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Review

Development of Quality Requirements of Chemical Analytical Measurements

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Abstract: The development of quality requirements for the analyses of chemical contaminants is reviewed from the formation of the first association of analytical chemists in 1884. Without attempting to give complete coverage, it is shown that the elaboration of quality systems is commanded by the needs of the industry and international trade. Progress along the line of the initial inter-laboratory comparison, methods validated with collaborative tests, and development of internationally harmonized guidelines and protocols to perform complex studies aiming to improve the accuracy and reliability of the results facilitate international trade, and protect consumer health, as well as the environment. The international cooperation for limiting the replication of various (e.g., analytical, toxicological) tests is promoted by multilateral agreements that are also supported by legal obligations. Notwithstanding, the rapid development of requirements and guidance documents provides only the frame for obtaining accurate, defendable results. The production of such results is the duty of the laboratory management, analysts, and study personnel who play the decisive role and bear full responsibility for the samples analyzed.

Keywords: quality assurance; quality control; analytical measurements; food safety

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1. Introduction

The results of analytical measurements can be associated with very serious consequences [1]:

1. health risk in relation to environmental or occupational exposure;
2. the fate of materials and products;
3. the outcome of research investigations;
4. the health status of a patient;
5. confirmation of regulatory non-compliance;
6. confirmation of committing a crime, etc.

Therefore, the results of analyses should be representative, and the laboratory should be able to verify the correctness of measurements with documented evidence. Each analysis could have significant consequences. Therefore, the responsible persons of a laboratory might have to give testimony about their findings in court proceedings. Decisions made on inaccurate data are total blunders. Analysts must be aware that their professional reputation and credibility could be at stake. They carry serious responsibilities both to

the public and to the companies whose products they analyze. Their obligations include producing correct and timely analytical results and being fully accountable for the quality of their work [1,2]. Though the criteria listed above seem self-evident, the practice is often quite different. Many chemists seem to have no reluctance in taking a newly published method out of the literature and applying it for the detection of some contaminants after performing minor modifications to enable them to publish a paper claiming that they modified X Y's method. Reading publications, it's not difficult to recognize that little attention is being paid by many analytical chemists to the question of the reliability of the analytical results they produce [2].

In the meantime, the situation has not changed. For instance, a typical problem derives from the opportunity of the test portion size reduction due to the high sensitivity of detection systems [3]. The reproducibility is reported based on the recovery tests [4,5], and the potentially serious effect of inhomogeneity of the comminuted material on the combined uncertainty and accuracy of the results is very frequently disregarded [6]. The importance of the problem is underlined by special sessions organized for the discussion of sample processing through international workshops, including the North American Chemical Residue Workshops (2014, 2016) and the European Pesticide Residue Workshop (2016).

As Horwitz pointed out, today most analytical operations are based upon physical, not chemical, principles [1]. We might think that physical rules would be harder to break than chemical ones, but Murphy's law 'If anything can go wrong it will' is overriding [1]. Unfortunately, the consequences of an analytical error would also be realized only after a tested lot is rejected or someone's property is affected. We must find ways of applying rigorous quality control measures to discover errors in our measurements and remove them before they have serious consequences.

The expanding national and international trade, the responsibility of national registration authorities permitting the use of various chemicals (e.g., medicines, pesticides, additives), and the continuously improved quality standards in every sector of society require reliable test methods, correct analytical data, and complete reports reflecting all findings of complex studies. The results should be acceptable to all concerned parties.

Reliability means 'The ability of an item to perform a required function under stated conditions for a stated period of time' [7].

It is important to recognize that the variability observed in sampling [8–12] is often larger than in the analysis though far more emphasis has historically been placed on the latter. Moreover, it should always be accepted that the combined errors in the sampling, sample processing, and analyses will affect the precision and reliability of the results [3,10,11,13,14].

Without attempting to give a complete historical background and describe current practices, this publication aims to summarize the main activities performed to improve the quality of data and the products. We also refer to early publications that provide applicable guidance.

2. The Need for Reliable Analytical Results

There was an early need to assess the available methods and test their performance under various laboratory and environmental conditions. The milestones of the development of quality requirements and related activities are presented in Table 1. It is worth mentioning that the Association of Official Agricultural Chemists (AOAC) was formed more than 100 years ago in 1884. The primary objective of AOAC, as stated in its bylaws, is to '... obtain, improve, develop, test, and adopt uniform, precise and accurate methods for the analysis of foods, vitamins, food additives, pesticides, drugs, cosmetics, plants, feeds, fertilizers, hazardous substances, air, water, and any other products, substances or phenomena affecting the public health and safety, the economic protection of the consumers, or the protection of the quality of the environment' [2]. The name of the Association of Official Analytical Chemists was adopted in 1991 to better reflect additional safety interest areas. Today, the organization's legal name is AOAC International, to reflect the global nature of its impact. 'The AOAC International brings together government, industry and academia to establish standard methods of analyses that ensure the safety and integrity

of foods and other products that impact public health around the world'. It regularly publishes the compendium of Official Methods of Analyses of AOAC International [15], as well as various guidelines related to the analyses of food.

Table 1. Milestones of the development of quality requirements and related activities.

Year	Action/Foundation
1884	Association of Official Agricultural Chemists (AOAC), now AOAC International
1903	International Dairy Federation (IDF)
1917	Smalley program started continued as American Oil Chemists' Society (AOCS) Laboratory Proficiency Program
1919	International Union of Pure and Applied Chemist (IUPAC)
1947	International Organization for Standardization
1954	Collaborative International Pesticide Analytical Council (CIPAC)
1961	European Committee for Standardization (CEN)
1963	Codex Alimentarius Commission (CAC)
1964	Codex Committee on Methods of Analyses and Sampling (CCMAS)
1964	Florida Pesticide Residue Workshop (FPRW), now North American Chemical Residue Workshop (NACRW)
1972	1st International IUPAC Congress on Pesticide Chemistry
1976	USDA Good laboratory Practice published
1977	International Laboratory Accreditation Cooperation (ILAC)
1982	OECD GLP Principles
1990	ISO/IEC Guide 25: General requirements for the competence of calibration and testing laboratories.
1992	European Pesticide Residue Workshop
2001	MRA Mutual Recognition Agreement
2005	ISO/IEC Guide 17025: General requirements for the competence of calibration and testing laboratories, now 17025-2017 is in effect
2008	EA-MLA European Cooperation for Accreditation Multilateral Agreement

The so-called Smalley program was started in the USA in 1917 to promote better performance within and between laboratories testing cotton seed meal. Frank Smalley, chief chemist of the Southern Cotton Oil Co., checked the proficiency of his firm's laboratories by distributing weekly replicate cottonseed meal samples among the company's laboratories to verify their comparability. By the sixties, the program expanded to include 32 fat/oil-related categories with 450 certified participants worldwide [16,17]. The program is continued within the American Oil Chemists' Society (AOCS) Laboratory Proficiency Program [18]. The Smalley program is the origin of current proficiency tests in which many laboratories take part to check for themselves the accuracy and precision of their measurements and demonstrate them to their government agencies or clients [19].

Participating in proficiency testing schemes provides laboratories with a means of objectively assessing and demonstrating the reliability of the data they are producing. The first and probably the easiest way to improve the results of the chemical analysis was to standardize the analytical methods. Many organizations (Table 2), both national and international, had undertaken this task on a commodity-by-commodity basis or by applying a horizontal approach for more than a century [20].

The analytical methods for various provisions were assessed and approved by several independent organizations competing for dominance in providing referee methods [20]. It resulted in the overlap and the multiplication of effort and the difficulty in deciding which of two or more well-authenticated methods, each properly established by the collaborative study, should be selected for standardization, referee, or arbitration purposes [1].

In the field of quality control of pesticides, the Collaborative International Pesticide Analytical Council (CIPAC), which was formed in 1954, is the leading authority in organizing collaborative studies and publishing standard methods [21]. CIPAC's objectives are to promote the international agreement on methods for the analysis of pesticide products and physico-chemical test methods for formulations; to promote inter-laboratory programs; to publish standardized methods of analysis. The FAO pesticide specifications are based on the relevant CIPAC methods [22]. CIPAC collaborates closely with AOAC. These organi-

zations, where appropriate, adopt each other's methods. This is indicated by a method designated as CIPAC-AOAC or AOAC-CIPAC.

Table 2. Organizations involved in establishing standards or guidelines.

Abbreviation	Full Name
AACC	American Association of Cereal Chemists
AOCS	American Oil Chemists Society
BCR	Community Bureau of Reference (under EU)
BIPM	International Bureau of Weights and Measures
CEN	European Committee for Standardization
CENELEC	European Committee for Standardization/Electrotechnical Commission
CIPM	International Committee on Weights and Measures
CIPAC	Collaborative International Pesticide Analytical Council
CITAC	Cooperation on International Traceability in Analytical Chemistry
EAL	European Accreditation of Laboratories (formed from WECC and WELAC)
ECCLS	European Committee for Clinical Laboratory Standards
EURACHEM	Network of Organizations in Europe
EUROLAB	Organization for testing in Europe
EUROMET	A collaborative initiative between national standards laboratories
GAFA	Grain and Feed Trade Association
ICSH	International Committee for Standardization in Hematology
IEC	International Electrotechnical Commission
IDF	International Dairy Federation
IFCC	International Federation of Clinical Chemistry
ILAC	The International Laboratory Accreditation Conference (international forum for accreditation)
ISO	International Organization for Standardization
ISO/CASCO	ISO Council Committee on Conformity Assessment
ISO/REMCO	ISO Reference Materials Committee
NAMAS	National Measurement Accreditation Service
NATA	National Association of Testing Authorities, Australia
NCCLS	National Committee for Clinical Laboratory Standards, US
NMKL	Nordic Committee on Food Analyses
OECD	Organization for Economic Cooperation and Development
UKAS	United Kingdom Accreditation Service
WECC	Western European Calibration Cooperation
WELAC	Western European Laboratory Accreditation Cooperation

The predecessor of the FAO/WHO Codex Alimentarius Commission (CAC), the Joint FAO/WHO Committee of Government Experts on the Code of Principles Concerning Milk and Milk Products, established in 1958, was among the first which recognized the need for harmonized methods [23]. Consequently, the Codex Secretariat formed a technical group consisting of experts from the International Dairy Federation (IDF), the International Organization for Standardization, and AOAC with the responsibility to supply jointly approved methods of analysis for supporting international CODEX standards [24]. The Codex STAN-234 provides a collection of methods recommended by the commodity committees [25]. The updating of the methods is being undertaken by the Codex Committee on Methods of Analyses and Sampling (CCMAS). Under CAC/GL 27, analysts are required to use the most updated version of the methods of analysis [26]. In addition, various committees of CAC, such as Pesticide Residues (CCPR) and Residues of Veterinary Drugs in Food, have provided lists of recommended methods for testing compliance with the relevant Codex standards and elaborated guidelines for good analytical practice related to the application of Codex Standards [27,28].

The detailed set of principles for the choice of methods of analysis adopted by CAC [24] may be summarized as follows:

1. Official methods of analysis elaborated by international organizations occupying themselves with food or groups of foods should be preferred;

2. Preference should be given to methods of analysis the reliability of which has been established in respect of the criteria specified in the Codex Procedural Manual;
3. The method selected should be chosen on the basis of practicability and preference should be given to methods that have applicability for routine use;
4. All proposed methods of analysis must have direct pertinence to the Codex Standard to which they are directed;
5. Methods of analysis that are applicable uniformly to various groups of commodities should be given preference over methods that apply only to individual commodities.

It was soon recognized that methods to be used by many laboratories had to be tested in many laboratories. The names of prestigious organizations alone were not accepted to guarantee the satisfactory performance of their recommended methods. Even ISO encouraged its technical committees to perform inter-laboratory performance tests to validate their methods to be suitable for submission to CAC using ISO 5725-1-6 standards [29–34]. Naturally, the isolated activities of various organizations led to independent guidelines for the design, conduct, and interpretation of collaborative studies. There was an urgent need to harmonize the guidelines. This task was undertaken by the International Union of Pure and Applied Chemistry (IUPAC), inviting experts from the Analytical, Applied, and Clinical Divisions and representatives of main international organizations (ISO, AOAC) sponsoring collaborative studies. Through a series of meetings, several harmonized protocols have been developed [35–39]. However, the IUPAC protocol and ISO 5725 are not quite identical: for example for the choice of outlier tests, the critical value to reject the outlier is 1% in ISO 5727-2, against IUPAC's 2.5%.

3. Vital Role of Proficiency

In addition to the use of reliable methods, the proficiency of the chemist and the testing laboratory are of vital importance in obtaining valid results. Chemists should only accept tasks for which the laboratory has appropriately validated methods and should not consider losing their professional credentials if they turn down tasks lying outside their competence. Pocklington's (1990) [38] conclusion is also valid today: it is more economical to contract out a few irregularly received samples requiring tests with special methodology and expertise to well-established and accredited laboratories than to introduce an in-house method for their analyses.

Setting criteria for testing the proficiency of laboratories have been elaborated by several national and international organizations that were competing with each other. Again, the joint effort of ISO, AOAC, and IUPAC resulted in harmonized protocols for testing the proficiency of laboratories [38,40]. Moreover, several scientific publications described the procedures for quality assurance and provided guidance for the validation of analytical methods, for example, Wood 1988 and 1999, King 1995, Jenke 1996, Fajgelj 2000, Taverniers 2004, Chandran 2007, Magnusson 2014 [41–47]. Various guidelines and standards were introduced by different national and international organizations setting out the requirements for a laboratory to demonstrate that it operates according to them if it is to be recognized as competent to carry out the specified tests.

The certification of competence is performed through a third-party conformity assessment that gives confidence to staff, management, and customers concerning the quality system employed in the laboratory [48].

In order that the national systems may be compatible with one another, and to facilitate bilateral and multilateral agreements, ISO has developed the basic standard ISO/IEC Guide 38-1983 (with revisions of 42, 44) that was replaced by the ISO/IEC Guide 25-1990. It was also regularly updated and expanded. The current version, ISO/IEC 17025-2017, includes a new section on risk assessment [49]. Simultaneously, the Joint European Standard Institution CEN/CENELEC developed its own standards (EN45001, 45002, 45003, 45011, 45012, and 45013) that had already been withdrawn or partly replaced, respectively, by ISO/IEC17025:2017, ISO/IEC 17011:2018, ISO/IEC 17065:2013, ISO/IEC 17021-1:2016, and ISO/IEC 17024:2013 [49–53].

The basic principles of the ISO guides and EN standards were very similar and can be summarized as follows:

1. A laboratory to produce consistently reliable data must implement an appropriate program of quality assurance and internal quality control;
2. Analytical methods must be thoroughly validated before use, preferably with a collaborative study that conforms to recognized protocol. These methods must be carefully and fully documented, staff adequately trained in their use, and control charts should be established to ensure the procedures are under proper statistical control;
3. Where possible, all reported data should be traceable to international standards, reliable and well-documented standard materials, or preferably certified reference materials if available;
4. Accreditation of the laboratory by the appropriate national accreditation scheme, which itself should conform to accepted standards, indicates that the laboratory is applying sound quality assurance principles. It is anticipated that accreditation assessments will increasingly utilize the information produced by proficiency testing [54].

There was an urgent need to harmonize the procedures of the certification of the competence of testing laboratories performed through the national third-party conformity assessments. The International Laboratory Accreditation Cooperation (ILAC) (1977) became a formal cooperation in 1996 (ILAC) [55] with the aim of developing international cooperation for facilitating trade by promoting the acceptance of accredited test and calibration results. The ILAC operates in accordance with ISO/IEC 17011 [50]. In 2000, the ILAC Mutual Recognition Arrangement (ILAC MRA) [56] was signed by 36 full members to promote the acceptance of technical tests and calibration data for exported goods. The Mutual Recognition Arrangement (MRA) for calibration and testing laboratories came into effect in 2001. The MRA was extended to include the accreditation of inspection bodies (2012) and proficiency test providers (2020). Each accreditation body that is a signatory to the MRA agrees to abide by its terms and conditions and by the ILAC evaluation procedures. Moreover, it ensures that all its accredited laboratories, inspection bodies, and proficiency testing providers comply with ISO/IEC 17025 or ISO 15189 (for medical testing laboratories) or ISO/IEC 17020 or ISO/IEC 17043 and related ILAC documents [56]. Besides ILAC, there are many regional accreditation organizations that provide forums for accreditation bodies operating in the region. For example, African Accreditation Cooperation (AFRAC), Asia-Pacific Accreditation Organization (APAC), European Cooperation for Accreditation (EA), and Inter American Accreditation Cooperation (IAAC).

The EA Multilateral Agreement (EA MLA) is a signed agreement between the EA Members whereby the signatories recognize and accept the equivalence of the accreditation systems operated by the signing members, and also the reliability of the conformity assessment results provided by Conformity Assessment Bodies (CABs) accredited by the signing members [57]. The EA-MLA is compulsory for all EU Member States. It makes the objective 'Accredited once, accepted everywhere' effective [57]. The objectives of the other regional organizations are practically the same.

The predecessor of the Hungarian Accreditation Authority, established in 1995, is a full member of EA and ILAC and a signatory of their MRA and MLA.

4. Reliable Studies and Guidance Documents for Laboratory Operations

The national registration authorities all over the world also found it necessary to introduce a system that ensures the reliability and traceability of the results obtained in very complex toxicological, metabolism, and environmental fate studies involving a number of analyses of different substrates at several test facilities operating often in different countries. Consequently, the principles of Good Laboratory Practice (GLP) were elaborated first by the US FDA in 1976 followed by other national organizations. Since medicines and pesticides are manufactured and distributed by multinational companies all over the world and most of the countries' legislations require the registration of such products, there was an immediate need for internationally acceptable harmonized guidelines. The

Organization of Economic Cooperation and Development (OECD) was found to be the best forum for the development of such guidelines. The basic GLP document was published in 1982 [58]. The GLP principles were accepted rapidly and they were applied to many new fields such as short-term toxicological studies, supervised pesticide residue field trials, cosmetics, etc. To meet the practical requirements, the OECD GLP Panel, consisting of the representatives of member countries, has elaborated a series of documents that have been published in 10 monographs. The OECD GLP Principles are regularly reviewed and updated as required. The provisions of Mutual Acceptance of Data (1981 and 1997) assure that 'test study data generated in any member country in accordance with OECD Test Guidelines and Principles of Good Laboratory Practice (GLP) shall be accepted in other member countries for assessment purposes and other uses relating to the protection of human health and the environment' [59]. The fully adherent countries (eight) have the same rights and obligations as the OECD member countries. In addition, the studies conducted in compliance with OECD GLP GLs are accepted by many non-OECD countries as well.

The international standards and guidelines provide the frame for performing the analytical measurements. Detailed technical instructions and acceptable performance criteria prepared by the responsible international and national organizations help the analysts verify the performance of their methods and carry out the measurements providing accurate, reliable, and defendable results complying with the provisions of ISO/IEC 17025 and GLP Guidance documents as appropriate. These guidance documents define the terms used for such purposes. Some of the most relevant documents are:

1. Protocol for the Design, Conduct, and Interpretation of Method Performance Studies [35–37];
2. The International Harmonized Protocol for the Proficiency Testing of (Chemical) Analytical Laboratories [39];
3. Harmonized Guidelines for Internal Quality Control in Analytical Chemistry Laboratories CXG-65-1997 [60];
4. Guidelines on Good Laboratory Practice in Pesticide Residue Analysis CXG-40-1993 [61];
5. Guidelines on Estimation of Uncertainty of Results CXG-59-2006 [62];
6. EURACHM-CITAC Guide: Quantifying Uncertainty in Analytical Measurement, 3rd Edition (2012) [63];
7. Guidelines on Performance Criteria for Methods of Analysis for the Determination of Pesticide Residues in Food and Feed CXG-90-2017 [27];
8. Analytical Quality Control and Method Validation Procedures for Pesticide Residues Analysis in Food and Feed SANTE 11312/2021 [64];
9. Guidance Document on Pesticide Analytical Methods for Risk Assessment and Post-Approval Control and Monitoring Purposes, SANTE/2020/12830, Rev. 1, 2021 [65];
10. Technical Guideline on the Evaluation of Extraction Efficiency of Residue Analytical Methods, SANTE/2017/10632 Rev. 4, 2022 [66];
11. Guidelines for the Validation of Chemical Methods in Food, Feed, Cosmetics, and Veterinary Products, 3rd ed. USDA, 2019 [67];
12. Good Samples: Guidance on Obtaining Defensible Samples, FDA, AAFCO, AFDO, APHL, 2015 [68].

The European Commission issued regulations on validation and performance criteria of chemical contaminants and veterinary drugs (EC 2021/808, EC401-2006) [69,70]. The guidance documents referenced above are regularly updated as needed to reflect the rapid developments of instruments and techniques affecting the analytical quality requirements, therefore their latest versions should always be considered. The terms defined by the major guidance documents and regulations are summarized in Table 3.

In addition, the applicable sampling methods providing the basis for legal actions are regulated in EC 2021/808, EC 401-2006, CXG33-1999, and CXG50-2004 [69–72].

Table 3. Performance parameters specified by the major guidance documents and regulations.

Parameter	EC 2021/ 808	EC 401/2006	CGX-90-2017	SANTE 11312/2021 2020/12830	USDA 2019
Accuracy	x	x	x	x	x
Applicability (matrix and concentration range)	x	x	x	x	x
Calibration	x	x	x	x	x
Confirmation	x		x	x	x
Limit of detection	x	x	x	x	x
Decision limit for confirmation (CCα)	x				
Screening detection limit				x	x
Limit of quantification	x	x	x	x	x
Precision/repeatability	x	x	x	x	x
Reproducibility	x	x	x	x	x
Recovery	x	x	x	x	x
Retention time	x		x	x	x
Selectivity/Specificity	x	x	x	x	x
Sensitivity	x		x	x	
Linearity	x		x	x	x
Matrix effect	x		x	x	x
Measurement uncertainty	x	x	x	x	x
Stability of analytes	x		x	x	x
Ruggedness	x		x	x	x
Reporting results	x	x	x	x	
Detection capability (CCβ)	x				

5. The Importance of Laboratory Environment

The guidance documents would facilitate obtaining accurate, defendable results only if the laboratory operations are performed by staff members (from the top manager to each member) who are aware of their own responsibility and are working in close cooperation with each other. Additionally, they maintain close contact with their customers/clients to meet their requirements. The key responsibility is rested on the manager of the laboratory.

Moreover, it is important to properly define the mission of the laboratory [73]. To obtain recognition of the work carried out by the laboratory, instead of simply reporting the results they should be communicated as providing scientific evidence for important decisions and the resulting benefits, such as:

1. Status of regulatory compliance (support for legal actions);
2. Evaluation results of consumers' health risks;
3. The outcome of research investigations (what have we have (not) learned);
4. The validity of a process/method.

No doubt there are many more aspects, and the selection will, of course, depend upon the organization the laboratory serves. These mission viewpoints remove the analytical laboratory from its isolation as a generator of numbers and place the products of the laboratory squarely in the center of much of the corporate (enterprise's) 'action'. A consultancy/advocacy approach is a more positive and proactive role for the laboratory, which in turn enhances its prestige and those who work there [73].

6. Conclusions

As we can see, the quality assurance/quality control (QA/QC) activities are intensive and the development in the field of quality management is rapid. Several workshops and symposia are organized every year. New scientific journals are published and new ideas and methods are introduced. It is getting difficult to follow up on the relevant publications, and evaluate and incorporate them into the existing frames of international standards. What was enough 3 to 5 years ago may be considered insufficient or obsolete at present.

However, we should be careful taking everything for granted which has been published. An attentive analysis of the principles is advisable before further action is taken. It is not sufficient to validate our methods or test the performance of already validated methods once. The laboratories should establish their own internal quality control program to be used on a daily basis for ensuring that their methods satisfy the specified performance characteristics when applied, for instance, to screen over several hundred analytes in samples of unknown origin limiting especially the false negative detection.

It is emphasized that the requirements of various guidance documents should be implemented in the creative spirit bearing in mind that the priorities are: (1) good science and good analytical practice; (2) minimum bureaucracy; (3) improving reliability and efficiency.

QA/QC measures should be an appropriate proportion of the activities related to the analyses of samples and reporting of the results.

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