

Needs for improvement of the measurement infrastructure in Europe

Philippe Quevauviller*

*European Commission, Competitive and Sustainable Growth Programme (MO 75 3/9),
Rue de la Loi 200, B-1049 Brussels, Belgium*

Carlos Nieto de Castro

*Universidade de Lisboa, Faculdade da Ciências, Departamento de Química e Bioquímica,
Campo Grande, P-1700 Lisbon, Portugal*

Roberto Morabito

ENEA, AMB/TEIN/CHIM, via Anguillarese 301, I-00060 S. Maria di Galeria, Rome, Italy

Miguel Válcárcel

*Universidad de Córdoba, Facultad de Ciencias, Departamento de Química Analítica,
San Alberto Magno s/n, E-14004 Córdoba, Spain*

Anastasios Voulgaropoulos

*Hellenic Institute of Metrology, Industrial Area of Thessaloniki, Block 18 (building 41),
Sindos, GR-57022 Thessaloniki, Greece*

Máire Walsh

State Laboratory, Abbotstown, IE-Dublin 15, Ireland

Whereas the concept of quality control and quality assurance is well understood by modern laboratories (either commercial or with national responsibilities) which are accredited in various analytical sectors, there is an enormous gap in the transfer of knowledge to smaller laboratories. A strong and urgent need has been highlighted for improving the measurement infrastructure in Europe, particularly in less favoured regions or countries. This article gives a summary of needs expressed in the course of five workshops funded by the Standards, Measurements and Testing Programme (European Commission) and held, respectively, in Greece, Ireland, Italy, Portugal and Spain. ©1999 Elsevier Science B.V. All rights reserved.

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1. Introduction

The technological advances in the past 30 years have completely revolutionised the way in which and the manner by which analytical chemists perform analytical work. These advances have opened new avenues and opportunities for legislators and regulators. Decisions on e.g. environmental management, quality of products etc., all depend on the data provided by analytical chemists. Forensic evidence often depends on chemical measurements. National and international trade relies on analytical results giving the basis for the definition of the nature of goods and tariff classification. The cost of the analytical chemist 'getting it wrong' can be enormous in all areas, e.g. repetition of analyses, court trials, wrong assessment of environmental quality or food products, etc. and leads to loss of confidence in the validity of analytical results [1]. In our modern society, quality in the analytical laboratory is a must, which has to be demonstrated to meet the needs of the customers (and all other stakeholders) and attract their confidence, and represent good value for money. There are innumerable areas where results of chemical analyses are

*Corresponding author.

important, e.g. determination of the quality of manufactured products, measurements in support of health and safety, environmental legislation, forensic science, etc.

The analytical chemistry community is faced with the above facts and has to solve many problems and challenges. International organisations such as ISO and CEN have set up quality standards which form the basis of accreditation systems [2,3]. There is, however, often a confusion over the meaning of quality control (designed to provide a quality product), quality assurance (designed to ensure that the quality control activities are being properly implemented), and quality system (set of procedures involving the organisational structure, responsibilities, processes and resources for implementing quality management). It is no longer sufficient for a given laboratory to know that it is generating quality data; in addition, it must be able to demonstrate that:

- analyses are under statistical control (internal QC)
- data are of known and proven quality (external QC)
- data are comparable to data generated by other laboratories
- analytical results are traceable to a well-defined reference point (e.g. reference method, certified reference material, SI unit).

These objectives require the design and implementation of a measurement infrastructure of which the main features are composed of:

- sampling strategy
- validation of analytical methods
- internal quality control (RM, CRM, calibrants, standards, etc.)
- external quality control (proficiency testing, inter-laboratory studies, accreditation)
- measurement uncertainty estimation
- interpretation of analytical data
- education and training.

The above features form the basis for the development of systems of *Metrology in Chemistry*. They also represent the minimum criteria for ensuring the mutual acceptance of test data and the elimination of technical barriers to trade. However, whereas the concept of quality control and quality assurance is well understood by modern laboratories (either commercial or with national responsibilities) which are accredited in various analytical sectors, there is an enormous gap in the transfer of knowledge to smaller laborato-

ries. A strong and urgent need has been highlighted for improving the measurement infrastructure in Europe, particularly in less favoured regions or countries.

2. State of discussions

The awareness for the need to improve the measurement infrastructure in Europe is not new since it led to the establishment of EURACHEM in 1989 which, since then, has generated expert discussions among the different EU member states and associated countries. A recent publication by B. King [4] discusses the issues involved in traceability of chemical analysis, outlining the current state of the art and stressing the 'cultural gap' existing between metrologists and the analytical community. EURACHEM opened the debate on traceability and metrology in chemistry at a workshop held in Brussels, entitled 'Traceability and comparability in measurements of amount of substances', which led to the establishment of a worldwide forum in 1993 with the inauguration of CITAC (Co-operation on International Traceability in Analytical Chemistry) [5].

The European Commission is also very active in facilitating group discussions at the European level as illustrated by a recent report generated from a study funded by the Standards, Measurements and Testing programme [6]. Furthermore, the programme has funded a series of five workshops to discuss the needs for improvement of the measurement infrastructure, which were held in, respectively, Chalkidiki (Greece) in June 1997, Dublin (Ireland) in May 1998, Lisbon (Portugal) and Madrid (Spain) in June 1998, and Rome (Italy) in March 1999. The present article gives an outline of the main needs identified and discussed at these workshops.

3. Traceability – general comments

The definition of traceability can be found in the International Vocabulary of Basic and General Terms in Metrology (VIM); from a functional point of view, comparability is the primary requirement and traceability is a tool to help to achieve it [5,6]. The key elements of the traceability concept are [6]: (1) link to stated references, (2) unbroken chain of comparison, and (3) stated uncertainties. A detailed discussion of this concept can be found in the literature [5–7]. Some key points of these discussions highlight challenges such as the needs (1) to make the traceability concept

understandable and accessible so that it is no longer the exclusive patrimony of theoreticians and bureaucrats, (2) to make the concept more flexible and practical in order to facilitate its use, (3) to expose the fallacy that traceability can only be acceptably referred to the mole and/or kilogramme (SI units), considering that traceability to a well-established accessible standard is also quite valid, practical and useful, (4) to avoid useless arguments (e.g. the mole vs the kilogramme as the ultimate reference in chemical metrology), and (5) to systematically introduce the concept in analytical chemical education (from the very beginning) and research.

Furthermore, traceability to 'laboratory of excellence' and/or to institutional permanent intercomparison exercises or proficiency testing was also discussed but the argument is still controversial.

The concept of traceability should be applied in such a way that it acquires a practical meaning, not solely a theoretical concept. Perceptions for metrology in chemistry are very different in relation to different types of end users: for routine laboratories, this concept is far away from their daily practice; for scientists, this concept is not considered to be a science but rather a sub-discipline; finally, theoreticians establish rules (e.g. ISO, IUPAC) which are very close to physical metrology and far away from reality. These aspects are further discussed in the present issue [8]. In addition, discussions on official methods vs traceable methods are also summarised [9].

In the fields of chemistry and biology, the establishment of a global uncertainty concept is greatly needed; procedures for the calculation of uncertainty should be clearly defined with a different approach than the bottom-up approach proposed in a recent Eurachem Guide [10]. Comments on the evaluation of uncertainty in routine analytical work are summarised in the present issue [11].

4. Reference materials

Detailed definitions and descriptions of requirements related to reference materials (RMs) and certified reference materials (CRMs) are available in the literature [12] and will not be repeated here; a discussion on the use and mis-use of reference materials is also included in the present issue [13].

The workshop discussions stressed that it is urgent and indispensable to harmonise the nomenclature related to reference materials. The present ISO definition is not considered to be clear enough and should be

modified to address the use of, respectively, laboratory reference materials (for interlaboratory studies, routine quality control, evaluation of the reproducibility of methods) and certified reference materials (calibration in some specific cases, verification of accuracy of methods). The discussions also highlighted the needs for an increasing number of reference materials, with well-defined characteristics and the necessary information to ensure their traceability (e.g. information on their origin, stability, transport and preservations, and instructions for use). Minimum requirements for the production of reference materials should be established, as well as the registration of producers which should comply with a recognised quality system. The role of official organisations, both national and the EC, in the production of reference materials should be clearly defined, including possible strategies for production at EU level. There is a clear need for the unification of the certification system via ISO 9000 and accreditation of CRM producers via EN 45000.

Without this quality framework, there is a clear risk of general bias for many analytical data produced in various fields. Negative comments have been made on some EPA (Environmental Protection Agency) certified standards which were not considered to be adequately tested for identity and purity, while used as 'national standards' in the USA [14]. Other discrepancies were noted with respect of PCB determinations in spiked CRM (from NIST) and soil CRM with naturally bound compounds (from BCR); in the first case, recoveries were generally excellent (99%), while in the second case, recoveries were around 25–30% [15]; this example shows that a biased estimate of accuracy can be made when using improper reference materials (in this case, spiked material versus natural material, more representative of real measurements). This stresses the urgent need for establishing minimum (verified) quality criteria for all types of materials used in quality control of analytical measurements, and clear boundary limits for their use.

Workshop discussions highlighted the confusion existing between CRMs, RMs, primary standards, calibrants, etc. As mentioned above, the ISO definitions and guides generally generate more misunderstanding than clarifications and work is needed to set up understandable nomenclatures and clear guidelines on how to use the different types of materials. One of the main characteristics of CRMs are their traceability to a stated reference; it was underlined that many so-called CRMs available on the market are far from being of suitable quality to ensure such traceability.

As a side comment, it should be noted that a very low percentage of published papers report information on the validation of analytical methods on the basis of CRM use; referees of papers should systematically verify that the method validation includes a relevant CRM (if available), i.e. spiking experiments are not sufficient for validation purposes if a CRM may be used. This calls for the increasing and needed production of CRMs which are lacking in many fields. Finally, the use of laboratory reference materials (not certified) should be recommended and promoted for the purpose of daily quality control (setting up of control charts).

In the framework of the EC workshops, a new definition has been proposed by R. Morabito, leading to a better and clearer distinction between RMs and CRMs:

A *reference material* (also known as 'laboratory reference material' or 'laboratory control material') is defined as a material, one or more properties of which are sufficiently well established to be used in an interlaboratory exercise for the evaluation of the comparability of data provided by the laboratories, or in the establishment of a quality control chart to evaluate the long term reproducibility of the laboratory.

A *certified reference material* (also known as 'standard reference material') is defined as a reference material, one or more properties of which are certified, with a stated uncertainty, by a technically valid procedure, which are traceable to a stated reference and accompanied by a certificate or other documentation issued by an accredited body, to be used for the evaluation of the accuracy of the method(s) used by the laboratory.

In these definitions, RMs are to be used solely for interlaboratory studies (including proficiency testing) and reproducibility evaluation, while CRMs are to be used exclusively for the evaluation of accuracy; in very rare and specific cases CRMs can be used for calibration purposes. It should be stressed that the CRM definition implies that the issuing body should be accredited; at present, there are still no well-established rules in this respect and general requirements for the competence of reference materials producers are still in discussion within ISO [16]. One may expect that this requirement will come into force quite rapidly in order to ensure a suitable quality frame for future CRM production.

5. Proficiency testing

Proficiency testing schemes are one of the pillars of external quality assurance assessment [17]. They rely on the availability of suitable reference materials and organisational capabilities of auditing bodies. Workshop discussions highlighted that it is mandatory to carry out critical evaluations of the systems employed for treatment of the data generated in proficiency testing schemes. Sampling procedures should be incorporated as part of proficiency testing when applicable. The organisers of interlaboratory trials should comply with normative requirements already established (proficiency tests ISO 43, collaborative studies ISO 5725, reference materials certification tests ISO 35). The inclusion of interlaboratory tests in method validation should be clearly established, together with a periodic evaluation of the quality of the results.

A user-friendly manual setting up minimum quality criteria for RM production and organisation of proficiency testing schemes should be produced and made available widely in various EU languages.

The workshop discussions highlighted, however, that generally PT schemes do not envisage a plenary discussion of the results among all the participating laboratories. The participating laboratory receives only a (critical) evaluation of the data provided. This means that the laboratories are informed that they are getting analyses wrong but no information is given on the reason(s) why they are getting them wrong. However, interlaboratory trials (intercomparison exercises, ring test, round robin test, etc.), including a plenary discussion, are very useful for the identification of the possible sources of errors and hence represent a more powerful tool for the laboratories.

6. Accreditation

The bases for accreditation systems have been extensively discussed in the literature [18] and some specific discussions, e.g. on the use of reference materials in accreditation systems, have also been published [19]. Workshop discussions pinpointed that the possible widening of scope of accreditation should be investigated, making it more generic and flexible, as indicated in the corresponding guides of the Accreditation Board. It is recommended to unify the criteria of the Accreditation Boards at the EU level, ascribing those to metrology in chemistry. Accreditation should be conceived in such a way that it takes into

account the specific and differentiated features of chemistry and biology metrologies versus traditional physics metrology. Technical requirements for implementing accreditation in a chemical laboratory were widely discussed and are summarised in the present issue [20].

A confusion has been noted between the terms 'accreditation' and 'certification' which, again, stressed the need for a harmonisation of terms at the ISO and CEN levels.

7. National chemical laboratory

The need for an entity in chemical metrology at the national level (in countries where such an entity does not exist) has been highlighted. Such an organisation should organise and co-ordinate issues regarding measurements in chemistry and biology, including the organisation and/or the supervision of interlaboratory trials. This entity/agency should offer global support to the infrastructure of measurements in chemistry and biology, favouring co-ordination at the national level in this matter. This national entity/agency could constitute an element of a future network of national centres of metrology in chemistry and biology in the EU, whose activities would be strongly interrelated.

8. Validation

Rules for the validation of analytical methods are described in detail in this issue, as presented during the workshop series [21]. As stressed during the workshop discussions, the concept of method validation should be strongly related to the objective of the measurement, i.e. the information obtained should respond to the customer's needs (fitness for purpose). Different schemes, corresponding to various examples, should be defined and proposed for internal validation.

9. Education

Beside basic training of laboratory staffs with respect to quality systems, education should be directed towards clients (e.g. legislators). An example of lack of awareness has been given on the basis of an Italian Decree of the Environment Ministry establishing quality criteria for the waters of the Venice Lagoon [22]: in this 'Quality', maximum concentration level

for total dioxins content is 13 fg (femtograms!)/l, for total PCB contents it is 0.04 ng/l, 3 ng/l for various PAH compounds, and 0.1–1 ng/l for various organo-chlorinated pesticides, which are far below the detection limits of most the analytical techniques applied in the usual experimental conditions adopted by routine laboratories. Furthermore, these maximum concentration levels are referred to the soluble phase. One could think that these values were only based on toxicological studies but the maximum concentration of TBT is set at 10 ng/l which is 10 times higher than the level given, e.g. in the Dutch regulation (1 ng/l based on toxicity tests on gastropods) [23].

The needs for harmonised education schemes at the EU level have been seriously considered by the European Commission, which has financed series of training courses on quality assurance for chemical analyses in five EU countries (in the respective languages of the countries); other courses exist on best practices for preparation and use of reference materials [24]. Obviously, these initiatives should be generalised and networked in a systematic way within the EU, possibly extending education networks to less favoured regions or countries necessitating a transfer of knowledge.

10. Further work

Efforts are timely to try to 'speak the same language' in terms of metrology in chemistry. While advanced research is of course necessary to progress in this area, most of the energy should now be focused on transferring knowledge and training for end users (mainly routine laboratories) which are producing most of the data for decision-making in various fields. This need has been recognised by the programme on 'Competitive and Sustainable Growth' of the European Commission through its Generic Activity 'Measurements and Testing' (in particular the third activity related to quality) and the Activity 'Support to Research Infrastructure' (including a framework for actions in support of the improvement of the measurement infrastructure); additional information on these actions can be obtained through the Internet at <http://www.cordis.lu/fp5> or directly at the Growth programme at the following e-mail address: growth@dg12.cec.be

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book reviews

Introduction to bioanalytical sensors

Introduction to Bioanalytical Sensors, by Alice J. Cunningham, Wiley-Interscience, 1998, hardback, 418 pages, ca £45, ISBN 0-471-11861-3

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During this decade biosensors have become of increasing importance – several are available to the bioanalyst and to those interested in understanding the minutiae of biomacromolecular recognition. Developments of transducers and the placing of active biological materials upon them to form the biosensor continue apace, as does the literature. There are about a dozen general biosensor monographs, and a similar number of texts devoted to biosensors based

on particular transducers. This book has six chapters and three appendices which link analytes, glucose sensing, and reviews on selected topics to the useful full-title bibliography of over 1200 references, with over half dating from 1994 or later.

Chapter 1, 'Biosensors and bioanalytical challenges', broadly covers: jargon – the aim being to familiarise the user with the language used in the biosensor field; transducers, molecular recognition components and attachment to transducers; assessment of sensor performance; application areas; theory and practice as illustrated for ion-selective devices, enzyme-loaded electrodes and acoustic wave systems; frontiers and progress covers improvements in immo-

bilisation, the benefits and problems of miniaturisation and implantable sensors. Most useful were the definitions of the various figures of merit (e.g. limit of detection, sensitivity and dynamic range) that even for those active in this area can lead to heated debate. Also illustrated was the power of chemometric analysis in the extraction of data obtained in complex media. Many biosensors function in complex media with imperfect selectivity, making chemometric, or the more efficient genetic algorithmic analysis (chapter 5), ideal partners.

Chapter 2, 'Designing for performance', covers among other things enzymes used in biosensors and the linking of enzyme reactions to amplify the response; the equations used to deal with antibody binding (in solution); nucleic acids