Chapter 3

Quality Management Systems for Laboratories and External Quality Assurance Programs

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Additional information is available at the end of the chapter

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Abstract

A quality management system (QMS) plans, controls, and improves the elements that impact on the achievement of the desired results by the laboratory and on the satisfaction of the users. There are different standards that establish requirements for the implementation of a quality management system for laboratories, and a cross comparison between them is shown. Additionally, external quality assurance or assessment (EQA) programs offer multiple benefits to laboratories: method validation, comparing of results with other laboratories, testing problem identification, accreditation requirement compliance, and credibility. In order to control the quality of the procedures, these programs are a tool to keep the laboratory procedures and every variable involved in (staff, equipment, and method) well controlled. In the frame of a quality management system, benefits from external quality assurance programs are discussed, and different available designs are reviewed. On the other hand, previous benefits will be real only if reported results for each program are analyzed in detail. Because additional advantages are achieved when the EQA results are integrated in the quality management system of the laboratory, a procedure is proposed. In addition, results from external quality assurance programs corroborate the usefulness of internal controls implemented by the laboratory as part of its quality management system.

Keywords: quality management systems, external quality assurance, quality control, laboratories, harmonization, quality indicators

1. Introduction

A quality management system (QMS) is formed by a series of coordinated activities that are carried out on a set of elements to achieve the quality of the products or services offered to the customer or user. In the case of a laboratory, the accuracy, reliability, and timeliness of the analytical results reported define its quality, and all aspects of analytical operations should be controlled [1].

The QMS plans, controls, shares, and improves the elements that influence the fulfillment of user requirements and satisfaction as well [2].

An alternative definition of a QMS is through the meaning of each word separately, according to the ISO 9000:2015 quality management system—fundamentals and vocabulary:

- System: a set of interrelated or interacting elements.
- Management: coordinated activities to direct and control an organization.
- Quality: degree in which a set of inherent characteristics of an object (product, service, process, person, resource, etc.) meet the requirements (established need or expectation, generally implicit or mandatory).

We can conclude from these three sentences that the business, planning, and control activities performed on a set of elements to achieve quality represent a QMS.

Many processes are performed in laboratories to guarantee the accuracy, reliability, and traceability of the results, avoiding that any error affects its users. All those processes make a necessary quality management system that controls, detects, and tracks them.

2. International standards for laboratories

Requirements from ISO 9001 for the quality management system implementation and certification are the most widely international standards used by laboratories.

ISO 9000 documents provide guidelines for manufacturing and service industry quality and can be applied to many kinds of organizations. ISO 9001 addresses the general requirements for integration of a quality management system [1] in companies' activities from different productive sectors, including laboratories independently of its size and preserving the organization characteristics. ISO 9001 is characterized by a process-based approach, hence establishing common processes to any activity or organization, product development, or service delivery (e.g., documentation control, equipment maintenance, traceability, or staff training). Specifically, ISO 9001:2015 indicates the issues whose records must be kept:

- Quality management system and its processes
- Quality objectives
- Monitoring and measurement of resources
- Competition
- Monitoring, measurement, analysis, and evaluation
- Internal audit
- Review of management
- Nonconformity and corrective actions

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In addition, there are two ISO standards especially focused on laboratory accreditation that will be detailed below:

- ISO/IEC 17025:2005. General requirements for the competence of testing and calibration laboratories (Geneva: International Organization for Standardization)
- ISO 15189:2012. Medical laboratories—requirements for quality and competence (Geneva: International Organization for Standardization)

Accreditation is an additional level in quality than certification. Anyway, ISO standards are voluntary norms at an international level and were created in order to standardize different activities to achieve high-quality products and services. However, accreditation is already a requirement in different government agencies for laboratory registration. Therefore, voluntary norms can become enforced in some countries and in some productive sectors.

Other important international standards for laboratories have been developed and provided by the Clinical and Laboratory Standards Institute (CLSI) by means of a consensus process from many stakeholders including the global laboratory community. These CLSI consensus-based medical laboratory standards are addressed to continually improve the testing quality, safety, and efficacy promoting medical care excellence. The quality management system model generated by CLSI is based on 12 key elements and is fully compatible with ISO standards for laboratories [1]. The CLSI has published two prominent reference documents for the clinical laboratory:

- A Quality Management System Model for Health Care (Document HS1-A2)
- GP26-A4 Application of a Quality Management System Model for Laboratory Services (fourth edition)

GP26-A4 is easy to implement because of its alignment with a variety of laboratory and accreditation standards, which helps requirement compliance in laboratories [3].

Good laboratory practices (GLPs) represent a quality management system related with organizational processes and normalized conditions, under which nonclinical health and environmental safety studies are planned, performed, controlled, recorded, archived, and informed. The main objectives of GLPs are:

- Resources optimization
- People, environment, and experimentation animals' protection
- Establishment of standardized operating methods
- To guarantee the quality and reproducibility of study results

However, GLPs is not focused on the continuous improvement.

On the other hand, good manufacturing practices (GMPs) specifically control the production variables that affect the final quality of medications according to the quality standards appropriate to the intended use [4].

Finally, there are many other standards for laboratories that are conducted only to specific laboratory areas, analysis, or programs and zones such as the standards developed by the World Health Organization (WHO), and some countries have even provided national quality standards for laboratories that are not the scope of this review.

3. ISO standards applicable to laboratories

As it was mentioned before, unlike ISO 9001 certification, the following standards accredit and are more often used by laboratories that wish or need to prove their proficiency.

3.1. ISO/IEC 17025: competence of testing and calibration laboratories

ISO 17025 establishes a set of requirements that must be met by entities performing tests and/or calibrations, including sampling. This standard is used by laboratories that want to develop and implement a quality management system for their services and to achieve laboratory accreditation. It establishes a model for the evaluation of the technical competence of the laboratory through a third-party audit.

ISO 17025 applies to all laboratories, regardless of the number of employees or the extent of the scope of testing or calibration activities and either for other organizations or individuals or their own organization. It covers tests based on standardized, non-standardized, or laboratory-developed methods.

ISO 17025 is formed by two groups of requirements:

- Management requirements: very similar to ISO 9001, they are related with the quality management of the laboratory.
- Technical requirements: aspects that influence directly on the results of laboratory testing and calibration activities.

Benefits of operating within a QMS like this are recognized by analysts thanks to the revenue increasing of laboratory business [5].

3.2. ISO 15189: competence of clinical laboratories

ISO 15189 includes all the requirements that medical laboratories in charge of human biological sample analysis must comply to guarantee that:

- They have a quality management system.
- They are technically competent.
- They have the capacity to produce technically valid results.

In the same way that ISO 17025, this standard does not certify but accredits specific testing techniques in function of the laboratory needs. Achieving ISO 15189, clinical laboratories

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demonstrate in an objective way and accredit that they have the necessary quality and technical competence, with a correct functioning of the laboratory. In an ISO 15189 laboratory, their processes are controlled and satisfy the technical requirements to ensure clinical diagnosis information, establishing a confidence framework between society, patients, doctors, and the laboratory service [6]. This standard is a good option for high-quality clinical laboratories and services [7].

Comparing ISO 9001, ISO/IEC 17025, and ISO 15189 (**Table 1**), ISO/IEC 17025 requires that "technical requirement" processes are documented. In other words, those factors that contribute to the accuracy, reliability, and validity of tests and calibrations, such as the staff, environmental conditions, equipment, or samples, must be recorded. These requirements related to human resource management (specifically in terms of qualification and competence or infrastructure (to guarantee test conditions) are due to test and calibration specificity and sensitivity.

ISO 15189 extends also its scope to analytical, pre-analytical, and post-analytical phases to establish interaction mechanisms between patients, medical staff, and the laboratory.

ISO 9001	ISO/IEC 17025	ISO 15189
Foreword	Foreword	Foreword
0 Introduction	0 Introduction	0 Introduction
1 Scope	1 Scope	1 Scope
2 Normative references	2 Normative references	2 Normative references
3 Terms and definitions	3 Terms and definitions	3 Terms and definitions
4 Context of the organizations	4 Management requirements	4 Management requirements
4.1 Understanding the organization and its context	4.1 Organization	4.1 Organization and responsibility of management
4.2 Understanding the needs and expectations of interested parties	4.2 Management system	4.2 Management system
4.3 Determining the scope of the quality management system	4.3 Document control	4.3 Document control
4.4 Quality management system and its processes	4.4 Review of requests, tenders, and contracts	4.4 Contracts for the provision of services
	4.5 Subcontracting of tests and calibrations	4.5 Analyses carried out by subcontractor laboratories
	4.6 Purchasing services and supplies	4.6 External services and supplies
	4.7 Service to the customer	4.7 Advisory services
	4.8 Complaints	4.8 Resolution of claims
	4.9 Control of nonconforming testing and/or calibration work	4.9 Identification and control of nonconformities
	4.10 Improvement	4.10 Corrective action

ISO 9001	ISO/IEC 17025	ISO 15189
	4.11 Corrective action	4.11 Prevention action
	4.12 Prevention action	4.12 continuous improvement
	4.13 Control of records	4.13 Control of records
	4.14 Internal audits	4.14 Evaluation and audits
	4.15 Management reviews	4.15 Management reviews
5 Leadership	5 Technical requirements	5 Technical requirements
5.1 Leadership and commitment	5.1 General	5.1 Personnel
5.2 Policy	5.2 Personnel	5.2 Accommodation and environmental conditions
5.3 Organizational roles, responsibilities, and authorities	5.3 Accommodation and environmental conditions	5.3 Laboratory equipment, reagents, and consumables
	5.4 Test and calibration methods and method validation	5.4 Pre-analytical processes
	5.5 Equipment	5.5 Analytical processes
	5.6 Measurement traceability	5.6 Assurance of the quality of the analysis results
	5.7 Sampling	5.7 Post-analytical processes
	5.8 Handling of test and calibration items	5.8 Notification of results
	5.9 Assuring the quality of test and calibration results	5.9 Comunicación de los resultados
	5.10 Reporting the results	5.10 Management of laboratory information
6 Planning		
6.1 Actions to address risks and opportunities		
6.2 Quality objectives and planning to achieve them		
6.3 Planning of changes		
7 Support		
7.1 Resources		
7.2 Competence		
7.3 Awareness		
7.4 Communication		
7.5 Documented information		
8 Operation		
8.1 Operational planning and control		
8.2 Requirements for products and services		

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ISO 9001	ISO/IEC 17025	ISO 15189
8.3 Design and development of products and services		
8.4 Control of externally provided processes, products, and services		
8.5 Production and service provision		
8.6 Release of products and service		
8.7 Control of nonconforming outputs		
9 Performance evaluation		
9.1 Monitoring, measurement, analysis, and evaluation		
9.2 Internal audit		
9.3 Management review		
10 Improvement		
10.1 General		
10.2 Nonconformity and corrective action		
10.3 Continual improvement		
Annex A Clarification of new structure, terminology, and concepts	Annex A Nominal cross-references to ISO 9001:2000	Annex A Correlation with ISO 9001:2008 and ISO/IEC 17025:2005
Annex B Other international standards on quality management and quality management systems developed by ISO/TC 176	Annex B Guidelines for establishing applications for specific fields	Annex B Comparison of ISO 15189:2007 and ISO 15189:2012
Bibliography	Bibliography	Bibliography

Table 1. Structure and items from the ISO 9001, ISO/IEC 17025, and ISO 15189 standards.

On the other hand, the choice between certification (ISO 9001) and accreditation (ISO 17025 standard applicable to testing or calibration laboratories or ISO 15189 when it is a clinical laboratory) will depend on the requirements from current or potential customers, regulatory boards, or the expected growth and development of the laboratory [8]. **Figure 1** shows the similarities and differences between certification and accreditation.

When customers need international recognition of their results or the laboratory wishes to incorporate users with international requirements, corresponding laboratory accreditation for the required tests is the best option, since it allows establishing the validity of their tests. If customers must ensure the sample traceability from the collection to result delivery, the easiest and cheapest option of quality management system is ISO 9001. At the local level, the ISO 9001 certification may be enough to provide confidence quality in the products or services offered, to be able to differentiate themselves from the competition and gain market share and public tenders, among other objectives.

Alternatively, laboratory mission, vision, and policy can include issues related with market positioning, so that specific objectives should be defined regarding to certification and accreditation in each case.

Benefits from implementation of ISO 9001, ISO/IEC 17025, and ISO 15189 in the laboratory are shown in **Table 2** [6].

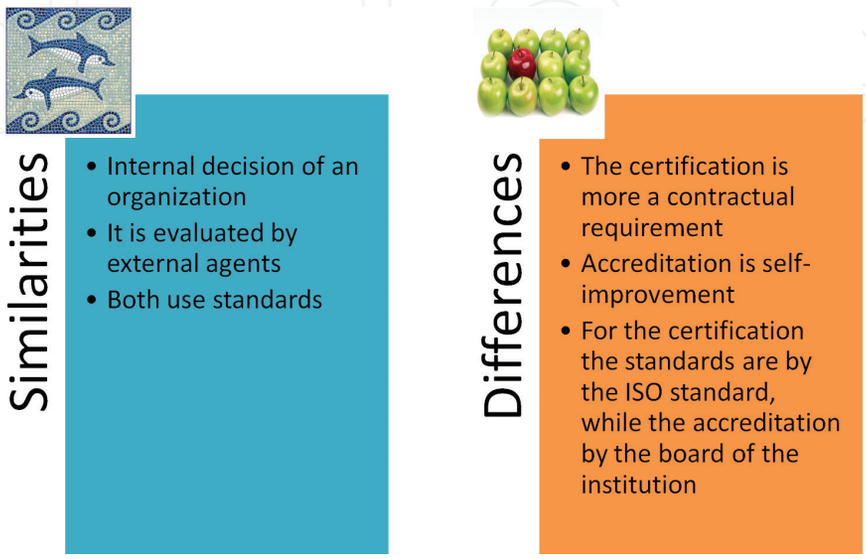

Figure 1. Similarities and differences between certification and accreditation.

Benefits	ISO 9001	ISO/IEC 17025	ISO 15189
Improvement of the company image	X	X	X
Allow to gain market share	X	X	X
Improvement of business efficiency	X	X	X
Improvement of qualification to access tenders	X	X	X
Improvement of internal processes	X	X	X
Achievement of strategic objectives	X	X	X
Establishment of mechanisms for the continuous improvement of service quality	X	X	X
Achievement of customer satisfaction	X	X	X
Customer loyalty	X	X	X
Allow formal recognition of technical competence		X	X
International recognition of trials		X	X
Commitment of staff in meeting customer requirements		X	X
Development of staff competencies		X	X
Fulfilled requirement for the registration of the laboratory in governmental organisms		X	

Table 2. Benefits from implementation of ISO 9001, ISO/IEC 17025, and ISO 15189 in the laboratory adapted from [6].

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4. External quality assurance programs

"External quality assurance or assessment" (EQA) programs are a tool designed by different providers (usually medical or scientific societies) with an educational, training, and helping purpose. They allow the evaluation of the analytical performance for every variable involved (staff, equipment, reagents, and method) in comparison with the expected results. Similarly, EQA schemes are an educational tool to evaluate the competence of the laboratory in relation with specific variables. In addition to internal quality control (IQC), EQA is complementary in the quality management system. Alternatively, proficiency testing (PT) is used as external quality assurance with a regulatory purpose for laboratory licensing and/or accreditation [9].

EQA programs allow comparing the laboratories' results and informing on global variation with the objective of working toward the harmonization. This goal is extremely important because medical decisions are based on comparisons of analytical results with time or a reference interval [10].

In this sense, international societies recognize the importance of EQA provision [11]. The World Health Organization has an available manual for organizing a national EQA program for health laboratories and other testing sites, providing guidance on the international standards ISO 17043:2010 Conformity assessment—general requirements for proficiency testing and ISO 13528:2015 Statistical methods for use in proficiency testing by interlaboratory comparison. Contrary to expectations, not enough evidences of quality improvement of the analytical performance as a result of EQA participation have been reported [12].

The EQA participation process is summarized in **Figure 2**. Samples prepared by the EQA provider are sent to the laboratories for their analysis. These samples of unknown nature are handled by the laboratory from their reception until the report emission as usual samples, although trying to participate each analyzer in the whole program [9]. EQA provider receives the analytical results from all of the laboratories and prepares a confidential report with the identified deviation regarding to an assigned value [13]. Optionally, report may establish acceptance limits for the assigned value in accordance with analytical performance specifications [14] and inform about the performance evaluation of the several methods employed by participants.

Acceptance limits have been classified as [13]:

- Regulatory: for identification of laboratories with a poor performance of the analysis.
- Statistical: an acceptable result is defined by its similarity with others derived from the same method. The disadvantage of this kind of acceptance limit is that it varies between methods.
- Clinical: based on medical decisions.

In case of nonregulatory EQA participation, the laboratories should decide the proper limits for the proposed objective. When the acceptance limit is defined as the "fitness for purpose", such purpose must be specified based on external requirements [15].

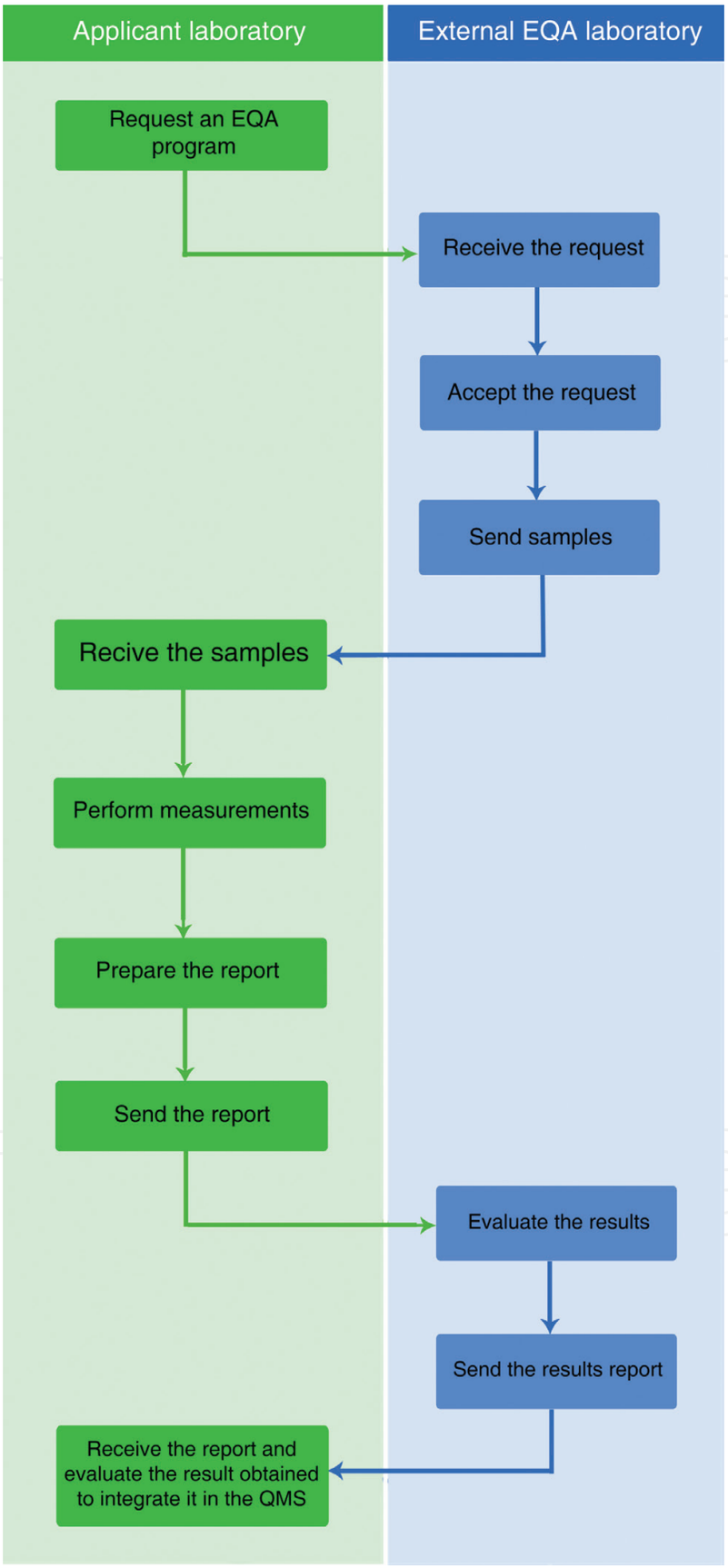

Figure 2. EQA participation process.

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The optimal EQA participation frequency has not already established, but targeted high-quality schemes with a proper number of samples are preferred instead of many schemes with a risky participation rate.

Quality of EQA programs depends on the properties of their design [16]. The use of validated commutable samples and the assigned value definition based on a reference measurement procedure or by comparison with a certified reference material makes an EQA program prominent.

An EQA sample is commutable when the result after the analysis by a variety of methods is equivalent to the result obtained from patient samples with the same amount of analytes. In other words, the results for different methods are comparable because there are no matrix-related biases in commutable samples [17, 18]. However, commutability is not always possible since enough volume of EQA samples with relevant concentrations must be prepared in homogeneous and stable conditions.

Additionally, to use biological samples as reference material is necessary in their certification precise information about their characteristics (processing, purity, characterization, "fitness for purpose", homogeneity, stability) and about their original clinical, biological, and pathological diagnosis. Only in this way, application of ISO Guide 34 requirements for reference material production to EQA samples would be achieved [19].

If commutable samples are not available, it is not possible to evaluate method accuracy. In this sense, laboratories are evaluated and classified by groups of participants with the same method and expected matrix-related bias (peer groups) because comparison to the same assigned value is impracticable. The assigned value is the group mean or median after outliers' removal or by using robust statistical tools and deviation is calculated. It is worth mentioning that the uncertainty of the estimated assigned value would be larger in a small peer group than in a bigger one [13]. Another disadvantage is that peer group evaluation is made impossible to identify a poor performance result when all reagents from the participants are affected. This is the reason why reagents' batch number should be recorded and took into consideration during evaluation by the EQA provider, contacting to the manufacturer when batch effects are observed [20, 21]. In spite of previous limitations, this type of EQA allows to measure the quality of the results with respect to the method and the other laboratories in the same group.

Independent of sample commutability, previous analysis tools are not valid for semiquantitative measures or measures reported on a discontinuous scale or where dichotomous results are provided for a continuous parameter [15].

Ideally, and with the previously commented objective of laboratories' result harmonization, international EQA programs are recommended. However, they are a nonviable option for routine use because of their cost and complexity, being precisely the challenge for EQA providers to find new solutions and overcome limitations related with EQA design [16]. In the meantime, an alternative option that has been proposed [10] would be to organize a global EQA characterized by its remarkable design (validated commutable samples and assigned value by references) for a few representative laboratories from different countries. In a second

phase, these laboratories would participate in smaller national or regional programs with an optimal design as reference laboratories. In the frame of this initiative, results from EQA should be reviewed by a professional international advisory board to inquire the root causes for global deviations.

A particular case of testing is the point-of-care (POC) technologies, which has the very prominent advantage of increasing the populations' access to diagnoses through introduction of a decentralized model. However, from the EQA program's point of view, POC analytical performance increases in the same manner the design difficulty: many EQA samples are necessary for multiple testing points, where nonspecialized staff is available with a poor and delayed participation [12]. To deal with this situation, connected devices to a central database for POC technologies have been developed to establish an efficient and on time EQA workflow. Sent EQA samples are distinguished thanks to specific IDs, obtaining a cheaper, fewer errors and simplified EQA approach for each step by means of direct data collection and analysis [22].

To be clear, EQA participation does not improve directly the quality, but it identifies and monitors poor performance issues. So, it is very important that a proactive participation is implemented in the laboratory [9], being recommended that an EQA manager is available.

The laboratory must choose an EQA organizer in function of the EQA designs offered and the own quality assurance or supporting needs of the laboratory. This selective process should be justified and documented. The choice is easier when proficiency testing with a regulatory purpose is imposed. EQA providers with professional committees and accredited laboratories are preferable. With this objective, EQA provider must inform about EQA programs' designs and especially about analytical performance specifications used in each case. This information will allow the comparison between different EQA programs, as harmonization of analytical performance specifications for the same analyte has not been achieved yet.

A proactive attitude by the laboratory is also necessary, even mandatory in the case of accreditation, for proper and timely EQA report revision. Reports from EQA providers are often used as a quality follow-up tool by auditors. Laboratory staff should know the laboratory's EQA analytical performance results by means of formal communications [9].

Three kinds of reports should be available [15]:

- A confidential and clear individual report for each laboratory, also for outliers, including its deviation regarding the assigned value and usually the acceptance limits. In addition, reports may contain the number and origin of the participants and their distribution of results to allow comparison between them and even the laboratory's performance history.
- Summary reports at the end of each scheme or program with global and anonymized information about analytical performance variation for different analyses.
- Periodic reports can be published as well to highlight the most significant results found.

A very important supporting element for the evaluation in the reports, and required by international standards, is graphical representations. Graphs are also powerful tools to show combined information from a variety of analysis with different samples, time points, or other relevant variables.

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Quality improvement of the laboratory after EQA participation will be only possible if changes in the deviated processes are developed. As part of their educational, training, and helping responsibilities, EQA providers should support and collaborate with the laboratory in this phase.

Proposed corrective actions must be documented and include the steps taken to find the cause of the deviation and to solve its consequences. As a troubleshooting tool for EQA concerning analytical performance, the Norwegian Clinical Chemistry EQA Program (NKK) has developed a flowchart with additional comments in collaboration with the External quality Control of diagnostic Assays and Tests (ECAT) Foundation [13]. It is a public instrument, only valid for quantitative analysis, which proposes actions to be initiated in the format of corrective and preventive action (CAPA) documentation or root cause analysis (RCA) after deviation identification by EQA. Four points are considered in the flowchart and associated comments: the potential cause of deviation, the corresponding responsibility for this cause, a brief, and, finally, a detailed explanation about the proposed actions.

The previous points are classified according to the consecutive steps in the EQA participation process:

- Transcription errors: the most frequent cause.
- Pre-survey issues: unrelated to the laboratory. Unfortunately, sample reanalysis is necessary.
- Sample receipt or handling: derived from incorrect address information, misunderstanding of EQA provider instructions, bad integrity of the EQA sample, or lack of records.
- Test performance: new or old causes that made necessary to identify who, when, and how, to look at the internal quality control data (IQC), and to look for systematic deviations from different participations over time.
- Data handling by EQA provider: these errors are due to the statistical procedure, their identification by the laboratory being difficult.
- Report and interpretation.

To sum up (**Figure 3**), the procedure to integrate the EQA results in the QMS of the laboratory is [16]:

1. Report interpretation
2. Initiating documented corrective and preventive (whenever possible) actions
    a. To collect information about who, when, and how in relation with EQA participation, IQC data, and previous and global EQA results
    b. To find the cause of deviation
3. Monitoring of actions taken
4. New analysis of a stored aliquot left of the EQA sample
5. Revision of EQA program selection

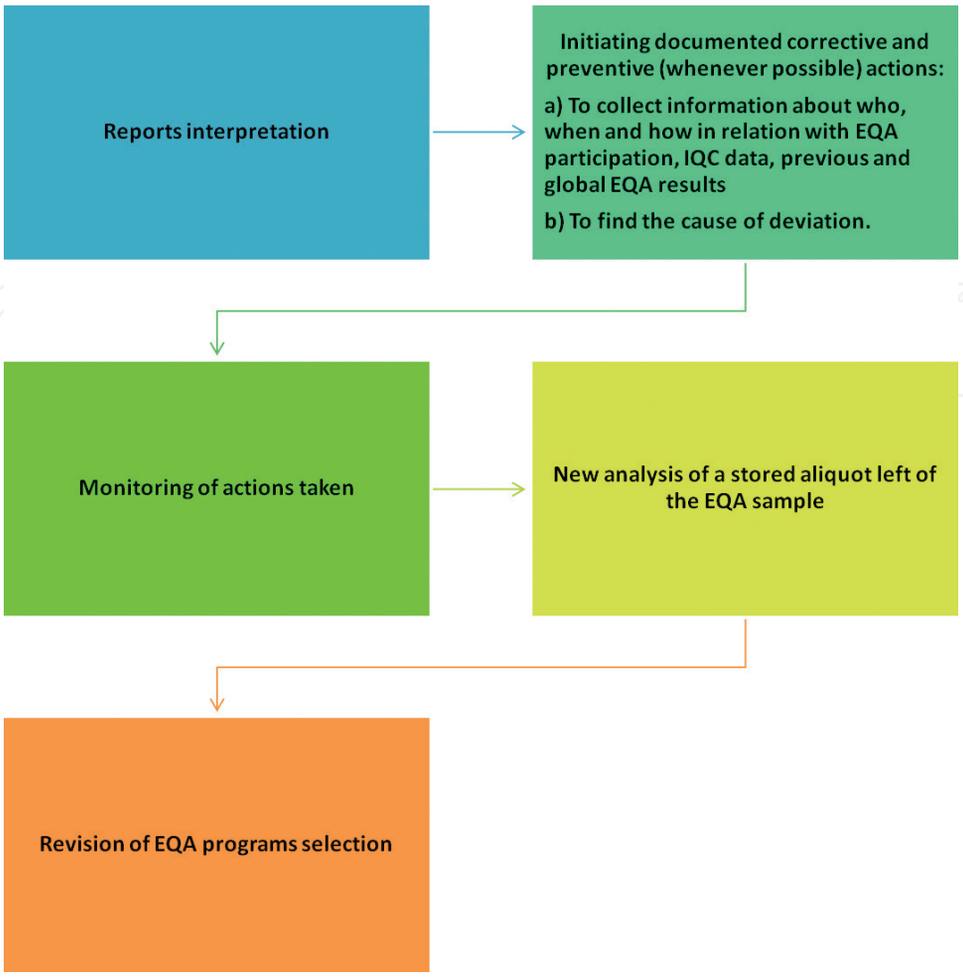

Figure 3. Procedure to integrate the EQA results in the QMS of the laboratory.

Although EQA has been usually applied to analytical performance, the EQA process should meet in the same manner the pre-analytical phases. Several efforts have been conducted trying to cover them, with three types of pre-analytical EQA schemes being categorized [23]:

- Type I: registration of procedures by means of questionnaires. Few resources are necessary to organize and participate, and relevant recommendations may be included.
- Type II: sample analysis with simulated problems. However, only limited pre-analytical deviations can be generated.
- Type III: registration of incidences. This kind of pre-analytical EQA schemes offers the opportunity to EQA providers for harmonization of quality indicators (QIs).

Pre-analytical EQA schemes are more difficult to standardize, but it is worth progressing in this sense because these phases are more prone to errors.

Furthermore, the requesting and reporting diagnostic phases should also be covered by EQA programs due to two main reasons: high rate of errors associated and the definition of quality

management system (QMS) mentioned at the beginning of this chapter of fulfillment user requirements and satisfaction [24]. The design of such programs should be developed carefully to obtain useful information.

Clinical laboratories' activities are based on evidences derived from research [10]. Biobanks are singular laboratories that provide samples for research. Differences between biobanks in preanalytical and processing methods for the same kind of samples may impact research results [25]. Therefore, EQA process provides an opportunity for harmonization in the biobanking field as well. With a main educational purpose, the International Society for Biological and Environmental Repositories (ISBER) have developed an EQA program focused on sample processing and testing [26] that represents a very important part of a biobank quality management system.

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