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Letter

Metrological Traceability of Measurement Results in Pharmaceutical and Chemical Sciences: Selection and Use of Certified Reference Materials

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Metrological traceability is a key technical requirement of the ISO/IEC 17025:2005 standard, applied to calibration and testing laboratories that intend to prove their technical competence. In this work, the concept of metrological traceability is discussed, with focus on chemical and pharmaceutical testing laboratories. Practical recommendations for the selection and use of certified reference materials (CRM) are given.

Keywords: reference materials, quality assurance and quality control, pharmaceuticals, metrological traceability, ISO/IEC 17025:2005

Introduction

Metrological traceability is defined 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".[1] According to Bièvre,[2,3] "a measurement is always a comparison" and, therefore, it is necessary to have a reference, which can be a measurement unit, a measurement standard (calibrator, called certified reference material or CRM) or a measurement procedure.

The ISO/IEC 17025:2005 standard is applicable to testing and calibration laboratories that intend to demonstrate their technical competence, as well as the ability to properly operate their management systems.[4] The technical requirements of this standard are based on metrological traceability both in calibration and testing. For medical (clinical) laboratories, the ISO 15189:2012 standard shall be used.[5]

Metrological traceability is essential to ensure that measurement results are comparable in time and space.[6] Some examples can make clear the importance of metrological traceability to ensure accurate and reliable results. In the environmental field, the accurate determination of the concentration of pollutants in water, air or soil is necessary to correctly evaluate the compliance with environmental regulations and to take measurements in case these levels are exceeded.[7] The amount of contaminants, residues and additives in foodstuffs has to be accurately determined to protect the consumers' health.[8] In case of clinical laboratory results (laboratory medicine), accuracy is essential to guarantee safety and efficacy in healthcare diagnostics and treatments.[9-11] The same happens in forensics, whenever results are used in court as evidence, and also in sports, to assess the (non-)compliance in doping control.[12] Finally, accurate and reliable measurements are essential to minimize technical trade barriers.[13]

This means that technically competent laboratories are expected to speak a common language. To do so, they have to be linked to each other, what can be done by using reference standards which are traceable to a "primary" reference standard (e.g., mass standards, certified reference materials or CRMs). Another option is to perform calibrations based on physical constants and measurements.

Measurement uncertainty and metrological traceability are interdependent concepts.[14,15] The expression of uncertainties is necessary to indicate to which extent calibration and testing measurement results can be relied on.[16] Without this indication, measurement results cannot be compared among themselves or with reference values.[17] This means that the measurement uncertainty has to be taken into account whenever the result will be compared with others and lead to a decision such as "pass *versus* fail" or "accept *versus* reject".[18]

Along the metrological chain, the uncertainties increase downstream. This means that if a calibration is performed using a "secondary" reference standard, its

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uncertainty is certainly larger than the uncertainty of the calibration carried out using a "primary" reference standard (calibration hierarchy). Similarly, a laboratory that uses a primary gas mixture to determine the gas concentration in a batch of gas cylinders will declare a testing result uncertainty which is certainly smaller than the uncertainty of further measurements carried out by other laboratories using one of the cylinders of this batch.

In this work, we discuss the metrological traceability in calibration and testing laboratories, with a practical approach for the selection and use of CRMs.

Discussion

Metrological traceability in calibration laboratories

Calibration laboratories that are accredited under ISO/IEC 17025:2005 must be able to perform calibrations that are traceable to the international system of units (SI).

The most illustrative example of metrologically traceable calibrations is given by the mass calibration (Figure 1). The SI unit of mass, the kilogram, is "equal to the mass of the international prototype of the kilogram".[19] Six mass prototypes are kept at the International Bureau of Weights and Measurement (BIPM) in Sèvres, France, under controlled ambient conditions and are used to calibrate national mass prototypes kept at the national metrology institutes (NMI). This type of calibration happens in intervals of about 40 years.[19] The national mass prototypes are then the references for the calibration of mass standards of accredited calibration laboratories.

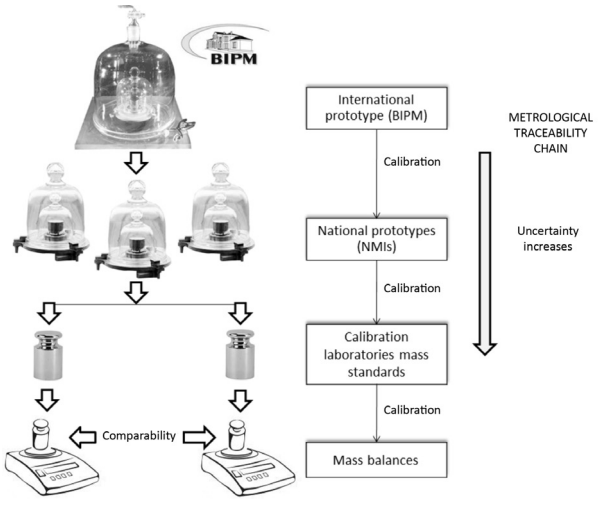

Figure 1. Metrological traceability in calibration laboratories: example for mass calibration.

However, the kilogram is the only SI unit which is still materialized. This creates a demand for extreme care in its conservation, to avoid any changes in the mass that it contains, and also periodic calibration of the other prototypes that constitute the calibration chain. Therefore, it is desirable to realize SI units by means "properties of nature", namely fundamental constants, which are expected to be invariable through time and space and may be available to anyone.[20-22] This is applicable to the seven SI units: length (meter; based on the speed of light in vacuum), time (second; based on the ground state hyperfine splitting frequency of Cesium 133), electricity (ampere; based on elementary charge), temperature (Kelvin; based on Boltzmann constant), luminance (candela; based on the luminous efficacy of monochromatic radiation of frequency 540×10^{12} Hz), amount of substance (mole; based on Avogadro constant), and finally mass (kilogram, which will be based on the Plank constant).[20,22]

Who can calibrate

In 2013, the International Laboratory Accreditation Cooperation (ILAC) has published the ILAC P10:01,[23] which describes who should perform calibration of equipment and reference standards. The options include, but are not limited to, calibration laboratories accredited under ISO 17025:2005 by an accreditation body (AB) covered by the ILAC Arrangement, as well as National Metrology Institutes (NMI) whose services can be found in the BIPM key comparison database (KCDB) (Appendix C).

Metrological traceability in testing laboratories

The mole corresponds to the ratio between the mass of a certain sample amount and its atomic or molecular mass.[24] The metrological traceability in chemical testing laboratories is ensured mainly by using: (*i*) a measurement procedure that can provide accurate and metrologically traceable results, (*ii*) calibrated equipment/system, or (*iii*) certified reference materials (CRM) (measurement standard).[25] Figure 2 summarizes this concept.

An example of measurement procedure which provides metrologically traceable results is the use of Harned cell as primary reference measurement procedure for pH, whose value is "unequivocally metrologically traceable to the International System of Units".[3] Equipment calibration is essential whenever it has a significant impact on the accuracy or validity of the result of the test, calibration or sampling, according to the ISO/IEC 17025:2005 standard. One example is the calibration of analytical balances, which are frequently used for the preparation of sample solutions, and can ensure metrological traceability in case of gravimetric analytical procedures. On the other hand, in

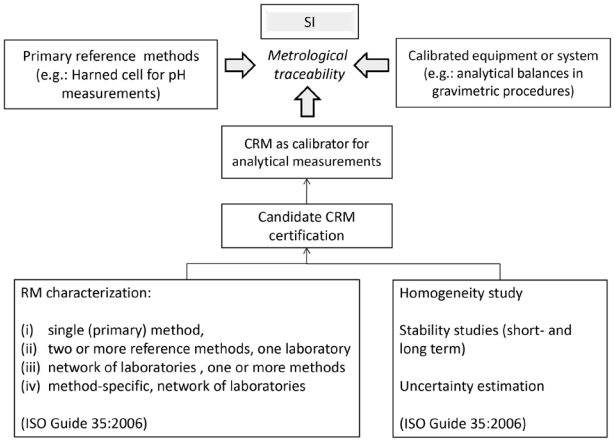

Figure 2. Metrological traceability in testing laboratories (pharmaceutical and chemical sciences).

case of equipment such as liquid and gas chromatographs, although equipment performance qualification is necessary, as well as preventive and corrective maintenance, the metrological traceability is given by the use of certified reference materials, which must be analyzed in the same run of the test samples. Therefore, such type of equipment does not need to be previously "calibrated" by laboratories accredited under ISO 17025:2005, since the calibrator (CRM) will be used in every run.

The metrological traceability ensured by the use of certified reference materials (CRM) is discussed in details in the following paragraphs.

Certified reference materials (CRM)

A certified reference material is a "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".[25] Based on this definition, the first things that the user has to check in the CRM certificate are the declaration of the certified property value (e.g., amount of substance in a given mass of material), the uncertainty associated to this property value, and also how the material was characterized to ensure metrological traceability. Another important information is the minimum CRM amount that has to be used to ensure the studied properties (e.g.: homogeneity).

The necessary steps for the certification of reference materials are given by the ISO Guides 34:2009 and 35:2006.[25,26] The whole procedure usually takes several months or even years to be concluded. The most important steps are the homogeneity studies, to verify (in) homogeneity within and between flasks, the short- and long-term stability studies, carried out at transportation and storage conditions, respectively, the characterization of the CRM candidate material to assign the CRM property value, as well as the estimation of uncertainties in all steps and their combination to determine the standard uncertainty of the CRM property value (u_{CRM}). Detailed descriptions of the production of pharmaceutical CRMs were previously published, with CRM characterization based on the mass balance approach (purity equals 100% minus the sum of impurities).[27-30]

CRM sources and reference material producers (RMPs)

Nowadays, CRMs can be purchased from NMIs and also from reference material producers (RMP). Some examples of CRMs available on the market are shown in Table 1.[31-42] The COMAR international data base was funded by the Federal Institute for Materials Research and Testing (Bundesanstalt für Materialforschung und -prüfung), BAM, in Germany, and contains thousands of CRMs produced worldwide by about 220 producers in 25 countries.[43] The data base name comes from COde d'Indexation des MAtériaux de Référence (hence COMAR) and is recommended by the ISO Committee on Reference Materials (REMCO). Another important database is maintained by the Joint Committee for Traceability in Laboratory Medicine (JCTLM), with more than a hundred higher-order reference materials for laboratory medicine and *in vitro* diagnostics, as well as measurement methods and services.[44]

The number of RMPs accredited under the ISO Guide 34:2009 has increased considerably, as shown in Table 2.[45-56] However, the availability of CRMs is still quite limited and does not fulfill the demand of testing laboratories.[37] In some fields, the use of non-certified reference materials (RM) is still the common practice, as it happens with pharmaceutical reference materials.[57] It should be noted that the ILAC Arrangement still does not cover the accreditation of reference material producers (RMPs).[24] Therefore, accreditation bodies (AB) such as the General Coordination for Accreditation (Cgcre) in Brazil are at the moment in contact with the Asian Pacific Laboratory Accreditation Cooperation (APLAC), which operates a mutual recognition arrangement (MRA) for RMPs.

CRM *versus* RMs, based on the characterization procedures

Considering that CRMs are not available for all the analyses to be performed, users usually ask if they are allowed to use non-certified reference materials (RMs) and still guarantee metrological traceability. A reference material is "sufficiently homogeneous and stable with

Table 1. Some types of CRMs available in the market

CRM description	Type of reference material	Producer	Type of organization	Reference
Microorganisms; cells; DNA	Biological reference materials	ATCC	Private non-profit organization	31
OCP (HCH, DDE, DDT), PCP, AOX, PCB, PAH, acrylamide, ochratoxin A	Organic reference materials	BAM, Germany	Federal institute	32
Elastomers	Elastomeric reference materials			
PS, PMMA, PEO	Polymeric reference materials			
Fluorescence standard for optical equipment calibration	Reference materials for optical calibration			
Lubricant and diesel oils	Certified oil mixtures			
Sulfur in petrol	Petrol impurities - reference materials			
CH_4, N_2	Gas reference mixtures			
Boric acid in water with ^{10}B isotope	Isotopic reference materials			
Iron and steel products	Iron and steel reference materials			
Special materials (high tech ceramics, refractory metals, glasses, pure substances, car catalyst, electronic scrap, ABS)	Special reference materials			
Nanoporous carbon, nanoporous glass	Porous reference materials			
Test materials for X-ray performance, nanoscale stripe pattern for testing of lateral resolution and calibration of length scale	Layered and surface reference materials			
Silicon carbide	Particle size distribution reference materials			
Bacteria and fungi reference cultures; cell lines	Biological reference materials	FIRDI, Taiwan	NMI	33
BTEX; PAH; sugar cane rum and its impurities; ethylcarbamate; combustible ethanol; PAH	Organic reference materials	Inmetro, Brazil	NMI	27-30,34,35
Sodium diclofenac, metronidazole, captopril	API reference materials			
CH_4, CO	Gas reference mixtures			
Conductivity; buffer solutions (pH 1.7, 6.9, 9.2)	Eletrochemical reference materials			
Viscosity (mineral oil)	Viscosity reference materials			
DNA, GMO mass fraction in food matrixes, C-reactive protein in human serum, aspartate transaminase activity, *Enterococcus faecalis* and *Candida albicans* bioballs (cfu/sphere)	Biological reference material	IRMM, Europe	European institute	36,37
PAH in dust, PCB in fish oil, aflatoxin in feedingstuff	Organic reference materials			
Vitamins in milk powder	Vitamins reference materials			
Veterinary drugs in bovine urine and in milk powder, chloramphenicol in pork muscle	Veterinary drugs reference materials			
Metallic elements in food and tissues (milk powder, rice, human hair, bovine muscle)	Element content in food and tissue matrixes			
Coal, coke, oil	Thermal properties reference materials			
Colloidal silica	Nanoparticles reference materials			
API impurities	API reference materials	LGC, UK	CRM manufacturer	38
APIs	Pharmaceutical impurities reference materials			
Pesticides and organic compounds	Organic reference materials	Dr. Ehrenstorfer		
CRM description	Type of material	Producer	Type of organization	Reference
PAH, PCB, BTEX, aliphatic hydrocarbons, dioxin, chlorinated biphenyl, FAME, HCH, DDT, DDE, organic contaminants in different matrixes (serum, milk, tissue, urine)	Organic reference materials	NIST, USA[a]	NMI	39
Drugs of abuse (hair, serum, urine)	Forensic reference materials			
Ethanol and methanol in gasoline	Organic contaminants in fossil fuels			
CH_4, SO_2, H_2S, CO, CO_2, propane, NO, O_2	Gas reference mixtures			

Table 1. Some types of CRMs available in the market

CRM description	Type of reference material	Producer	Type of organization	Reference
pH standards, pH biological buffers (HEPE), conductivity	Electrochemical reference materials			
Zinc, selenium, copper	High purity metals			
Metallic elements in solution	Element standard solutions (spectrometry)			
Trace elements in different matrixes (water, dust, soil, fossil fuels)	Metallic elements in matrixes			
Chloride, fluoride, bromide, sulfate, nitrate, iodide, phosphate	Anion reference materials			
Boric acid isotope standard, silver isotope standard	Stable isotope reference materials			
Stainless Steels, alloy steels, aluminum base alloys, lead base alloys	Ferrous and non-ferrous metals			
Ores, clays, rock and minerals, soils, sediments, sludge	Geological materials and ores			
Peanut butter, flour	Foods and beverages			
Tomato leaves, apple leaves, peach leaves	Agriculture reference materials			
Cholesterol, creatinine, uric acid	Clinical laboratory reference materials			
DNA profiling and nucleic acid materials, serum and plasma materials	Biological reference materials			
CH_4, N_2, H_2, O_2, CO, CO_2, H_2S, NO, ethane, propane, butane, pentane, hexane	Reference gas mixtures	NPL, UK	Measurement institute	40
VOCs and BTEX in gas reference mixtures	VOC gas standards			
Metallic elements	Element reference materials for AAS and ICP	Merck KGaA	Chemical producer	41
Conductivity; buffer solutions	Electrochemical reference materials			
Acids; esters; alcohols; aldehydes; amine; amides; amino acids; aromatics; FA / FAME; hydrocarbons; natural products; pesticides; phthalates; PAH, SVHC	Organic reference materials	Sigma-Aldrich	Chemical producer	42
AMOZ; tetracycline; phenylbutazone; sulfamethoxazole	Antibiotics / drugs reference materials			
Benzoic acid, maleic acid and other 11 compounds	Reference materials for qNMR			
Metallic elements	Element reference materials for AAS and ICP; multielement reference materials for ICP-MS			
Anions and cations	Single-ion and multi-ion reference materials for IC			
Titrimetric substances	Reference materials for titrimetry	Sigma-Aldrich; BAM, Germany	Chemical producer and NMI	42

AAS: atomic absorption spectroscopy; ABS: Acrylnitrile-butadiene-styrene-copolymerisate; AMOZ: nitrofurane 3-amino-5-morpholino-methyl-2-oxazolidinone; AOX: halogenated organic compound; API: Active pharmaceutical ingredients; ATCC: American type culture collection; BTEX: Benzene, toluene, ethylbenzene, xylene; DDE: dichlorodiphenyldichloroethylene; DDT: dichlorodiphenyltrichloroethane; FA: fatty acids; FAME: fatty acid methyl esters; GMO: genetically modified organism; HCH: hexachlorocyclohexane; HEPES: 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; ICP-MS: inductively coupled plasma mass spectrometry; NMI: national metrology institute; OCP: organochloride pesticide; PAH: polycyclic aromatic hydrocarbons; PCB: polychlorinated biphenyls; PCP: pentachlorophenol; PEO: polyethyleneoxide; PMMA: polymethylmethacrylate; PS: polystyrene; qNMR: quantitative nuclear magnetic resonance; SVHC: substance of very high concern; [a]Standard Reference Materials (SRM).

respect to one or more specified properties, which has been established to be fit for its intended use in a measurement process".[25] Comparing the CRM and RM definitions, we can see that both have to comply with the homogeneity and stability requirements. However, differently for the RMs, the CRMs are characterized in a much more detailed way using a metrologically valid procedure, and the uncertainty of the CRM property value has to be estimated and declared.

According to the ISO Guide 35:2006,[26] the metrological traceability of a CRM property value can be ensured by using (*i*) a single (primary) method, (*ii*) two or more independent reference methods in one laboratory, (*iii*) a network of laboratories using one or more methods of

Table 2. Number and types of some reference material producers (RMP) accredited under ISO Guide 34:2009

Country	Accreditation body	Number of accredited RMP	Some CRM types	Reference
Australia	National Association of Testing Authorities (NATA)	16[a]	(not available)	45
Brazil	Coordenação Geral de Acreditação (CGCRE)	05[b]	Elastomers, minerals, electrochemical, viscosity, ores	34,46,47
China	China National Accreditation Service for Conformity Assessment (CNAS)	09[b]	Organics, inorganics, trace elements in soil and sludge, gas mixtures, electrochemical, alloys, ores, pure iron, solid fuel (coal and coke)	48
Japan	International Accreditation Japan (IAJapan)	07[b]	Organics, inorganics, electrochemical, high purity gases, gas impurities, pollutants in food and environmental matrixes, components in bioethanol fuel, steroids in serum and other clinical chemical CRMs, polymers, steel, salts in sea water, GMO content in food matrix, radioactive Cesium in food matrix, CRMs for thermal properties	49
Japan	Japan Accreditation Board (JAB)	02[b]	Enzymes calibrators	50
Russia	Association of Analytical Centers (AAC)	02[a]	(not available)	51
Switzerland	Swiss Accreditation Service (SAS)	02[b]	Organics; gas mixtures	52
Taiwan	Taiwan Accreditation Foundation (TAF)	02[b]	Gas mixtures, biological CRMs	53
UK	United Kingdom Accreditation Service (UKAS)	11[b]	Organics; inorganics; electrochemical; gas mixtures; drugs of abuse in urine; clinical laboratory CRMs; elements in ferrous metals, non-ferrous metals, alloys, ores, cements, clays, ceramics or glasses; RMs with optical properties; CRMs for thermal conductivity and diffusivity; CRMs for viscosity, density, flash point; biological CRMs	54
USA	A2LA	25[b]	Organics, inorganics, electrochemical, biological CRMs, alloys, ferrous metals	55
USA	ACLASS	16[b]	Organics, inorganics, electrochemical, biological CRMs, rocks, ores, minerals, coal, coke, soils, sludge, ashes, metals on filter media, gas mixtures	56

[a]Based on the presentations given in the Aplac Workshop on Reference Material Producers, Tokyo, Japan, November 2013; [b]based on the accreditation body website.

demonstrable accuracy, or (*iv*) a method-specific approach giving only method-specific assessed property values, using a network of laboratories, as previously shown in Figure 2.

Briefly, a primary reference method (first option given by the ISO Guide 35:2006) does not depend on a reference standard of the material being tested. This concept somehow resembles to the description given above for calibrations that do not rely on the use of reference standards and are solely based on physical constants. Ideally, a primary reference method should be used, but some aspects have to be considered. First, the number of primary reference methods is quite limited and the available methods are gravimetry, titrimetry, coulometry, differential scanning calorimetry (DSC), cavity ring-down spectrometry (CRDS), isotopic dilution mass spectrometry (IDMS),[3,58] and instrumental neutron activation analysis (INAA). The quantitative nuclear magnetic resonance (qNMR) has also been included among the primary methods of measurement. The method requires the addition of an internal standard to the analyte solution in deuterated solvent, which is not the same substance as the analyte being tested,[27,59] being therefore called a "ratio" reference measurement procedure.

Additionally, primary reference methods may not be applicable in all cases. Titrimetry, for instance, revealed to be not the most appropriate method for the characterization of pharmaceutical CRMs, since it was not specific enough to differentiate between the analyte and some of the structurally related impurities.[28] What laboratories usually do is to compare the results obtained by two or more methods, for instance qNMR, DSC, HPLC-DAD, HPLC using different columns or experimental conditions, and gas chromatography using different detectors (e.g.; GC-MS,

GC-ECD, GC-FID).[27-30] The IRMM has published that "its results obtained from primary methods are confirmed by independent methods to rule out the possibility of gross errors".[60]

At this point, it may be clear for the user that a RM does not substitute a CRM. This means that a RM will not guarantee that the analytical results are metrologically traceable. What the user can do is try to characterize the material according to the steps given in the ISO Guide 35:2006,[26] which will be easier if carried out in cooperation with NMIs, RMPs, or ISO/IEC 17025:2005 accredited laboratories. According to Priel *et al*.,[61] the starting point may be an analytical reagent-grade material bought from a good chemical supplier, which can be used to estimate the measurement uncertainty of the declared property value, or which can be characterized to determine its purity (amount of substance in a given mass), by using methods such as qNMR or the mass balance approach.

Non-certified reference materials may be used for trend monitoring of analytical measurements performed along the time, in order to check if the process is under control, but shall not be used in analytical procedures aiming to provide accurate measurement results.

A quite important concept related to metrological traceability is that "in a given measurement, a RM can function as a calibrator or a trueness control material, not as both".[3] This explains why ISO/IEC 17025 technical assessors usually check if testing laboratories have "second source standards" available. This means that a first reference material, usually a CRM, is used to construct calibration curves (calibrators), while a second reference standard is used to check if there is no significant deviation of the results compared to what was expected (trueness control material). This second reference standard may be a CRM or a RM which was previously calibrated against a CRM. The most important is that they are not the same material, e.g., reference materials from different producers or from the same producer but with different batch numbers.

RM commutability

Another important property to be discussed is commutability. Reference materials are commutable if "the behavior of the target analyte towards a given measurement procedure is equivalent in the reference material and in routine test samples" and "statements about commutability of a reference material always require specification of the measurement procedures for which it is found to be commutable".[25]

Commutability is particularly important for, but not limited to, clinical laboratories, which usually employ different procedures for routine clinical testing, with varying degrees of interferences caused by different RM matrixes, different sample matrixes, and different responses to the analytes.[25] According to Armbruster,[11] the commutability in clinical laboratories means that "a SRM should give an analytical response that mimics that of fresh patient specimens". Commutability studies are quite important, for instance, in the assignment of catalytic activity values to primary enzyme calibrators, since these values strongly depend on the used analytical method,[62,63] and also in the determination of glycated hemoglobin Alc in total hemoglobin, since changes in the measurement methods demands new stated reference standards.[10]

Method validation

Method validation is between the essential activities to establish metrological traceability and "is not an optional activity".[64] According to the ISO 17025:2005,[4] methods published in international, regional or national standards shall preferably be used, and if standard methods are used, the laboratory shall at least confirm that it can properly operate these methods (according to Eurachem Citac Guide 2003,[13] some level of validation still remains necessary in case of standard methods). If laboratory-developed methods are used, validation is required to demonstrate their suitability for the intended use.[4] The guideline Q2(R1) of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)[64] discusses in details all parameters required for analytical method validation.

Participation in proficiency testing (PT) programs

Testing and calibration laboratories accredited under ISO 17025:2005 are expected to take part on a regular basis in PT programs carried out according to the ISO 17043:2010,[65] aiming to prove their technical competence and to ensure the quality and comparability of measurement results,[61,66,67] as discussed in the paragraph 5.9 of ISO 17025:2005.

However, the participation in PT programs does not guarantee the metrological traceability of calibration and testing results. It can at most ensure the metrological equivalence of measurement results or the metrological compatibility, which is the "closeness of the PT results to the certified value in comparison with the measurement uncertainty of their difference".[3,68] Whenever the competence of one or more laboratories is evaluated (measurement capability), a known reference standard shall ideally be used rather than the average of the participant

measurement results. The use of a consensus value (average) represents the risk that the participant laboratories are precise, but not accurate, i.e., all laboratories can be wrong in the same direction.

In case of NMIs, their technical competence in testing and calibration and the equivalence of the national measurement standards is ensured by the satisfactory participation in Key Comparisons (KC) organized by the Consultative Committee of Amount of Substance (CCQM) of CIPM, as registered in the BIPM Key Comparison Data Base (KCDB).[19]

Conclusions

The metrological traceability is the technical basis of the ISO 17025:2005 standard and it is necessary to guarantee that calibration and testing laboratories can perform accurate and reliable equipment calibration or provide accurate analytical measurement results, respectively.

This can be done by creating a metrological traceability chain between the laboratories standards and a primary reference standard (e.g., mass prototype or CRMs) or by using of physical constants in calibrations. The uncertainties increase downstream along the traceability chains and are essential to inform how much the results can be relied on.

The availability of CRMs is still quite limited and does not fulfil the demands of the laboratories. Therefore, it is essential to encourage worldwide the accreditation of reference material producers under the ISO Guide 34:2009 and the production of new CRMs.

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