. These included the requirement for laboratories to qualify their instrumentation using properly characterised test and control materials. GLP has since been adopted (in 1981) in the Organization for Economic Corporation and Development (OECD) guidelines [2], it is also enshrined in EU law [3], alongside all the other GxP (where x=m, etc.) related standards used in the pharmaceutical industry. GLP specifically has expanded out of the pharmaceutical sphere in to most areas of laboratory analysis, notably into the food and environmental sectors. Instrument qualification is now mandatory in any laboratory working in a regulated environment – and represents significant benefit to those that are not.

Instrument Qualification

Analytical instrument qualification is conventionally described as a four-step process: Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ) [4]. In simple terms, DQ and IQ are usually performed by the instrument supplier, OQ demonstrates that the instrument meets its published performance specification, and PQ verifies the fitness for purpose of the instrument under the actual conditions of use. In a routine situation, only PQ will need to be performed on a regular basis, whereas OQ is done less frequently, usually after maintenance or repair have been carried out on the instrument. All major pharmacopoeias and regulatory authorities publish standards specifying the qualification tests required for compliance, which must be conducted using recognised test materials or standards. While it is perfectly possible for laboratories to prepare their own test solutions, such procedures have several attendant risks, such that it is now widely accepted to be more convenient, cost effective and less prone to error to purchase certified reference materials from a suitably accredited supplier. Indeed, General Chapter <857> of the US Pharmacopeia [5] states: "Wherever possible…. certified reference materials (CRMs) are to be used in preference to laboratory-prepared solutions."

From NMIs into the private sector

The GLP requirement for instrument test materials to be properly characterised led to a surge in the demand for standards from the NMIs, exceeding their production capacity. NIST therefore decided to investigate whether the skills to be found in private sector companies like Starna Scientific could be harnessed to the production of reference material to meet the demand. Indeed, Starna had previously worked closely with NIST and its UK equivalent the National Physical Laboratory (NPL) for many years and had developed the technology to permanently heat-fuse seal reference solutions into far UV quartz cuvettes, similar technology being a concept used by NIST for its own sealed-cell products.

Clearly any commercially produced reference materials would only be useful if they were accepted by regulatory authorities as being equivalent to NIST SRMs. The NTRM™ (NIST Traceable Reference Material) program [6] was developed to provide a mechanism whereby the measurement values provided with commercially produced reference materials would be traceable to NIST primary standards, via an accredited process.

Traceability is defined in ISO/IEC Guide 99:2007 [7] as the "property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty". This normally means that the instrument used to generate the calibration values has itself been qualified using NIST SRMs. Such materials can then be referred to as 'Certified Reference Materials', defined by the International Standards Organisation (ISO) Technical Committee on Reference Materials (ISO/REMCO) as a "Reference Material, characterised 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."[8]

At the inception of the NTRM program, the range of SRMs for UV/Visible spectrophotometry was rather limited, see *Table 1*.

Table 1. NIST SRMs for UV/Visible spectrophotometry (1998) [9]

SRM	Parameter	Type	Wavelength range (nm)	Unit size
930e	Transmittance	Neutral Density glass	440-635	3 filters, 1 'blank' holder
931e	Absorbance	Co/Ni in nitric/perchloric acids	302-678	Set of 12 ampoules
935a	Absorbance	Potassium dichromate powder	235-350	15 g
1930	Transmittance	Neutral Density glass	440-635	3 filters, 1 'blank' holder
2030a	Transmittance	Neutral Density glass	465	1 filter, 1 'blank' holder
2031a	Transmittance	Metal-on-quartz filters	250-635	3 filters, 1 'blank' holder
2032	Stray light	Potassium iodide solid	240-280	25 g
2034	Wavelength	Holmium oxide solution	240-650	1 sealed cuvette
2035	Wavelength	Rare-earth glass	1000-2000	2.5 cm disk

Ideally, reference materials used for instrument qualification should have certified values as close as possible to the conditions used for the proposed analysis. The primary goal of the NTRM program was for commercially produced NTRM filters to supplement or in some instances replace the coverage afforded by SRMs. For example, as mentioned above, Pharmacopoeias and other regulatory bodies recommend the references to be used for instrument qualification. For wavelength, this is invariably holmium oxide solution, which certainly covers the widely-used region between 240 and 640 nm, and an instrument qualified with this filter could in principle be described as 'pharmacopoeia compliant'. If the analytical wavelength is outside this range the qualification is less relevant, and indeed best practice would be that the qualification uses references whose certified wavelengths 'bracket' the analytical wavelength. Under these circumstances, the pharmacopoeias allow the use of other certified materials, and today, a whole series of commercially available liquid references allow instrument qualification in the wavelength range, from the deep UV to the near-Infrared:

Reference material	Usable range (nm)
Starna Deep UV (DUV)	190 – 230
Starna 'Rare Earth' solution	200 - 270
Samarium perchlorate	230 - 500
Holmium oxide	240 - 650
Didymium oxide	290 - 870
Combined Holmium/Didymium oxides	240 - 795
Starna Near IR reference	930 -2550

Furthermore, where competence has been demonstrated by the private sector, NIST has been able to discontinue the manufacture of many of the SRMs in *Table 1*, as certified traceable equivalents are now available commercially, via the appropriate accredited standards.

Most certified values are given at specified spectral bandwidths. Other variables, such as temperature, could affect the certified values of reference materials. An accredited Reference Material producer should be able to provide certified values under any reasonable customer-specified operating conditions.

Examination of *Table 1* also reveals that to use some of the SRMs, users are obliged to conduct dissolution or liquid transfer operations, with their attendant risks. This is largely overcome by the purchase of ready-made solutions in flame-sealed cuvettes that have been prepared under carefully controlled conditions – which also avoids such risks as evaporation or contamination.

Accreditation

A basic requirement of the NTRM program was that commercial reference material suppliers be accredited. Accreditation is not just about the ability to make accurate calibration measurements, it also covers aspects such as documentation, record keeping and the supplier's quality control systems. There are several detailed and continuously evolving international standards that impact directly or indirectly on the production of reference materials, and not all commercially offered products comply with them. Suppliers will usually claim accreditation to one or more of the following ISO Standards, but caution should be exercised when evaluating potential CRM suppliers as accreditation to a standard may not indicate the necessary competence for the job in hand?

ISO Guide 25 or ISO/IEC 17025 – ISO Guide 25 was first published in 1990 [10] and describes "General requirements for the competence of calibration and testing laboratories". It replaced EN 45001:1989, "General criteria for the operation of testing laboratories". In 1999 it was revised to become ISO 17025 [11], which was again revised in 2005 and at the time of writing is being revised again. It is the gold standard against which any calibration laboratory is judged, so accreditation to this standard is a prerequisite for a reference material producer. Accreditation is granted and periodically re-assessed by a competent third party, normally the national accreditation body, in the case of the UK the UK Accreditation Service, UKAS. A very important aspect of a Calibration Laboratory's accreditation is its Scope. This defines the types of material and the measurements that the laboratory is entitled to perform. A laboratory could claim to be 'accredited to ISO 17025' on the strength of just one measurement process, so users should check the proposed supplier's Schedule of Accreditation to satisfy themselves that it includes the reference materials they propose to purchase. Recently, is has become possible for laboratories to extend their accreditation to allow calibrations to be performed that are not specifically listed in the existing Scope, providing that:

- The method, procedure or standard does not introduce new principles of measurement.
- The method, procedure or standard does not require measurements to be made outside the parametric boundaries defined in the Schedule.

This flexibility allows laboratories to calibrate references to customer requirements, giving them, within their sphere of competence, virtually the same authority as an NMI. Starna Scientific was accredited to ISO/IEC 17025 in 2001 and the associated Scope extended to cover the above protocol in May 2017.

ISO Guide 34 or ISO/IEC 17034. 'General requirements for the competence of reference material producers'. Like ISO/IEC 17025, this standard, first published in 1999 [12], has undergone revisions, in 2000 and 2009. In 2004 the International Laboratory Accreditation Cooperation (ILAC) resolved that reference material producers should be accredited to this standard, in combination with ISO/IEC 17025, and ISO/ REMCO, the ISO Committee on Reference Materials, decided in 2005 to revise ISO Guide 34 to align it more closely with ISO/IEC 17025. This has caused some confusion, as it is sometimes thought that

accreditation to ISO Guide 34 or ISO 17034 alone is sufficient for a producer to claim CRM status for its products, but as the standard states that "the reference material producer shall meet the requirements of ISO/IEC 17025 with respect to tests, calibrations and measurements……" CRM producers should therefore be accredited to both standards. Starna Scientific was accredited to ISO Guide 34 and ISO/IEC 17025 for 'the related laboratory activities' in 2006, the first UK reference material supplier to be accredited to both standards. In November 2016 the standard was revised again, by the ISO Committee on Conformity Assessment (CASCO), in collaboration with the ISO Committee on Reference Materials (REMCO) to become ISO 17034 [13]. One of the reasons for this transition was to allow a Mutual Recognition Agreement (MRA) to be signed, whereby laboratory inspections and assessments made by the regulatory authorities in one country will be recognised by another.

ISO 9001 [14] – This family of standards is a general quality management tool. While producers accredited to ISO/IEC 17025 will also satisfy the requirements of ISO 9001, conformity to ISO 9001 does not of itself demonstrate the competence of the laboratory to produce technically valid data and results.

Conclusions

Commercial suppliers, working closely with regulatory authorities and NMIs, have greatly expanded the range of reference materials available for the qualification of UV/Visible & NIR spectro(photo)meters, among the most widely used tools in analytical chemistry. An evolving system of accreditation gives users confidence in the CRMs they purchase provided care is exercised in the choice of supplier. The continuing evolution of these ISO 17xxx (where xxx = 025, 034, and 043) series standards now allows suitably accredited suppliers to extend their calibration services to include a wide range of additional reference materials not within their normal catalogue, and to expand the function, and format of these materials to cover the ever-expanding range of instrumentation which fundamentally has optical spectroscopy as its primary analytical measurement technique.

References

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