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Practical Quality Control: the Experiences of a Public Health Laboratory

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1. Introduction

In the 1930's W.A. Shewhart pioneered the application of statistical principles to the quality control (QC) of production processes, eventually publishing the landmark book "Economic Control of Quality of Manufactured Products" (Shewhart, 1931). In this book, he states that a phenomenon is *under control* if its future variation can be predicted (within limits) based on previous experience. This is precisely the idea behind the control charts used in measurement processes—specifically, for chemical analysis. The International Organization for Standardization (ISO), in its standard ISO 9000 (ISO, 2005a), defines *quality control* as "the part of quality management focused on fulfilling quality requirements". According to the standard, quality management also includes quality planning, quality assurance and quality improvement. The above definition is rather vague, because quality management systems based on the ISO 9000 family of standards can be applied to any kind of organization regardless of its field of activity, its size or whether it is from the public or private sectors. Testing laboratories typically distinguish between *internal* and *external* QC. In this context, the International Union of Pure and Applied Chemistry (IUPAC, 1998) gives a definition of internal QC that is well-suited to an analytical laboratory: "the set of procedures undertaken by laboratory staff for the continuous monitoring of operation and the results of measurements in order to decide whether results are reliable enough to be released". Although the aforementioned document does not formally define *external* QC, it does mention that *external control* may be done by submitting blind samples to the measuring laboratory. This activity can be organized in the form of a collaborative test.

The aim of these QC activities is to verify that the quality parameters of an analytical method ascertained in the method validation are maintained during its operational lifetime. Thus, method validation or revalidation tasks are periodic activities that end with a validation report, whereas QC activities are recurrent activities implemented in routine work. Apart from the use of fully validated methods, QC assumes the use of properly maintained, verified and calibrated equipment, reagents and consumables with the proper specifications; standards with well-established traceability; and qualified technicians working in suitable environmental conditions. However, fulfilling all these requirements is not enough to ensure the delivery of appropriate quality results over time: a laboratory's capacity to produce technically correct results must be continuously monitored. Indeed, according to Thompson *et al.* (Thompson & Lowthian, 1993), QC is the only quality

management measure that provides a high level of protection against the release of inaccurate data. The authors demonstrate a significant relationship between the efficacy of a laboratory's QC and its subsequent performance in proficiency tests. They also consider that the implementation of QC activities and the participation in proficiency tests are two sides of the same coin: a laboratory's commitment to quality.

Once a laboratory has implemented a method in its routine work, is performing adequate QC, has taken any appropriate corrective and/or preventive actions, and its staff has acquired sufficient expertise, it may consider including this method in its scope of accreditation. Figure 1 shows these activities in the context of the operational lifetime of an analytical method.

This chapter was written to explain, in practical terms, the QC activities and management at an analytical laboratory—namely, the Chemical Analysis Service at the Laboratory of the Public Health Agency of Barcelona (*Laboratori de l'Agència de Salut Pública de Barcelona*; hereafter, *LPHAB*).

2. History and present context of the LPHAB

The LPHAB has its origin in the Municipal Laboratory of Barcelona, a microbiology laboratory created in 1886 to provide support to the sanitary authorities in their efforts to prevent rabies; since its inception, the Municipal Laboratory of Barcelona was a reference laboratory in Spain. In 1907, owing to its ever-increasing activities, it was given a new structure that led to creation of a section dedicated to chemical analysis of foods, with the then innovative objective of studying health problems attributable to the presence of hazardous chemicals in foods.

From the 1950's onwards, the section on chemical analysis of foods underwent major development. This stemmed from advances in knowledge on food chemistry and was catalyzed by various international food crises caused by chemical pollutants such as mercury and methanol. A case of widespread food poisoning in Spain in 1981, traced to denatured rapeseed oil, triggered the modernization of many Spanish public health laboratories, including the Municipal Laboratory of Barcelona. The Laboratory's equipment was soon updated, and its organization and management were overhauled. These changes enabled the Municipal Laboratory of Barcelona to face new analytical challenges. In addition to assessing the nutritional properties of food, it also focused on detection and determination of additives, residues and contaminants in food. The Municipal Laboratory of Barcelona began serving customers outside of the municipal administration; the challenge of providing these customers with the data they sought at specific analysis costs and response times proved highly stimulating. By the year 2000, it had analyzed 20,000 samples. In 2003 the Municipal Laboratory of Barcelona merged with the Public Health Laboratory of the Autonomous Government of Catalonia (*Generalitat de Catalunya*) in Barcelona to form the LPHAB. This union led to significant investments in instrumentation and to the recruitment of new staff; consequently, the newly formed LPHAB became one of the strongest laboratories in Spain for food analysis.

The LPHAB currently comprises four departments: two technical departments (the Chemical Analysis Service [CAS] and the Microbiological Analysis Service) and two management & support departments (the Quality Assurance Unit [QAU] and the Logistics & Services Unit). It presently employs 65 people, 31 of which work in the CAS (11 senior technicians and 20 mid-level technicians and support staff). The CAS encompasses four

areas: two dealing with applications (food analysis and environmental analysis) and two dealing with analytical techniques (spectroscopic analysis and chromatographic analysis).

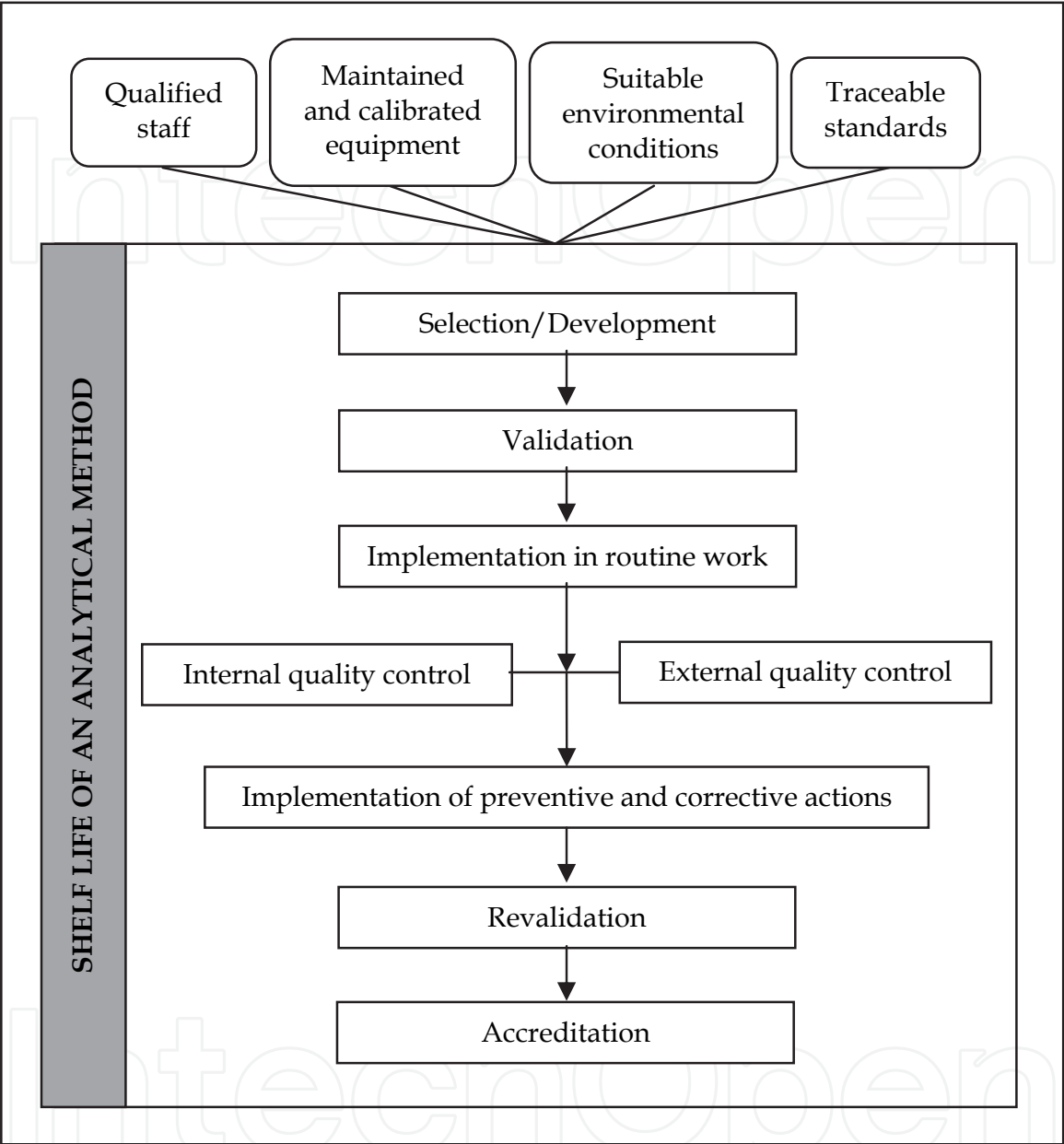


Fig. 1. Activities that determine the reliability of test results.

The LPHAB features a broad array of state-of-the-art equipment: roughly 500 instruments, including those for sample treatment, chromatography and spectroscopy. These include various gas and liquid chromatographs coupled to tandem mass spectrometry plus two inductively coupled plasma spectrometers, one equipped with photometric detection, and the other, with mass spectrometry detection. The LPHAB also uses a laboratory information management system (LIMS).

To date, the CAS has implemented about 110 analytical methodologies included in the scope of accreditation according to the requirements of the ISO 17025 standard (ISO, 2005b). In 2010, the CAS portfolio included approximately 1,800 different determinations, 1,400 of

which correspond to its scope of accreditation. Moreover, the flexible scope includes some 55 analytical methods, grouped according to instrumental techniques, and numerous analytes.

In 2010 the LPHAB tested 32,225 samples, for which it performed some 550,000 determinations. Roughly half of these samples were food samples, and the other half, environmental samples (chiefly, potable water and filters for atmospheric control). The LPHAB’s main customers are the Public Health Agency of Barcelona (which owns it), and the inspection bodies of the Catalanian and Spanish governments.

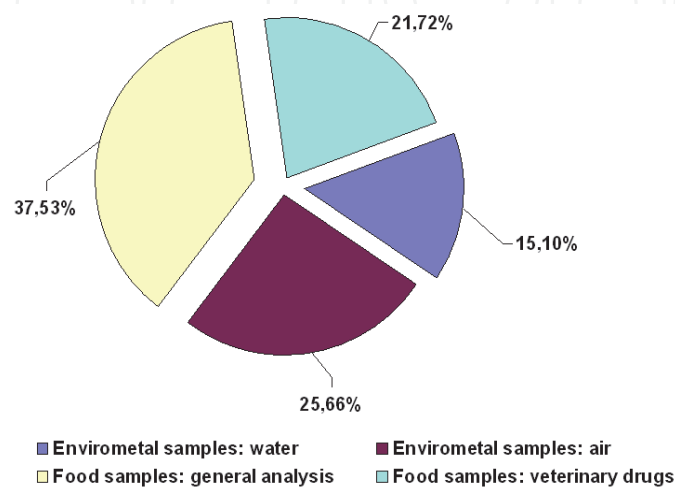


Fig. 2. Breakdown of analyses performed at the LPHAB in 2010, by sample type.

In 2010, the LPHAB’s budget, excluding staff costs, was €1.2 million. This includes consumables, gases, reagents, culture media, equipment maintenance, participation in proficiency testing, and small investments. Its revenue contracts and invoices totaled €7 million.

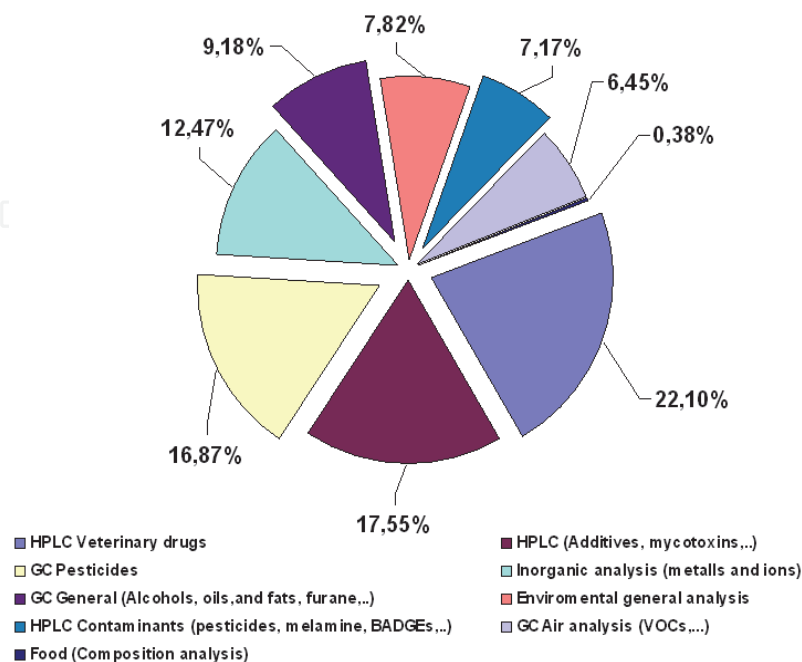


Fig. 3. Breakdown of analyses performed at the LPHAB in 2010, by analytical technique

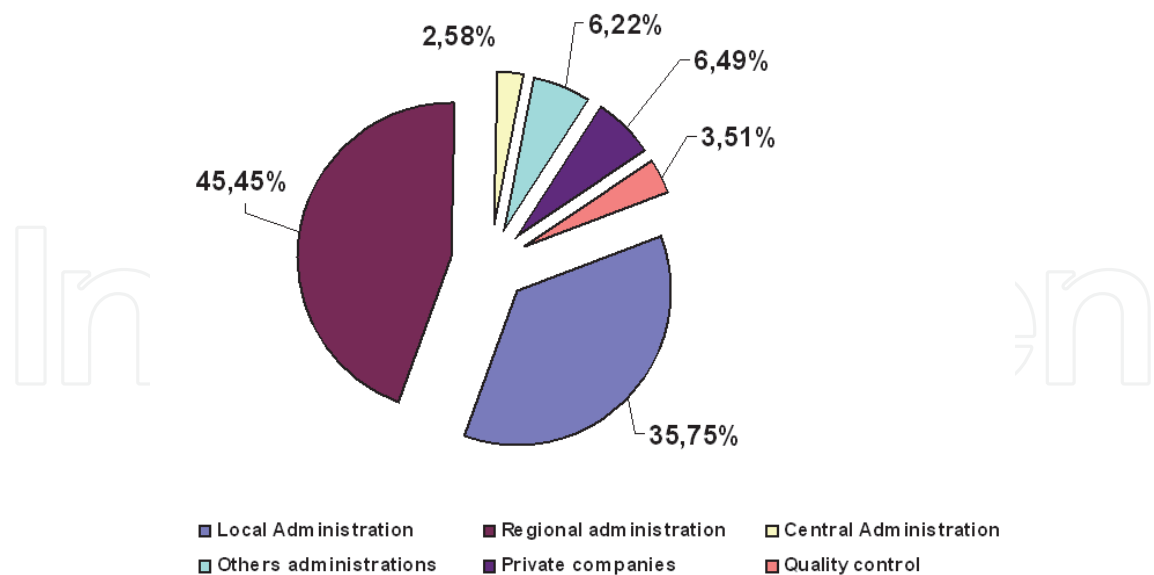


Fig. 4. Breakdown of the LPHAB’s customers

The LPHAB performs research on developing and improving analytical methodology, both on its own and in collaboration with various universities. Its staff members often participate as experts in training courses organized by universities or government bodies, and some of its senior technicians are regularly asked by the Spanish Accreditation Body to participate as technical experts in laboratory accreditation audits for the food sector. Lastly, the LPHAB regularly hosts university or vocational students for training stays and internships.

3. QC within the framework of the ISO/IEC 17025 standard

Since it was issued in 2005, the ISO/IEC 17025 standard (ISO, 2005b) has been the international reference for accreditation of the technical competence of testing and calibration laboratories. The requirements of ISO/IEC 17025 (ISO, 2005b) concerning QC are concisely set out in Section 5.9 of the Standard, entitled “Assuring the Quality of Test and Calibration Results”. Briefly, the Standard states that QC activities are mandatory and dictates that their results must be recorded. It also mentions the most frequent internal QC and external QC activities, without excluding other possible activities:

“The laboratory shall have QC procedures for monitoring the validity of tests and calibrations undertaken. The resulting data shall be recorded in such a way that trends are detectable and, where practicable, statistical techniques shall be applied to the reviewing of the results. This monitoring shall be planned and reviewed and may include, but not be limited to, the following:

- a) Regular use of certified reference materials and/or internal QC using secondary reference materials;
- b) Participation in proficiency test or proficiency-testing programs;
- c) Replicate tests or calibrations using the same or different methods;
- d) Retesting or recalibration of retained items;
- e) Correlation of results for different characteristics of an item.”

The standard goes on to state that the results of the monitoring activities performed must be analyzed and that appropriate measures should be taken:

“QC data shall be analyzed and, where they are found to be outside pre-defined criteria, planned action shall be taken to correct the problem and to prevent incorrect results from being reported.”

4. Legislative requirements

Food safety and environmental protection are top priorities in the EU, which has implemented widespread legislation to support its policies in these fields. Noteworthy examples include Regulation (EC) No 178/2002, which establishes a legal framework for food; Directive 2000/60/EC, which establishes a framework for actions in the EU's water policy; and Directive 2008/50/EC, which outlines measures on ambient air quality. Currently, there is also a proposal for a framework Directive to create common principles for soil protection across the EU.

The EU has high standards for food safety and environmental protection. For instance, Regulation (EC) No 1831/2003 defines maximum levels for certain contaminants (*e.g.* mycotoxins, dioxins, heavy metals, and nitrate) in foodstuffs; Regulations (EU) No 37/2010 and (EC) No 853/2004 stipulate maximum residue levels of pharmacologically active substances or pesticides, respectively, in foodstuffs; and Directive 98/83/EC defines values for several microbiological and chemical parameters for water intended for human consumption. Regarding the environment, Directive 2008/50/EC defines objectives for ambient air quality and establishes limits on the concentration levels of air pollutants; Water Framework Directive 2000/60/EC presents a list of 33 priority pollutants based on their substantial risk; and Directive 2008/105/EC establishes environmental quality standards for these 33 pollutants.

Laboratories in charge of official controls provide essential support for these policies, by proficiently monitoring environmental and food samples. These laboratories should be equipped with instrumentation that enables correct determination of maximum levels as stipulated by EU law. According to Regulation (EC) No 853/2004, the laboratories designated for official controls in feed and food samples must operate and be assessed and accredited in accordance with ISO/IEC 17025 (ISO, 2005b). Likewise, Directive 2009/90/EC establishes that laboratories that perform chemical monitoring under Water Framework Directive 2000/60/EC must apply quality management system practices in accordance with the ISO/IEC 17025 standard or an equivalent standard accepted at the international level. Moreover, the laboratories must demonstrate their competence in analyzing relevant physicochemical parameters or compounds by participating in proficiency testing programs and by analysis of available reference materials representatives of the monitored samples. In Spain, Royal Decree 140/2003 stipulates that laboratories designated for official controls of water intended for human consumption that analyze more than 5,000 samples per year must be accredited in accordance with ISO/IEC 17025 (ISO, 2005b), and that other laboratories, if they are not accredited as such, must be at least certified according to ISO 9001 (ISO, 2005a).

There has been a shift from using official analytical methods to a more open approach that allows the laboratories involved in official controls to use validated analytical methods that have been proven to meet established performance criteria. Thus, different scenarios are presently possible: in very few cases, such as Commission Regulation (EEC) 2676/90, on the analysis of lead in wine, the method is defined; more frequently, as in Directive 2008/50/EC on air quality or in Directive 98/83/EC on water intended for human consumption,

although methods are explicitly specified, laboratories are allowed to use alternative methods, providing they can demonstrate that the results are at least as reliable as those produced by the specified methods. Another approach is that of Decision 2002/657/EC, concerning analytical methods for the analysis of residues and contaminants in food products, which establishes the performance criteria for methods. Directives 2009/90/EC and 98/83/EC establish analogous analytical method criteria for monitoring water status, sediment and biota, as do Regulation (EC) 333/2007 (on sampling and analytical methods for the control of some contaminants in foodstuffs), to SANCO/10684/2009 (on method validation and quality control procedures for pesticide residues analysis in food and feed), or to Regulation (EC) 401/2006 (on methods of sampling and analysis for the control of mycotoxins in foodstuffs). Representative examples of performance criteria for methods used to analyze patulin in foodstuffs are shown in Table 1.

This flexible approach to method performance criteria allows laboratories to quickly incorporate advances in analytical techniques and to apply new methods to address new problems when required. The crucial issues here are that the required performance criteria are met and that the method has been properly validated.

| Level (µg/kg) | RSD _r % (a) | RSD _R % (b) | Recovery % |
|---------------|------------------------|------------------------|------------|
| < 20 | ≤ 30 | ≤ 40 | 50 to 120 |
| 20 to 50 | ≤ 20 | ≤ 30 | 70 to 105 |
| < 50 | ≤ 15 | ≤ 25 | 75 to 105 |

Table 1. Performance criteria for methods of analysis of patulin in foodstuffs, from Regulation 401/2006. (a: Relative standard deviation, calculated from results generated under repeatability conditions, b: Relative standard deviation, calculated from results generated under reproducibility conditions.)

Since its publication, Decision 2002/657/EC has been a key document for analytical laboratories involved in food analysis and has proven utile for laboratories in other fields, such as environmental analysis. It introduced a change of mindset, replacing reference methods with the criteria approach, and launched new definitions, such as *minimum required performance limit (MRPL)*, *decision limit (CC_α)* and *detection capability (CC_β)*. Decision 2002/657/EC determines common criteria for the interpretation of test results, establishes the performance criteria requirements for screening and confirmatory methods, and presents the directives to validate the analytical methods. However, it is a complex document, and guidelines for its implementation have been published (SANCO/2004/2726-rev-4-December-2008). The most relevant aspects of Decision 2002/657/EC are further described below.

Minimum required performance limit is defined as the minimum content of an analyte in a sample that has to be detected and confirmed. It is intended to harmonize the analytical performance of methods for banned substances. The minimum required performance level for a method of a banned substance should be lower than the MRPL; however, very few MRPL values have been established to date.

The decision limit is the limit at and above which one can conclude, with an error probability of α , that a sample is non-compliant. For substances with no permitted limit α is 1%, whereas for all other substances α is 5%. Thus, the result of an analysis shall be considered non-compliant if the CC_α of the confirmatory method for the analyte is exceeded.

The detection capability is the smallest content of the substance that may be detected, identified and/or quantified in a sample with an error probability of β (β is 5%). Procedures to determine the $CC\alpha$ and $CC\beta$ are given in Decision 2002/657/EC and its corresponding guidelines document (SANCO/2004/2726-rev-4-December-2008). Decision 2002/657/EC also introduces the concept of *identification point (IP)*. A minimum of three IPs is required to confirm the identity of a compound that has a permitted limit, whereas at least four IPs are required for a banned compound. The number of IPs provided by the analytical method depends on the technique used. For instance, with low-resolution MS each ion earns 1 point, and with low-resolution MS^n each precursor ion earns 1 point, and each transition product, 1.5 points. More details on IPs for the different techniques can be found in Decision 2002/657/EC. This IP system has made MS an essential technique for laboratories that analyze residues and contaminants in foodstuffs. In addition to the performance criteria requirements for screening and confirmatory methods, Decision 2002/657/EC also provides guidelines for the validation of analytical methods. Validation should demonstrate that the method complies with its performance criteria. Therefore, depending on the method category (e.g. qualitative or quantitative; screening or confirmatory), different performance characteristics must be determined. Table 2 shows an overview of EU legislation on analytical methods for environmental and food samples

| | |
|--------------------------|---|
| Directive 98/83/EC | Quality of water intended for human consumption |
| Directive 2008/50/EC | Ambient air quality and cleaner air for Europe |
| Directive 2009/90/EC | Technical specifications for chemical analysis and monitoring of water status |
| Regulation (EC) 333/2007 | Methods of sampling and analysis of lead, cadmium, mercury, inorganic tin, 3-MCPD and benzo(a)pyrene in foodstuffs. |
| Decision 2002/657/EC | Performance of analytical methods and interpretation of results |
| Regulation (EC) 401/2006 | Methods of sampling and analysis of mycotoxins in foodstuffs |

Table 2. Overview of EU legislation on analytical methods for environmental and food samples

5. QC management

At the LPHAB QC activities are managed by the Quality Assurance Unit (QAU), in close cooperation with the head of the Chemical Analysis Service (CAS) and the senior technicians responsible for each analytical technique or methodology. The QAU comprises two senior technicians and one mid-level technician. Its functions include:

- Coordinating implementation and maintenance of the Quality Management System (QMS)
- Cooperating with the LPHAB’s top management in the annual system review and in preparation of the annual staff training program
- Preparing and conducting an annual internal audit
- Managing any complaints received from customers or third parties

- Defining corrective and preventive actions, supervising their implementation and verifying their efficacy
- Managing documentation (Quality Manual, general procedures and SOPs, etc.), distributing and maintaining documents, and preparing lists for flexible-scope accreditation
- Approving the auxiliary equipment program control
- Advising technicians on method validation and QC activities
- Managing the LIMS

Moreover, the LPHAB’s QC activities are described in several documents of its QMS. Table 3 shows these documents in a hierarchical order.

| Document | Scope |
|--|------------------|
| Quality Manual (Section 14) | Whole laboratory |
| General procedure: “Assessment of the Quality of Analytical Results” | Whole laboratory |
| General procedure: “Management of Complaints, Non-conforming Work, and Corrective and Preventive actions” | Whole laboratory |
| General procedure “Management of Flexible-Scope Accreditation” | Whole laboratory |
| Standard Operating Procedure (SOP): “Application of the General Quality Criteria to the Chemical Analysis Service” | CAS |
| SOP: “Management of Standards” | CAS |
| Annual QC Plan | CAS |
| Specific SOPs (per method) | CAS |
| Records | CAS |

Table 3. Major QC documents from the LPHAB’s QMS (CAS: Chemical Analysis Service).

One of the chapters in LPHAB’s Quality Manual defines the basis of QC in accordance with the requirements of the ISO/IEC 17025 standard (ISO, 2005b). General procedures, which are applicable either to the whole laboratory, or to the Microbiology Analysis Service or the CAS, outline the LPHAB’s general QC activities. Standard operating procedures provide detailed specifications on the CAS’s QC activities (both internal and external QC). Internal QC activities are either performed within each analytical run or are scheduled. The within-run activities are done in accordance with the specific SOP for regular samples received by the LPHAB; these encompass analysis of reagent blanks, blank samples, spiked samples and verification of instrument sensitivity. They are employed to prevent releasing of any erroneous results to customers. Scheduled activities are used to check the efficacy of within-run controls. External QC (EQC) relies on the regular and frequent participation of the LPHAB in proficiency tests organized by competent bodies (whenever possible, accredited as Proficiency Test Providers). All these activities are agreed upon by the head of the CAS, the director of the QAU and the senior technicians and are reflected in the Annual QC Plan. Table 4 shows a sample page from the CAS’s Annual QC Plan.

All of the QC activities are described in the SOP entitled “Application of General Quality Criteria to the Chemical Analysis Service”, as are the procedures for handling of all scheduled internal and external QC samples (in terms of ordering, analysis and evaluation). These activities are summarized in Table 8.

| | | | |
|---|-------------------------------------|--------------------------|---|
| Technical Unit: Instrumental Organic Chemistry | | | |
| Technician: XXXXXX | | | |
| SOP | External Quality Control | Internal Quality Control | |
| MA/2/19510 Determination of Chlroramphenicol by LC-MS/MS | FAPAS Progetto Trieste CNA | Periodicity: | |
| | | Blank | <div><div>✓</div></div> Every run |
| | | Reference Material | <div><div>✓</div></div> At least once a year |
| | | Spiked samples | <div><div>✓</div></div> At CCα level- every run |
| MA/2/19560 Determination of Nitrofuran metabolites by LC-MS/MS | FAPAS Progetto Trieste Anfaco | Others | <div><div>✓</div></div> Matrix matched surrogates/ Internal standard in samples checking |
| | | Periodicity: | |
| | | Blank | <div><div>✓</div></div> Every run/ Internal standard checking |
| | | Reference Material | <div><div>✓</div></div> At least once a year |
| MA/2/19560 Determination of corticosteroids by LC-MS/MS | FAPAS Progetto Trieste | Spiked samples | <div><div>✓</div></div> At CCα level-every run |
| | | Others | <div><div>✓</div></div> Calibration curve from processed samples, including MRPL (1 µg/kg). Internal Standard in samples checking |
| | | Periodicity: | |
| | | Blank | <div><div>✓</div></div> Every run/ Internal standard checking |
| MA/2/19560 Determination of corticosteroids by LC-MS/MS | FAPAS Progetto Trieste | Reference Material | <div><div>✓</div></div> At least once a year |
| | | Spiked samples | <div><div>✓</div></div> At CCα level- every run |
| | | Others | <div><div>✓</div></div> Calibration curve from processed samples, including MRL (2 µg/kg). Internal Standard in samples checking |

Table 4. Sample page from the CAS’s Annual QC Plan.

5.1 Management of external QC

External QC is managed through proficiency tests. Participation in each test is scheduled according to proposals by the technician responsible for each analytical procedure. Each procedure is to be tested in at least one exercise per year, if possible. In parallel, certain samples are requested in duplicate for use in scheduled internal QC.

The LPHAB tends to be extremely active in this area, since it considers external QC among the strongest point of its QC system. In the CAS, in 2010, 458 samples were analyzed in proficiency tests that encompassed 1,915 assays, 420 different analytes and 89 analytical procedures (SOPs).

Given that the market lacks universal exercises for all types of matrices and assays, the CAS aims to assess all families of analytes and all instruments. Usually, matrices included in the accreditation scope are used. Importantly, for assays included in the flexible-scope accreditation, different matrices that represent the entire assay category should be employed whenever possible. To evaluate some of the procedures for which no exercises are currently available, the CAS, together with other laboratories, has organized specific activities.

It is extremely important that any organization that aims to organize these types of evaluations be accredited according to ISO/IEC 17043 (ISO, 2010). For non-accredited entities, the quality of their exercises will be assessed.

In accordance with the aforementioned principles, CAS actively participates in the programs FAPAS® (for food) and LEAP (for water), both of which are accredited by the United Kingdom Accreditation Service (UKAS).

For each exercise, a technician is assigned to handle and follow the sample, which must be analyzed using the typical procedures and which must not be treated differently because of its interlaboratory status. Once the organizer's report has been received, an internal evaluation report is written up, which includes the results found by CAS, the mean result assigned by the organizer, and the calculated z-score for each analyte.

Upon receiving the report, each manager performs a complementary evaluation of the results obtained, considering all of the documentation referring to the analysis performed, in order to confirm that all of the QC criteria have been met. Another very important and highly utile aspect to consider is the information on the methods applied by different laboratories, which can help the CAS to improve its methods.

If the evaluation is unsatisfactory, then a report on corrective actions is written up. The results of proficiency tests are generally evaluated based on the z-scores. Nonetheless, other criteria (*e.g.* compatibility index) may also be used; these are described in the final evaluation report for the exercise.

One of the critical points for evaluating z-scores is the standard deviation used in the calculations. The standard deviation used is generally that which is documented by the organizer, which tends to the value obtained from the Horwitz equation. Nevertheless, another value can be used, as deemed necessary by the technician responsible for the evaluation, as long as it is justified in the internal evaluation report for the exercise. Fig. 5 shows a sample evaluation form for external QC samples.

The results obtained are introduced into a database, which enables tracking of any possible trends as well as confirmation of validation data over time.

The figure below illustrates moisture analysis results for various types of samples from the FAPAS® exercises in which LPHAB has participated over the past few years.

PROFICIENCY TEST REPORT

| | |
|---|-------------------------------|
| Sample No. : 11_00237 | Date of entry : 11/01/2011 |
| Proficiency Test : LEAP - Series: CHEM 72 | Round: C1316 |
| Sample : Potable water | Laboratory id No.: |
| Area : 2/0103 Chromatography | Responsible: Dr. Laura Pineda |

| ANALYTES: | RESULTS | | | | SOP / Equipment used | |
|-----------------------------|--|------|------|-----|----------------------|-------|
| | LIMS / Sent result / Consensus value / z-score | | | | | |
| Toluene | 3,9 | 3,87 | 3,2 | 1,7 | MA/2/30470 | 2-170 |
| Ethylbenzene | 0,9 | 0,89 | 0,75 | 1,5 | MA/2/30470 | 2-170 |
| Benzene | 1,7 | 1,65 | 1,37 | 1,6 | MA/2/30470 | 2-170 |
| Xylene (mixture of isomers) | 6,1 | 6,13 | 5 | 1,8 | MA/2/30470 | 2-170 |

ASSESSMENT OF RESULTS:

| | | | | | |
|-----------------------|-------------------------------------|--------------------------|--------------------------|--------------------------|----------------------|
| Successful results: | <input checked="" type="checkbox"/> | | | | |
| Questionable results: | | Punctual | Repetitive | Preventive action | PA number |
| | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="text"/> |
| | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="text"/> |
| Unsuccessful results: | | Non-conforming work No. | | Date. | |
| | <input type="text"/> | <input type="text"/> | | <input type="text"/> | |
| | <input type="text"/> | <input type="text"/> | | <input type="text"/> | |

OTHER METHODS USED IN THE PROFICIENCY TEST:

| | | |
|---|--|---|
| After reviewing the methods used by the other participants, an improving opportunity has been detected: | | |
| Yes <input type="checkbox"/> | No <input checked="" type="checkbox"/> | Preventive action No <input type="text"/> |

GENERAL COMMENTS ON RESULTS:

| |
|--|
| |
|--|

Date:
Signature:

| | | |
|---|--------------|------|
| Final assessment of the head of the Chemical Analysis Section | Revision QAU | Date |
| Date: | Signature: | |

Fig. 5. Sample evaluation form for external QC samples (completed by CAS based on the organizer’s report).

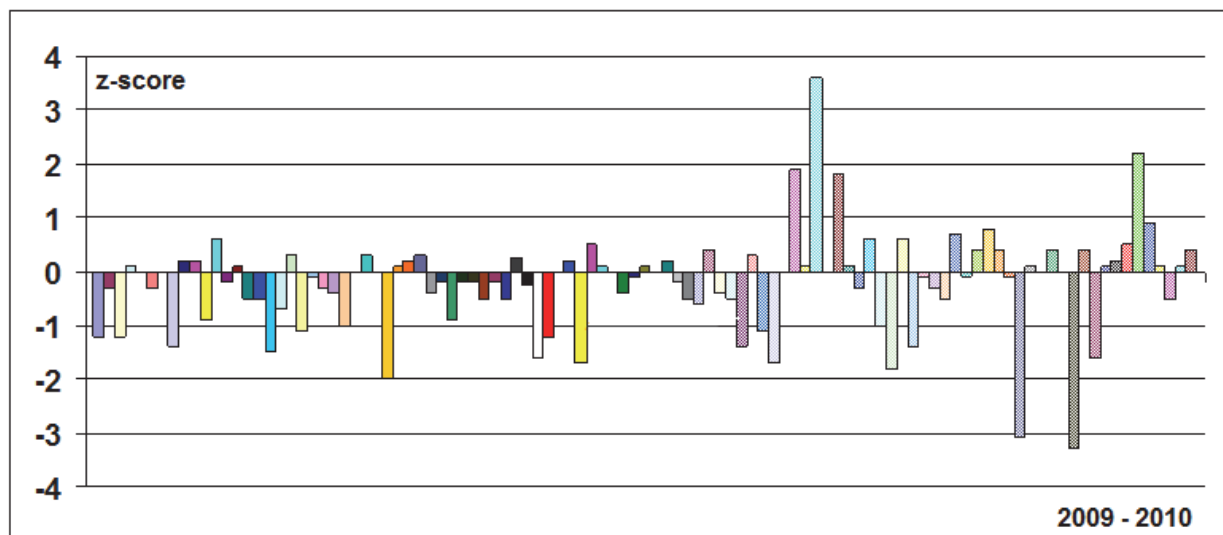


Fig. 6. Proficiency testing: results from moisture analysis of different samples performed for FAPAS® exercises.

Another important factor concerning the results obtained from proficiency tests is their utility for systematic expansion of validation data. The CAS has established a dynamic validation system in which the overall validity of the uncertainty of a procedure is checked against the different sample types and different concentration levels analyzed.

5.2 Management of internal QC

The scheduled internal QC samples generally correspond to duplicates of samples from proficiency tests (the duplicates are purchased annually at the time the test is performed). In 2010 the CAS analyzed 99 samples for internal QC, encompassing 371 assays, 209 analytes and 77 SOPs.

Once the samples arrive at the LPHAB, their information is entered into the reference materials database, and they are carefully handled, taking their particular storage needs and expiration dates into account. The new sample is added to the sample registry in the LIMS according to the schedule. The results are analyzed using an internal evaluation form in which the z-score (accuracy) is re-calculated, and the reproducibility is calculated based on the results from the external QC and from the internal QC test. This approach enables evaluation of both accuracy and precision. Fig. 7 shows a sample evaluation form for internal QC.

5.3 Handling of any inconsistencies detected in the QC activities

Results obtained in both internal and external QC activities are suitably recorded. Out of control situations can be categorized as incidences and deviations. Incidences are sporadic events that usually do not occur in subsequent applications of the analytical method. Contrariwise, deviations are non-conforming work that must be managed through corrective actions. Detection of these events, and subsequent causal analysis, sometimes leads to proposal of preventive actions. Fig. 8 shows a general schematic of QC management.

INTERNAL QUALITY CONTROL REPORT

| | |
|----------------------------|--------------------------------|
| Sample No. : 11_00065 | Date of entry : 04/01/2011 |
| Sample reference : 2-R0525 | Original sample: 10_28944 |
| Sample : Meat | |
| Area : 2/0401 Food | Responsible: José Antonio León |

| ANALYTES: | RESULTS | | | | | | | | SOP |
|------------------------|---|-----|------|------|-------|----|----|-------------------------------------|------------|
| | Result / Certif. value / ± U / Recovery / z-score / Reprod. / Correct | | | | | | | | |
| Nitrate (E-251, E-252) | 205 | 226 | 55 | 90.7 | -0.76 | 12 | 77 | <input checked="" type="checkbox"/> | MA/2/30102 |
| Nitrite (E-249, E-250) | 121 | 150 | 36,6 | 80,6 | -1,58 | 24 | 51 | <input checked="" type="checkbox"/> | MA/2/30101 |

ASSESSMENT OF RESULTS:

| PARAMETER | ACCEPTANCE CRITERIA | COMMENTS |
|--------------------------|---------------------|----------|
| Uncertainty | | |
| Recovery | | |
| Z-scores | | |
| Reproducibility | | |
| Cause analysis: | | |
| Non-conforming work No.: | | Date: |

GENERAL COMMENTS ON RESULTS:

Date:
Signature:

| | | |
|---|--------------|------|
| Final assessment of the head of the Chemical Analysis Section | Revision QAU | Date |
| Date: Signature: | | |

Fig. 7. Sample evaluation form for internal QC samples.

Figures 9 and 10 show the number of scheduled internal QC and external QC samples in absolute values and as percentages of the total number of samples analyzed, respectively, in the CAS. These figures are testament to the LPHAB’s major efforts to ensure the reliability of its results and demonstrate its commitment to quality. Moreover, this approach also implies sizeable financial investment: participation in proficiency testing costs the LPHAB roughly €60,000 per year.

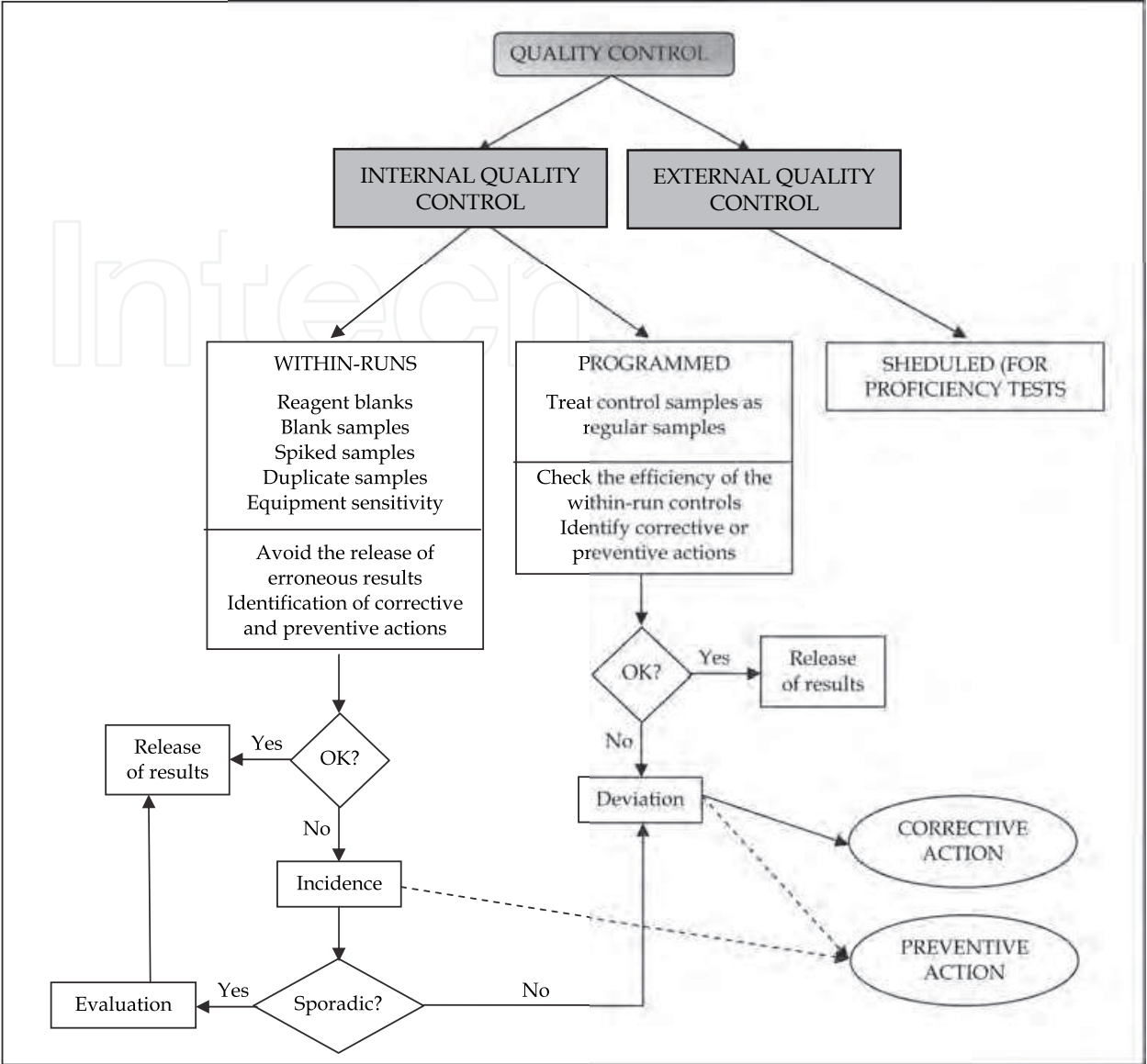


Fig. 8. General schematic of QC management.

The reliability of QC activities is greatly based on the suitability of the criteria applied. Depending on whether the limits established are too strict or too lax, α or β errors, respectively, may be committed. Over the past few recent years, the CAS has adapted the criteria applied in its internal QC to the values obtained during method validation. Improving the frequency and quality of internal QC has enabled improved detection of non-conforming results, and therefore, has enabled optimization of external QC activities.

5.4 QC in the framework of flexible scope accreditation

Accreditation of a laboratory is usually based on a concrete definition of the laboratory’s scope. Thus, the technical annexes for accreditation certificates comprise detailed lists of the tests for which the laboratory has been accredited. The lists clearly specify matrices, analytes, ranges of concentration, and methods. This scheme is known as *fixed-scope accreditation*.

However, in recent years, in order to meet the needs of customers, laboratories have had to quickly expand their accreditation scope without compromising their technical competence or altering definition of the scope. Thus, highly experienced laboratories with a long history of accreditation can now adopt a new scheme, known as *flexible-scope accreditation*, whereby they perform analyses using appropriate validated methods, and then report the results as being accredited, without prior evaluation by the accreditation body. This may entail incorporation of new matrices or analytes, or inclusion of new tests within a generic method. Thus, the flexibility of the accreditation scope implies sufficient technical competence and operational capacity, which places more of the responsibility on the laboratory. This in turn means that the laboratory must endeavor to increase its QC operations in order to guarantee the quality of the results of the expanded scope. In any case, the bounds within which a scope is flexible must be precisely stated.

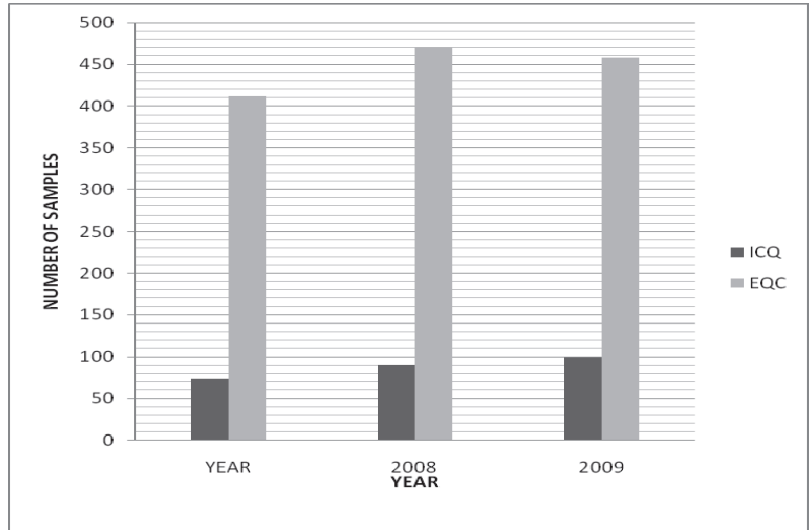


Fig. 9. Scheduled internal and external QC samples (ICQ and ECQ, respectively), expressed as number of samples.

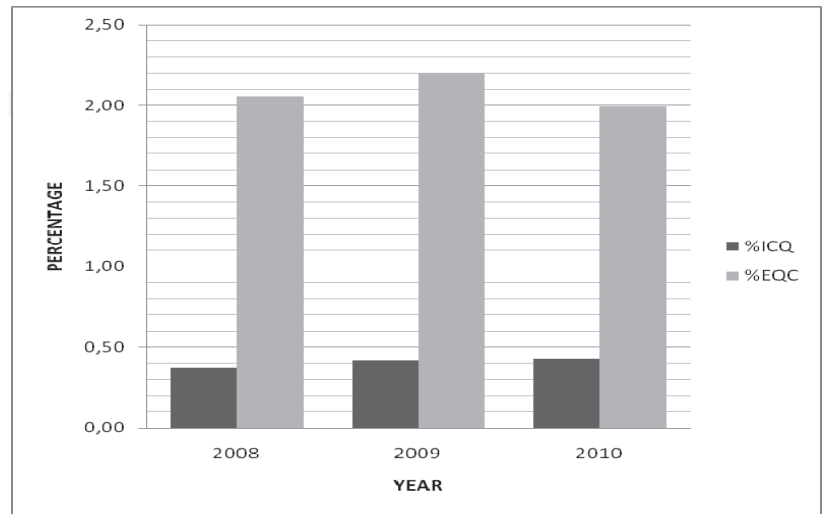


Fig. 10. Scheduled internal and external QC samples (ICQ and ECQ, respectively), expressed as percentage of total samples.

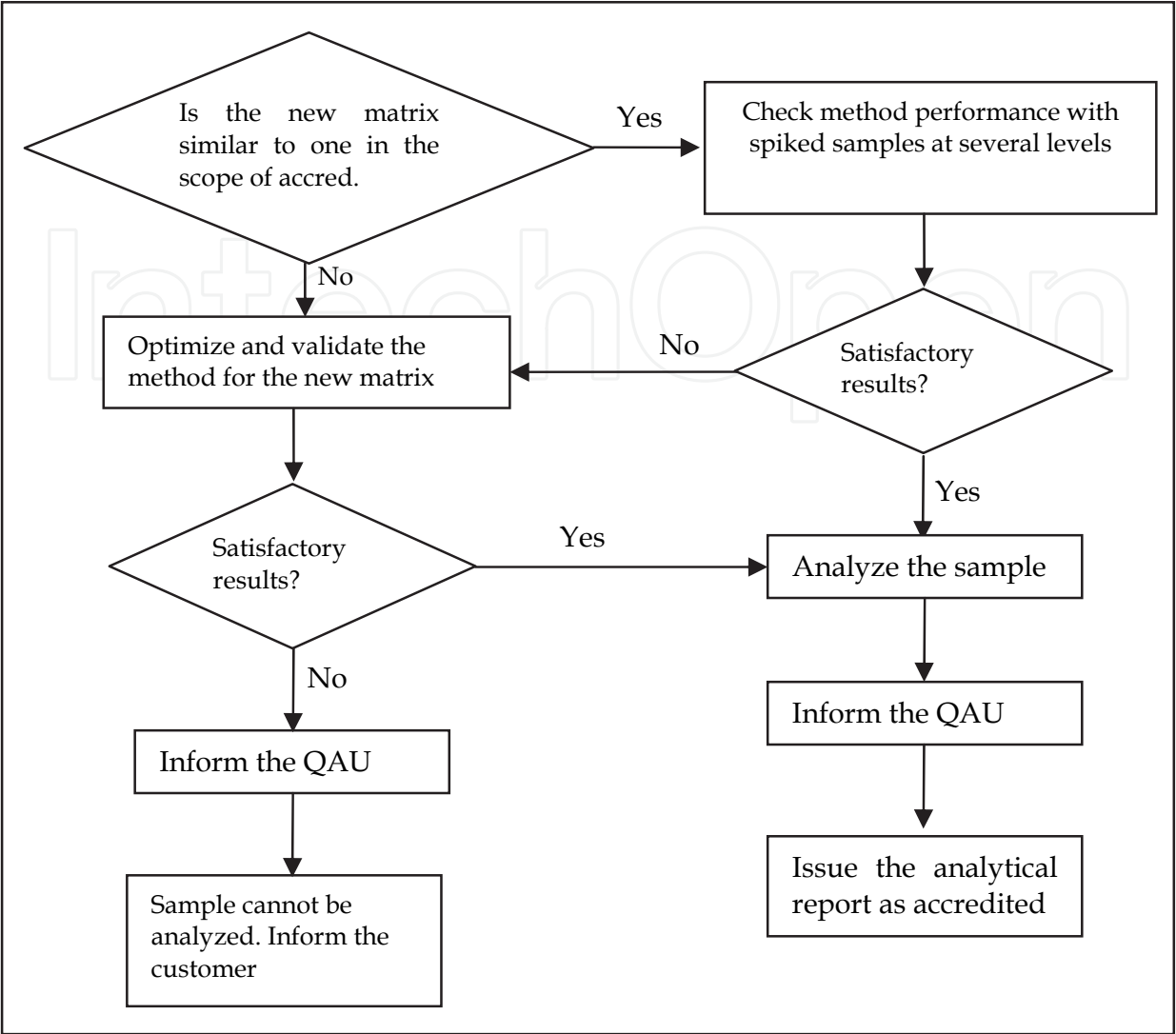


Fig. 11. Procedure for analysis of an established analyte in a new matrix.

In this context, once a laboratory receives a request for an analysis that falls within the bounds of a flexible scope, it must do the following:

- Inform the customer that the analysis will be performed in the framework of a flexible scope, and therefore, prior validation studies will be required; this will involve some delay in the delivery of results; and, if the results of the validation studies are unsatisfactory, then the report cannot be issued as being accredited.
- Perform validation studies. A scheme of this process for analysis of an established analyte in a new material is illustrated in Fig. 11. An analogous process would be employed for the opposite case (*i.e.* analysis of a new analyte in an established matrix).

Flexible-scope accreditation was initiated in 2004 for pesticide analysis and was later extended to other analyte families. The LPHAB defines these families according to the type of analyte studied and the analytical technique used. Therefore, these vary from very broad (organic compounds studied by chromatographic techniques) to rather narrow (ions studied by liquid chromatography). The CAS’s current fixed-scope and flexible-scope of accreditation are summarized in Table 5.

| PARAMETER MATRIX | ANALYTE OR FAMILY OF ANALYTES (NUMBER OF ANALYTES) | FIXED SCOPE | FLEXIBLE SCOPE |
|--|--|-------------|----------------|
| Additives by LC Food | Phenolic antioxidants (7), artificial dyes (14), Sudan dyes (10), preservatives (7), sweeteners (3) caffeine | | X |
| Organic pollutants by LC and GC Food / Water Air sampling supports | Acrylamide, BFRs (8), BTEX (5), 3-MCPD, 3-MCPD ester, VOCs (15), ethyl carbamate, drugs (3), furan, PAHs (17), BADGEs (11), melamine, PBCs (7), PCNs (5) pesticides (44) , nicotine, | | X |
| Ions by LC or segmented continuous flow analysis Food / Water | BrO ₃ ⁻ , BrO ⁻ , Cl ⁻ , F ⁻ , P, NO ₃ ⁻ , NO ₂ ⁻ , SO ₄ ²⁻ , NH ₄ ⁺ , Ca ⁺² , Mg ⁺² , K ⁺ , Na ⁺ , ClO ₃ ⁻ , ClO ₂ ⁻ , SO ₂ | X | X |
| Heavy metals by atomic spectroscopy Food / Water Air sampling supports | As, As inorganic, Ba, B, Cd, Ca, Co, Cu, Cr, Sn, Fe, Mg, Mn, Hg, CH ₃ Hg, Ni, Ag, Pb, K, Se, Na, Ti, V, Zn | | X |
| Mycotoxins by LC Food | aflatoxin M1, aflatoxins B i G (4), fusarium mycotoxins (6), ochratoxin A, patulin | | X |
| Residues of veterinary drugs by LC Food of animal origin | Antibiotics: β-lactams, macrolides, quinolones, sulphonamides, tetracyclines (41), coccidiostats (10), anthelmintics (1), tireostatics (6), benzodiazepines (3), chloramphenicol, dyes (5), corticosteroids (6), synthetic hormones (9), metabolites of nitrofurans (4), nitroimidazole, β-agonists (18) | | X |
| Residues of pesticides by GC and LC Food | Pesticides (200) | | X |
| Physicochemical parameters Food | Mass, volume, density, acidity, pH, fat (3), alcohol degree, peroxide index, moisture, ash | X | |
| ELISA determinations Food | Gluten | X | |
| Ions by flow techniques Food / Water | P _{total} , P _{soluble} , N _{total} , NO ₃ ⁻ , NO ₂ ⁻ , Cl ⁻ , NH ₄ ⁺ , SO ₂ , volatile nitrogenous bases, trimethylamine | X | |
| Several compounds by chromatographic techniques Food | Biogenic amines (6),sugars (6), methanol, ethanol, other alcohols (5), ethyl acetate, fatty acids, steroids and estradiols | X | |
| Physicochemical parameters Water | Colour, turbidity, conductivity, suspended solids, dissolved matter, pH, chemical oxygen demand, alkalinity, cyanide, oxidisability | X | |

Table 5. The CAS’s current fixed-scope and flexible-scope of accreditation.

Managing the flexible scope implies a significant amount of extra documentation that must be completely updated. Indeed, in 2010 alone six new analytical methods were added, together with numerous matrices and analytes. The flexible scope is currently in its 22nd edition (an average of three editions are created per year).

6. QC in the analytical method SOPs: examples of general and specific QC activities

This section provides examples of the some of the QC activities summarized in Table 8, as well as the corresponding documentation for recording and evaluating the data. Generally,

each analytical procedure (SOP) features a section describing internal QC activities that are performed within each run and the corresponding criteria for accepting the results, which must be evaluated by the technician responsible for the procedure before they are communicated to the customer. Several concrete examples are presented below.

6.1 Spiked samples

An example of control analysis of spiked samples is illustrated in Fig. 12, which shows a plot of arsenic analysis in food samples by inductively coupled plasma mass spectrometry (ICP-MS). The results are evaluated based on the recovery (% Rec) of samples spiked at different concentrations and with different matrices, such that the entire scope of the flexible-scope accreditation can be addressed.

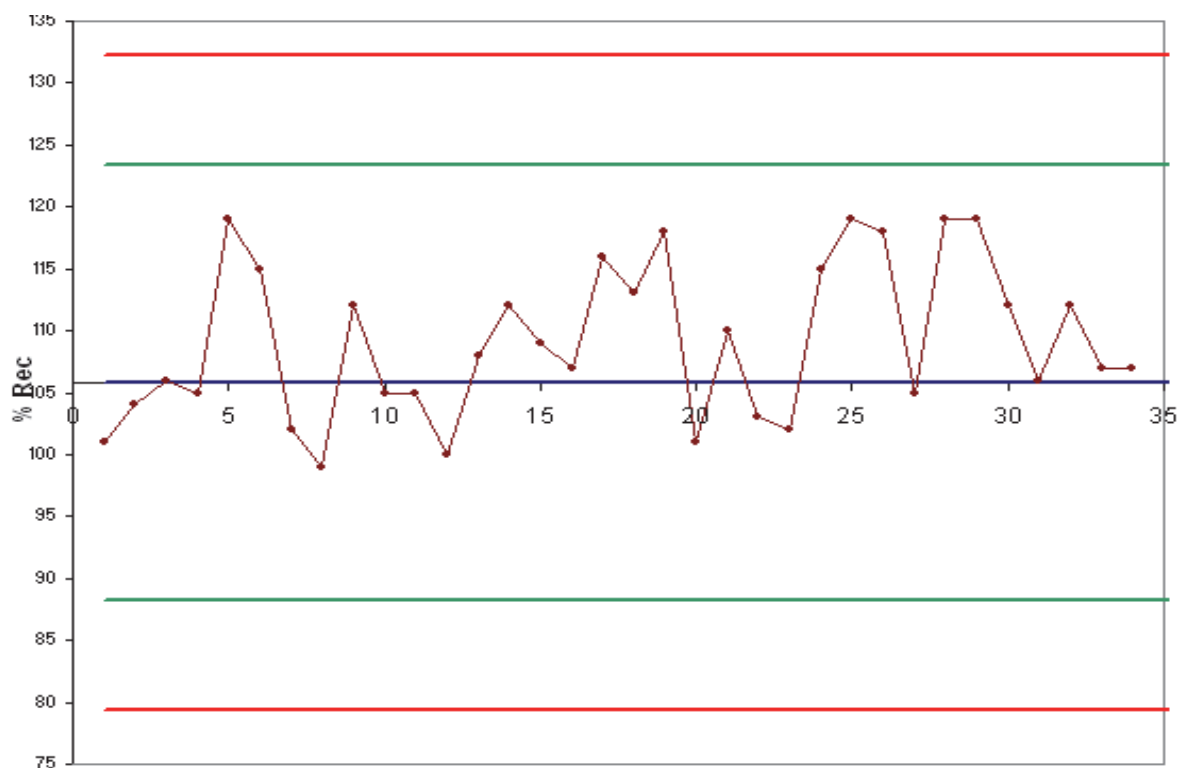


Fig. 12. Plot of arsenic recovery levels from spiked samples of different food types, as determined by ICP-MS.

6.2 Use of QC records for an LC-MS/MS procedure (detection of antibiotics)

Table 6 shows an example of a QC records for a procedure in which 44 antibiotics are analyzed in samples of products of animal origin by LC-MS/MS. The following data are recorded for representative analytes (in the case of Table 6, two antibiotics): the area of the peak corresponding to the standard used for verifying the instrument; retention time (TR) and the ratio of transitions (ion ratio [IR]) at CC α level, which are the data used for identifying and confirming the two compounds. The peak area value is checked against the minimum peak area that guarantees response at the lowest level of validation, which also verifies the confirmation. Lastly, the analytical sequence and the user's initials are also recorded.

| | | | | | | | | |
|---------------|----------------|--------|---------------------------------------|----|--------------|------|------------|-------------|
| SOP | MA/2/19210 | | Analysis of antibiotics by CL / MS-MS | | | | | |
| Instrument | 2-201 | | CL MS-MS | | | | | |
| Compound | SULFAMETHAZINE | | | | ENROFLOXACIN | | | |
| Average | 4,50 | | | | 4,30 | | | Antibiotics |
| Maximum value | 4,75 | | | | 4,55 | | | |
| Minimum value | 4,25 | 100000 | 0,8 | | 4,05 | 1000 | 1,0 | |
| DATE | TR | Area | I.R. (CC α) | CK | TR | Area | I.R.(CC α) | CK |
| 15/02/2011 | 4,35 | 135483 | 0,9 | | 4,45 | 1022 | 1,1 | |
| 22/02/2011 | 4,60 | 175563 | 0,8 | | 4,20 | 1156 | 1,0 | |
| 01/03/2011 | 4,55 | 115632 | 0,8 | | 4,15 | 1325 | 1,2 | |
| 08/03/2011 | 4,34 | 134886 | 0,8 | | 4,35 | 1278 | 1,2 | |
| 15/03/2011 | 4,57 | 142569 | 0,9 | | 4,10 | 1486 | 1,2 | |
| | | | | | | | | Run/User |

Table 6. QC records from analysis of antibiotics in products of animal origin by LC-MS/MS.

In similar QC records, the responses of the internal standards (which are typically deuterated or C¹³-labeled analogs of the test compounds) from analysis of various types of samples are recorded. This control step can also be used to broaden the validation data by incorporating new matrices (*i.e. online validation*). Based on the values of the responses of the internal standards, one can deduce the validity of the matrix-matched surrogate quantifications in the different sample types that can be incorporated into the analytical sequence.

6.3 QC records for verification of the instrument, its calibration levels, and the blank in the turbidity analysis procedure

The format of the QC records used for turbidity analysis of water samples is illustrated in Table 7 as a representative example of a physicochemical assay.

The upper and lower limits traceable to the values obtained in the validation are shown. In this case, the experimental readings obtained are recorded for each certified standard and are used to verify calibration of the instrument and to confirm the response of the blank (in this case, ASTM type I purified water).

| | | | | | | | |
|------------|--------------|-------|-------------------------------------|--------|--------|-------|-----------|
| SOP | MA/2/30504 | | Determination of turbidity in water | | | | |
| Instrument | 2-001 | | Turbidimeter | | | | |
| STABCAL | 0,5 NTU | 3 NTU | 6 NTU | 18 NTU | 30 NTU | Blank | Turbidity |
| Upper val. | 0,48 | 3,11 | 6,43 | 19,1 | 32,5 | 0,094 | |
| Lower val | 0,32 | 2,81 | 5,81 | 17,3 | 29,4 | | |
| Date | Result (NTU) | | | | | | User |
| 10/03/2011 | 0,38 | 2,85 | 5,93 | 17,7 | 30,1 | 0,079 | NG |
| 11/03/2011 | 0,37 | 2,92 | 5,98 | 17,8 | 30,3 | 0,07 | NG |

Table 7. QC records from turbidity analysis of water samples.

| QC factor | Action | Objective | Calculations and tolerance limits | Frequency at the LASPB |
|--|--|--|---|--|
| General internal QC | | | | |
| Reagent blank | The analytical procedure is performed using only the reagents. | Enables monitoring for any contamination in materials, reagents, the environment, etc. | LOD: limit of detection Evaluation: Blank < LOD | Within-run (the type of blank depends on the method) See Table 7 |
| Matrix blank | The analytical procedure is performed using a blank sample. | Enables monitoring for any contamination, and confirmation that the matrix is not responsible for any interference | | |
| Duplicate samples (intermediate precision) | Full analysis of duplicate samples on different dates | Enables monitoring of the reproducibility (R) relative to the standard deviation of the validation (s _R) | $R = 2 * \sqrt{2} * s_R$ Evaluation: $x_1 - x_2 \leq R$ x ₁ and x ₂ are the results of duplicate samples | Scheduled: usually, once per year, using a reference material (normally, a duplicate sample from a proficiency test) |
| Spiked samples | The analytical procedure is performed on a sample that has been spiked with the analyte (whenever possible, previously analyzed samples containing the analyte at levels lower than the limit of detection). | Enables monitoring of the bias or the trueness based on the recovery (% Rec), and compared with the recovery (% Rec _{val}) and the standard deviation (s) obtained in the validation | $Re\ c(\%) = \frac{(x_{lab})}{x_{spiked}} \times 100$ X _{lab} : obtained value X _{spiked} : spiked value Evaluation: Re c(%) = Re c _{val} (%) ± 2s | Within-run See Fig. 12 |
| Reference materials | The analytical procedure is performed on a sample which has been prepared under concrete specifications and which contains the analyte in question at a known value. | Enables monitoring of the accuracy of the results based on the compatibility index (CI), which is calculated from the reference value (x _{ref}) and the obtained value (x _{lab}) | $CI = \frac{ x_{ref} - x_{lab} }{\sqrt{(U_{ref}^2 + U_{lab}^2)}}$ U _{ref} : expanded uncertainty of reference material U _{lab} : expanded uncertainty laboratory Evaluation: CI ≤ 1 | Scheduled |

Table 8. Part I

| QC factor | Action | Objective | Calculations and tolerance limits | Frequency at the LASPB |
|---|--|--|---|--|
| External QC | | | | |
| Proficiency test | The analytical procedure is performed on a sample which has been part of an interlaboratory comparison scheme. | Enables monitoring of the accuracy of the results based on the z-score (z), which is calculated from the assigned value, the obtained value (x _{lab}) and the standard deviation of the participants (σ _p). | $z = \frac{ x_a - x_{lab} }{\sigma_p}$ <p>Evaluation: z ≤ 2 satisfactory result 2 < z ≤ 3 questionable result z > 3 unsatisfactory result</p> | Scheduled See Fig. 5 |
| Internal QC to verify equipment or reagents | | | | |
| Verification of instrument at the beginning of the run and monitoring of instrument drift | A standard is injected under the instrumental conditions established in the analytical procedure. | Enables verification of proper instrument performance before the sequence is started, and at every n samples, based on confirmation that the response of the standard (A) falls within a pre-established range of acceptable values (x %) that guarantee the limit of quantification (LOQ) | A : response of the standard Evaluation: $A \leq \pm x\%$ | Within-run See Table 7 |
| Calibration of the instruments associated with the analytical method | The standards used to generate the calibration curve are injected. | Enables monitoring of the quality of the fit of the calibration curve , based on at least two different criteria: for example, the coefficient of correlation (r) and the residual error of the standard (Er %), which is the ratio of the value of the concentration of the standard in the curve (V _{curve}) to the nominal concentration value (V _{nominal}) | $r \geq$ (see specific SOP) $E_r (\%) = \frac{V_{curve}}{V_{nominal}} * 100$ <p>Evaluation: $E_r \% \leq r \geq$ (see specific SOP)</p> | Upon generation of a new calibration curve |
| Verification of a new lot of standards | Two different samples of the same standard are injected: one from a regularly used lot, and one from a newly prepared lot. | Enables confirmation that a standard has been correctly prepared, based on verification that the ratio of the response of the new sample (A) to the response of the sample from a previously used lot (B) falls within a pre-established range of acceptable values (x %) | A/B : response ratio Evaluation: $A/B \leq \pm x\%$ | Upon preparation of new lots of standards |

Table. 8. Part II

| QC factor | Action | Objective | Calculations and tolerance limits | Frequency at the LASPB |
|--|--|--|--|--|
| Specific internal QC procedures: chromatographic methods | | | | |
| Verification of the response of the internal standard | Addition of the internal standard to all samples, spiked samples, and other standards (matrix-matched surrogate) at the beginning of the procedure | Verification of the procedure for each sample: extraction, and performance of different matrices | Signal traceable to previous analyses Quantification based on internal standard | Within-run |
| Identification of the chromatographic peak | Retention time of each compound relative to that of the internal standard | Verification of the criteria described in the chromatographic method | According to chromatographic system; TR ± % tolerance limit | Performed for each chromatographic peak identified that corresponds to a standard See Table 6 |
| Confirmation of the identified compounds | DAD, FLD, etc.: The compound spectra are compared to the internal standard spectra | Verification of the criteria described in the chromatographic method | Spectral match | Performed for each chromatographic peak identified See Table 6 |
| | MS (SIM): Mass spectra ion ratios | | According to analysis; generally ± 20% | |
| | MS/MS: Transition ratios | | According to regulations, analysis type, concentration, intensity of the transitions, etc. | |

Part III

Table 8. QC activities at the LPHAB’s Chemical Analysis Service (CAS).

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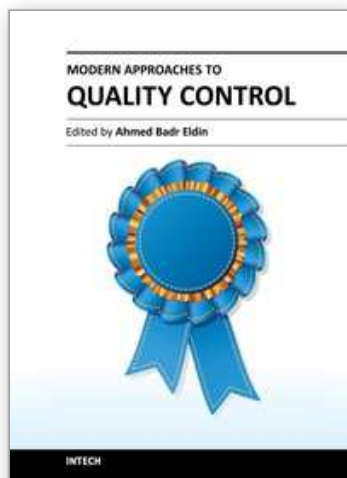
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