# Behind the scenes of EQA: characteristics, capabilities, benefits and assets of external quality assessment (EQA)

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**Review**

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# Behind the scenes of EQA – characteristics, capabilities, benefits and assets of external quality assessment (EQA)

Part V – Benefits for stakeholders other than participants

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**Abstract:** External quality assessment (EQA) enhances patient safety through the evaluation of the quality of laboratory-based and point of care testing. Regulatory agencies and accreditation organizations utilize the results and the laboratory's response to them as part of assessing the laboratory's fitness to practice. In addition, where EQA samples are commutable and the assigned value

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has been determined using reference measurement procedures (RMPs), EQA data contributes to the verification of metrological traceability of assays as part of the post-market surveillance of *in vitro* diagnostic (IVD) medical devices (IVD-MDs). More broadly, the scientific and medical communities use EQA data to demonstrate that medical laboratory examination procedures are fit for clinical purposes, to evaluate common reference intervals, and inclusion of data in clinical databases. Scientific groups, the IVD industry, reference laboratories and National Metrology Institutes can work with EQA providers to identify measurands, which should urgently be supported by the development of reference materials or methods. The ability of health systems to respond effectively to fast-evolving medical challenges, such as the Coronavirus Disease-19 (COVID-19) pandemic, is reliant on EQA to demonstrate confidence in the performance of new laboratory methods and testing services. EQA providers are uniquely positioned to assess the performance of IVD-MDs in addition to individual laboratories and testing sites. Although the primary focus of EQA providers remains the improvement of the performance of individual laboratories, there are many stakeholders who benefit from EQA performance data.

**Keywords:** external quality assessment (EQA); proficiency testing (PT); interlaboratory comparison; stakeholders

# Introduction

This is Part V of a five-part series of articles describing principles, practices and benefits of External Quality Assessment (EQA) of the clinical laboratory. Part I describes the historical, legal, and ethical background of EQA and the properties of individual programs [1]. Part II deals with crucial properties of EQA cycles [2]. Part III is focused on the characteristics of EQA samples [3]. Part IV summarizes the benefits for participant laboratories [4], and Part V addresses the broad benefits of EQA for stakeholders other than participants.

Since the first survey on the assessment of accuracy of several measurands in medical laboratories in 1947 [5], the practice of EQA has become established as an essential component of quality management. The primary aim of EQA is to focus on the laboratory's analytical performance compared to its peers or a trueness/equivalence based reference system [6]. However, as EQA providers collect and analyze data from many individual laboratories and can therefore provide a neutral "bird's-eye" view of the analytical performance of different examination methods and IVD-MDs, they can present a valuable contribution to reports on the performance of IVD-MDs under validation or evaluation conditions [7]. The list of examples is long, and EQA providers must meet the challenge of managing the sometimes contradictory expectations of different stakeholders (Table 1).

# Stakeholders that benefit from EQA results and the services of their providers

## Patients, clinicians and other users of laboratory services

The major stakeholders of the laboratory are patients and clinicians as their medical representatives, and an important question is, therefore, how they benefit from EQA. Medical laboratory testing can have a major impact on patient management concerning the diagnosis of a disease and monitoring of treatment [8]. However, published evidence that participation in an EQA program results in improved patient care and safety is limited [9–18]. Implementation of quality management systems based on ISO 15189 and ISO 9001 [15], involving participation in EQA and striving for continuous improvement of services, provides a solid foundation for quality in the laboratory and enhances patient safety. Another study demonstrated that about 70 % of laboratory errors impact on the diagnosis of patients [10]. Although patients are usually not aware of this, EQA and the

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**Table 1:** Benefits of EQA data and EQA providers' services for stakeholders other than participants.

| Category: Stakeholders | Further use of samples for internal technical activities | EQA providers services, programs and cycles | Performance data | | | |
|---|---|---|---|---|---|---|
| | | | Of individual examination procedures/IVD-MDs | | Of individual participants | |
| | | | Assessment outcome | Comparison between methods | Assessment results | User competence monitoring and development |
| Patients and clinicians | | Advance development and effective utilization of precision diagnostics. | Ensure diagnostic tests are safe, clinically effective, and appropriate for clinical purposes at relevant clinical decision limits | Evaluation of the extent of harmonization between examination procedures | Laboratory results with monitored accuracy | |
| IVD manufacturers | Examinations of the EQA material by the IVD manufacturer can be helpful in root cause analysis after laboratories failed in an EQA cycle. | Publications presenting and interpreting EQA data | Performance assessment of IVD-MDs in routine use for post market surveillance purposes<br>Identification of tests with suboptimal performance (unsafe, ineffective)<br>Comparison with performance of market companions<br>Identification of measurands needing harmonization | Extent of harmonization between methods | Indications of technical issues | |
| Scientific community | | Publications presenting and interpreting EQA data<br>Education<br>Support in the creation of clinical guidelines<br>Expertise on metrological traceability<br>Maintain databases of performance data | Fitness for purpose at relevant clinical decision limits<br>Detection of tests with suboptimal performance (unsafe, ineffective)<br>Identification of measurands needing harmonization<br>Evaluation of metrological traceability and equivalence of measurement procedures | Extent of harmonization between methods | | |
| Regulators | | Notification about the abnormalities of the performance of individual IVDs | Performance assessment of devices in routine use for post market surveillance purposes<br>Detection of tests with suboptimal performance | Extent of harmonization between methods | Monitoring the meeting of analytical goals[a] | |
| Notified bodies | | Publications presenting and interpreting EQA data | Performance assessment of devices in routine use for post market surveillance purposes<br>Detection of tests with suboptimal performance<br>Long term monitoring of performance of individual tests<br>Recognizing major operational challenges that impact the reliability of results | | | |

**Table 1:** (continued)

| Category: Stakeholders | Further use of samples for internal technical activities | EQA providers services, programs and cycles | Performance data | | | |
|---|---|---|---|---|---|---|
| | | | Of individual examination procedures/IVD-MDs | | Of individual participants | |
| | | | Assessment outcome | Comparison between methods | Assessment results | User competence monitoring and development |
| Accreditation bodies | | Dialogue between EQA providers and accreditation bodies so that laboratories may meet expectations of ISO 15189:2022 at accreditation audits | Verification of stable performance of validated laboratory-developed tests | | Third-party assessment of analytical performance of a laboratory | Part of the proof of competence of individual employees<br>EQA results as the content of internal training measures |
| National health organisations and policy makers | | Publications presenting and interpreting EQA data | Show the variability of values obtained by multiple identical and different test systems and thereby inversely show the extent of harmonization of measurement results for a measurand | Extent of harmonization between methods<br>Performance data of different health technologies<br>Effectiveness data by comparing laboratory assays for health technology assessments | | |
| Public health authorities | | Publications presenting and interpreting EQA data on overall analytical performance to underpin reliability of epidemiological data | Support in decision-making about the approval of test systems and operator groups other than medical laboratories for infection diagnostics<br>Monitoring reliability of laboratory data serving as basis for epidemiological data | Extent of harmonization between methods | Individual monitoring of the members of groups that are authorized to carry out analytical procedures during pandemics | |
| EQA networks | | Information exchange<br>Publications presenting and interpreting EQA data<br>Get together users, experts, public health authorities<br>Organizing super challenges to collect EQA data from larger groups of participants and devices<br>Joint procurement of materials for economic reasons | Monitoring the effectiveness of harmonization and standardization activities | Extent of harmonization between methods | | |

[a]Where applicable. EQA data and providers' services offer benefit for participants as well as for other stakeholders; depending on the stakeholder, the benefit concerns six areas (EQA providers' services; further use of samples for internal technical activities; assessment outcome of individual test systems; for the purpose of comparing different test systems; assessment of results of individual participants; user competence management) that offer varying extent of benefits for them (high; moderate; low/none); >1 items per category or one extraordinary important item=high benefit; one moderately important item per category=moderate benefit as shown in Figure 1.

support of participant laboratories by its providers, contribute to the enhancement of patient safety as part of a quality management system that aims to minimize the risk of the release of erroneous results [16, 17]. Performance assessment in EQA with samples at concentrations used in guidelines to distinguish between different clinical decisions, can identify whether the performance of laboratories meets the assumptions made in such guidelines. A recent study used EQA based performance data to demonstrate the difference in the ability of laboratories to comply with the guidelines of the European Society for Cardiology on the assessment of non-ST-elevation myocardial infarctions (NSTEMI). In that study, misclassification between rule in and rule out was 0.0001 % for laboratories passing EQA performance and 2 % for those who did not, where the guideline allows for 1 % misclassification [18]. Such studies make clinicians aware of the relevance of laboratory performance for patient safety and the relevance of EQA to be the safe keeper of this.

Another group of users of laboratory services are institutions that do not require laboratory results directly for the treatment of individual patients, but indirectly, such as the pharmaceutical industry in the context of clinical studies, or users of blood products and derivatives who expect reliability of results and compliance of examination procedures with the requirements for immunohaematology and infectivity testing with sufficient competence and using appropriate methods. They can accept confirmation of the responsible laboratory's successful participation in EQA as proof of general testing competence, even without being technically familiar with the subject of the laboratory's activities.

EQA providers should select samples that provide clinically relevant challenges, mimic patient specimens as far as practicable, i.e. which are commutable [19]. Several studies have demonstrated the educational value of including clinical case scenarios in EQA or interlaboratory studies [20, 21] to support patient awareness of potential problems, the appropriate interpretation of laboratory results, and the correct diagnosis. Therefore, EQA providers benefit patients by focusing on all phases of the diagnostic process and not solely on analytical performance.

## Manufacturers of IVD systems

EQA programs can reveal the relative performance of different examination procedures and IVD-MDs, contributing thereby to post-market surveillance of IVDs as required by European Standard (EN) 14136:2004 and the IVDR [22, 23]. EQA data reflects real-time laboratory performance with different IVD-MDs and can often include results from multiple laboratories, instruments, operators and reagent lots. Data from validation or evaluation studies, on the other hand, refer to specific settings to test and present the performance of an IVD-MD at a specific time. These two types of performance data complement each other and present far more aspects than just one type alone.

The quality and reliability of EQA data in this regard depend on the completeness of the information provided by participants about the IVD-MD used and the commutability of the EQA samples. Laboratories are responsible for providing detailed information to their EQA provider about the examination procedure used and to declare any deviation from the protocol of the IVD manufacturer so that they can be classified as using a laboratory-developed test (LDT) and be excluded from data used for post-market surveillance. The need for commutable sample material to be used in EQA is to ensure that observed differences between examination procedures are not the result of a property of the sample material but relate to the examination itself, for example, lack of accuracy and/or selectivity for the measurand. Therefore, the commutability of EQA samples should be examined wherever possible [24].

## The scientific community

### Medical laboratory science and research

EQA providers play a prominent role in the scientific and medical laboratory community, supporting the following scientific and medical objectives:

(1) Ensure diagnostic tests are appropriate for clinical purposes.

Medical tests should fulfill clinical needs, deliver actionable results and have a defined test purpose in the clinical care pathway. In the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) landmark paper on test evaluation [25], the five key elements of test evaluation (analytical performance, clinical performance, clinical effectiveness, cost-effectiveness and the broader impact) are structured in a cog wheel framework around the clinical care pathway, which implies that the clinical utility of a test

is dependent on its analytical performance. As evidence-based clinical guidelines evolve, the analytical performance of tests should be aligned to ensure that the required clinical performance specifications can be met [26]. Fitness for clinical purpose becomes challenging when tests with lower clinical decision limits and higher analytical sensitivity are needed. EQA programs should ideally be able to evaluate performance at critical decision-making limits, e.g., highly sensitive cardiac troponin in the 0/1 h NSTEMI algorithms for detecting acute coronary syndrome [18, 27–29]. For albumin, the selectivity based interference of Bromocresol Green examination methods renders them unsafe for decisions on protein loss in patients with nephrotic syndrome, which can be demonstrated in EQA performance when samples reflect the composition in real life patients [30].

(2) Ensure diagnostic tests are safe, clinically effective, and do not cause harm to patients.

EQA program designs should enable the detection of suboptimal examination methods and identify underperforming IVD manufacturers and/or IVD-MDs. The selectivity of the examination procedure for the measurand, the result accuracy (encompassing both trueness and precision), and the degree of standardization or harmonization between examination methods are all determinants of test fitness for purpose and support the universal application of clinical guidelines and decision limits. Ideally, pre-examination, examination and post-examination aspects of the total testing process should be assessed, to estimate whether the combined measurement uncertainties are within the allowable limits, e.g., prolactin immunoassays that do not differentiate an insignificant macroprolactinemia from a real hyperprolactinemia in case of a prolactinoma, in this case offline preparation, for example, by polyethylene glycol precipitation, may be required. The impact of this will need to be taken into consideration [31].

(3) Advance development and effective utilization of precision diagnostics.

EQA providers have a role in the monitoring and evaluation of test quality of all IVDs, as long as the statistical sample size is adequately met for comparison's sake. In this era of precision medicine, all IVD users should participate in EQA, especially institutions that develop and utilize LDTs for clinical care. As classified by the U.S. Food and Drug Administration (US FDA) and the European IVDR, LDTs are IVD-MDs that are designed, manufactured and used within a single clinical laboratory that meets certain requirements [32]. A specific example of this is for molecular oncology applications, where EQA providers need to manufacture carefully molecularly characterized samples (e.g. through (glyco-)proteotyping of specific dysfunctional protein proteoforms) that allow a clear molecular definition of a patient's health baseline and disease states, and which will enable effective patient management.

Other examples include the proteotyping of specific glycoproteoforms of prostate-specific antigen (PSA) that distinguish benign prostate hypertrophy from malign prostate cancer [33], and the proteotyping of antithrombin to improve the detection of antithrombin deficiency [34, 35]. For this type of advanced testing and quality assurance, EQA providers should consider direct collaboration with expert laboratories to design EQA programs that best evaluate these specialized molecular tests. EQA participation and collaboration support innovative precision medicine by providing objective testing data and preventing underdiagnosis and undertreatment of patients.

The US FDA issued a Final Rule on May 6, 2024, that will, over the next four years, radically alter the landscape for LDTs and "correct the imbalance" between IVDs marketed outside a laboratory and those IVDs manufactured by a laboratory [36]. Regulatory compliance expectations will be introduced for certain types of IVDs offered as LDTs in five stages. Each stage adds additional compliance expectations, with which clinical laboratories using LDTs will need to comply. These requirements are regulatory tools already applied in enforcement against traditional IVD manufacturers: adverse event reporting, establishment registration and device listing, labeling standards, investigational use requirements, and, as new IVDs enter the market or are significantly modified, CGMPs and premarket review [37, 38].

## Scientific and professional associations

Professional and scientific associations may look to EQA programs that are able to evaluate metrological traceability and equivalence of examination procedures to support pan-laboratory activities [39]. EQA programs provide evidence that can be used by clinical guideline developers and clinical groups to show that results from different laboratories, examination methods, or IVD-MDs provide equivalent results. Without this assurance, clinicians cannot interpret results from different laboratories using common approaches. For example, EQA with commutable materials with reference method target values provides direct evidence about metrological traceability within allowable limits of measurement uncertainty (MU) of examination methods. Suppose methods are demonstrated to have traceability within allowable MU. In that case, the results from these examination methods can be combined in databases or can be interpreted using common decision criteria. That is, the results are metrologically equivalent. Specifically, under these circumstances, results from different methods can be used:

– Common reference intervals. Common reference intervals allow safer and easier interpretation of patient

results from different laboratories. However they can only be used if the results from different examination methods are demonstrated to be equivalent [40].
- Combined data into clinical databases. Results from different examination methods must be shown to be equivalent before they can be combined into a common database. Clinical databases are becoming more common and are driving improved health outcomes and reduced costs by avoiding unnecessary repeat testing.
- Clinical guidelines. Guidelines are developed with a decision level for a rule-in or rule-out assessment of a disease (e.g. anemia, diabetes). For these decision levels to be applicable across different examination methods, they must report equivalent results.

Particularly worth mentioning within the scientific community are groups working on the improvement of harmonization and metrological traceability of medical laboratory results. They may identify routes by which results' harmonization and/or accuracy should be improved, for which reference methods and/or reference materials are needed, and in what format to underpin traceability. This is of particular importance, given the high number of measurands for which reference materials and/or RMPs, which, when used together to provide traceability across a network of reference laboratories, are described as reference measurement systems [41] are lacking. The prioritization of the measurands for which reference measurement systems are the most urgently needed is essential. This is important in areas where reference systems are being developed to support more complex measurands, such as in bioanalytical testing using proteins ranging from smaller biomarkers (e.g., procalcitonin) to more complex protein structures such as antibodies [42] or nucleic acids, including DNA [43] and RNA [44] analytical techniques. Activities and achievements of the initiative for Harmonization of measurands in Laboratory Medicine through data Aggregation (HALMA) [45], the International Consortium for Harmonization of Clinical Laboratory Results (ICHCLR) [46], the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) [47–49], the Joint Committee for Traceability in Laboratory Medicine (JCTLM) [50, 51], the international meeting forum "Standardization of Genome Amplification Technologies" (SoGAT) [52], and the European Metrology Network in Laboratory Medicine (EMN TraceLab) [43, 53, 54] are summarized in Table 2. EQA can serve as a mechanism to check the success of harmonization initiatives but can also provide samples and data to initiate harmonization, as shown in recent international collaboration using EQA programs from six different providers to study and improve the harmonization of tumor markers [55].

Of course, there are also scientific and professional associations that deal with qualitative tests and for whom metrological traceability of results has limited relevance. In specialized laboratory networks linking patients with complex biological products (like transfusion or transplantation), professional organizations provide mandatory EQA to standardize and secure crossmatch and allocation procedures. The Eurotransplant (ETRL) network operating in Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, the Netherlands and Slovenia, requires for participation in this network that member states fulfill as a prerequisite, among others, Human Leukocyte Antigen (HLA)-typing and cross-matching by a European Federation for Immunogenetics (EFI) accredited laboratory [56]. EFI standards require participation in an EQA program that covers all the accredited laboratory applications (i.e. HLA typing, antibody screening and identification, crossmatching, etc.) and all techniques used to produce a final result. EFI standards also have explicit requirements concerning the EQA procedure itself, the minimum number of samples circulated per year and the reporting of EQA results. The EQA program used for most applications is that of the ETRL reference laboratory network, which has provided regular EQA for decades. Correct and reproducible identification of HLA antigens and antibodies within the network of HLA labs linked to the regional transplant centers finally allowed virtual crossmatching as a standard procedure in organ allocation within ETRL since 2024.

## EQA data as an investigation and monitoring tool

Analysis of EQA results allows for a more generalized view of success factors for good laboratory performance. The impact of operating quality management systems, the degree of specialization of laboratories, national regulatory and economic conditions, and EQA provider's services using EQA outcomes were investigated using immunohaematology EQA data. Laboratories with ISO 9001 certification or accreditation showed only about half the number of errors in EQA results in comparison to laboratories without. Also the degree of specialization of participating laboratories is reflected in EQA performance, with significantly better results of transfusion services compared to hospital or independent laboratories [15]. Based on a large international study, legally required quality standards or national economic conditions seemed not to correlate with error rates in EQA but rather the support provided by the EQA provider in case of incorrect results [17]. These two articles are examples that show that performance in EQA can be determined by external influences. Still also – and this is the topic here – that EQA performance can be used as a means of identifying the effects of certain influences on the laboratory.

**Table 2:** Groups working on improvement of harmonization and metrological traceability of medical laboratory results.

| Group | Activities and achievements |
|---|---|
| HALMA – HArmonization of measurands in Laboratory Medicine through data Aggregation | ICHCLR and the European Organisation for External Quality Assurance Providers in Laboratory Medicine (EQALM) have joined forces for an initiative to combine results from various EQA providers which may provide a powerful tool to monitor harmonization of examination procedures in the medical laboratory [44]. |
| ICHCLR – International Consortium for Harmonization of Clinical Laboratory Results | ICHCLR provides a centralized process to organize global efforts to achieve harmonization of clinical laboratory test results and presents a list of the harmonization and standardization status of a number of measurands [45]. |
| IFCC – International Federation of Clinical Chemistry and Laboratory Medicine | The IFCC Scientific Division structurally manages for decades the establishment and adoption of reference services by ~25 IFCC working groups [47] and committees [46]; among them is the IFCC Committee for Traceability in Laboratory Medicine (C-TLM) [48] that organizes an interlaboratory comparison program for reference laboratories. |
| JCTLM – Joint Committee for Traceability in Laboratory Medicine | JCTLM was established through a declaration of cooperation between the International Bureau of Weights and Measures (BIPM), the IFCC, and the International Laboratory Accreditation Cooperation (ILAC). The aim of this consortium is to support worldwide equivalence and comparability of measurement results in laboratory medicine, for the purpose of improving health care [49]. The main output of the JCTLM is the global database of higher order reference materials; reference measurement methods/procedures; and reference measurement services [50]. |
| SoGAT – international meeting forum "Standardisation of Genome Amplification Technologies" | With a focus on infectious diseases, this forum of scientific and clinical experts, IVD manufacturers, regulatory laboratories and EQA providers identifies and prioritizes the needs of the diagnostic community for higher order reference materials established by the World Health Organisation Expert Committee for Biological Standardisation [51]. |
| TraceLabMed – National Metrology Institutes, recently organized in the European Metrology Network "TraceLabMed" | To fulfill their legal mandate, National Metrology Institutes (NMI) develop RMPs and are also responsible for developing advances in metrology at an international level. They can respond to the needs of EQA providers and their stakeholders. Examples in bioanalysis include the development of reference measurement procedures for protein [52] and nucleic acid analysis [42, 53] to improve standardization by complementing material standards and providing novel routes for traceability. |

### Groups publishing on scientific EQA projects

In 2023, a review of the current literature on interlaboratory comparison, EQA, and proficiency testing (PT) by members of the European Organisation for External Quality Assurance Providers in Laboratory Medicine (EQALM) Scientific Committee showed inconsistency on the items reported in publications on such results and omission of essential details for EQA. EQALM has, therefore, decided to prepare guidelines on items that are considered essential (recommended) for inclusion in papers reporting interlaboratory comparison studies. These comprise the description of the activity, information on items (samples) used, information and instructions provided to the participants, information on participant entities and on participating examination procedures and IVD-MDs, way(s) of submission of results, procedures for evaluation and assessment of results, reports to participants (and other interested parties), findings from the study, limitations of the study, and impact of the outcome of the activity [57].

## Regulatory authorities

Accuracy, timeliness and reliability of laboratory results are of crucial importance in healthcare. Consequently, many jurisdictions mandate a minimum performance that laboratories must achieve to practice. This usually involves accreditation to a standard such as ISO 15189 and local regulations to protect the public from harm and ensure consistency in laboratory practice. The local regulation may dictate performance criteria, frequency, number of failures allowed before a practice license is in jeopardy, and identification of measurands that require EQA and/or authorized EQA providers. Regulatory Authorities of European Union (EU) and European Free Trade Association (EFTA) member states and other European countries are listed elsewhere [58]. In some countries and for certain measurands, enrolment in appointed EQA programs may be required. This is of particular importance when laboratory results are used in legal cases and decisions, like ethanol tests are used to judge

on driving ability and Carbohydrate-deficient transferrin (CDT) tests are used to decide on successful alcohol abstinence to gain back a driver's license after withdrawal [59].

Where appropriate, EQA providers ensure that regulators are informed of poorly performing test systems that could result in patient harm. Examples are American Clinical Laboratory Improvement Amendments (CLIA), and the Guidelines of the German Federal Medical Society for the Quality Assurance of Laboratory Medical Examinations (RiliBÄK) [60, 61]. Failure of a test system to meet the performance standard can result in the suspension of approval until the expected performance is achieved again.

There can, however, be unintended consequences from this approach. A regulatory program typically includes a set number of samples for all measurands specified in the regulations. Consequently, there is less flexibility, and the concentrations do not challenge the limits of the measuring interval or if examination procedures may be influenced by interfering substances. Also, these EQA samples may be treated differently to patient specimens to ensure acceptable performance, and the performance criteria usually can be met by nearly all laboratories [62].

## Notified bodies for IVDR compliance

Notified bodies are legal entities established under the national laws of EU member states, which fulfill the criteria of Annex VII of IVD-Regulation 746/2017 [23]. They are entitled to authorize manufacturers to use the Conformité Européenne (CE) mark for IVD products after a thorough conformity assessment. This assessment process accompanies the products throughout their whole life cycle. They must act independently and impartially. They must not have any commercial relations with the manufacturer of the assessed products except for the agreement on the conformity assessment. Notified bodies are not allowed to provide consultancy services. They have to make sure that all their personnel involved in an assessment are completely independent of the manufacturer and are not part of the design, manufacture, marketing or installation of the products assessed at any time. Notified bodies are supervised by national authorities of the member state and by the EU Commission.

The relevance of EQA programs for regulatory purposes is described in the article 11.2 of the IVD-Directive 98/79 on IVD-MDs (IVDD) [63]. Consequently, the European Commission mandated the new standard, ISO/IEC 17043:2023 Conformity Assessment – General Requirements for proficiency testing, which was harmonized with IVDD. As parts of the supervision of IVDs have been transferred to notified bodies by IVDR, these institutions will have considerable interest in the results of EQA-programs, because they give important information about the performance of an IVD in the field, as required by Annex XIII, 5.2 of the IVDR [23]. The benefit of EQA results is that they were obtained by IVD-MDs in routine use but not under special conditions focused on performance assessment in validation or evaluation settings. IVDR requires manufacturers to practice life cycle management for their products by periodically doing surveys of the relevant scientific literature and systematically searching for information about the performance of the product in the market. Depending on the risk classification of the product, manufacturers will have to deliver safety reports, for example summary of safety and performance (see article 29 IVDR) or periodic safety update report (PSUR, see article 81 IVDR) to their notified body. These two reports have to include, among other things, summaries of the performance evaluation, residual risks and benefit-risk determination. Results of EQA programs are an excellent means to get summarized information about IVDs based on independent samples, tailored to mimic patient specimens and analyzed in multiple laboratory settings. Due to the requirement of the IVDR to have the performance of high-risk products checked in reference laboratories, cooperation between EQA providers and notified bodies is desirable.

Also, since IVDR requires batch releases on an ongoing basis for high-risk IVD-MDs (Class D), it would be of interest to both manufacturers and notified bodies to consider whether some EQA programs could be used for this process. For the recently described method of evaluating the EQA variability of assays for POCT, please refer to Section 4.2 of the IVDR on Manufacturers of IVD systems [23]. The variation of different test systems in EQA programs can be put into context and provide the notified body with information on the variability of individual measured values for the same samples, which should be as low as possible in POCT systems. A limitation of this tool is that EQA data are only available for post-market surveillance, but not for the initial assessment for the approval of devices.

## Accreditation bodies

### Regarding ISO 15189:2022

The ISO standard 15189:2022 requires medical laboratories to participate in an interlaboratory comparison for each examination procedure employed in the laboratory. Some assessors for accreditation bodies, including laboratories, may consider that such EQA participation is an end in itself, without consideration of the suitability of the interlaboratory comparison for the laboratory's purpose; however, this enrollment should not be the end of the quality partnership. ISO 15189:2022 focuses on the purpose of EQA participation as a tool to verify that the performance of an examination procedure remains as adequate as when accepted during validation or verification. To meet that goal,

an EQA program needs to be suitable. In reality, only an EQA using commutable samples, values assigned with reference measurement procedures [64], is suitable for the full verification of metrological traceability. It is an advantage if the report has tolerance limits based on medical need for the measurand and the report provides relevant information for the guidance of corrective action.

However, notwithstanding value assignment by a reference measurement procedure, EQAs may still be used to verify a between-method harmonization process by examining equivalence of results. If sample materials are not commutable, this is limited to method-specific performance evaluation. EQA providers accreditation to ISO/IEC 17043:2023 alone does not make a program suitable for EQA purposes. EQA providers should educate accreditation bodies and their assessors in evaluating EQA participation from this perspective rather than check-listing that the laboratory participates in an ISO/IEC 17043:2023-accredited program and performs corrective action where performance is outside limits. An active dialogue between EQA providers and accreditation bodies should be encouraged.

#### Regarding ISO 17025:2017

ISO 15189:2022 was developed as a medical field specific version of ISO 17025:2017 [65] to serve the specific needs and challenges in medical laboratories. Regarding EQA, these ISO 15189 aspects relate to specific performance specifications for specific medical indications, which could differ between different indications for the same measurand.

The existence of ISO 15189 as a medical version of the ISO 17025 does not mean ISO 17025 is irrelevant for the medical field. Since ISO 17025 accreditation is required for calibration activities, it is a requirement for reference laboratory services in ISO 15195:2018 [66] and providers of reference materials in ISO 15194:2009 [67], in the medical field. In order to meet the standard's requirement for interlaboratory comparisons, parties working together in the JCTLM have decided to require a specific EQA service specifically set up to cover the needs for such services [68]. In contrast to routine laboratories, the identity of the participating laboratories is disclosed. This allows medical EQA providers serving ISO 15189 accredited laboratories make use of the services of laboratories participating in RELA for the assignment of target values of their EQAs where possible and relevant [4, 68].

#### Regarding ISO 17043:2023

In many aspects, EQA providers serving medical laboratories are comparable to EQA providers in other fields. For all these identical aspects, all elements in ISO 17043:2023 have to be covered to ensure an EQA service with a low risk of malperformance. However, as illustrated in the previous paragraphs, the field of laboratory medicine has specific aspects that add challenges to organizing a suitable EQA for this sector. There are at least two elements that deserve to be mentioned here. First, the definition of the measurand is not clear or even univocal in many cases as different proteoforms of the same measurand co-exist, other techniques have different specificity for those proteoforms. Secondly, although (lack of) commutability could in theory complicate any laboratory discipline, in practice, especially the field of laboratory medicine, seems to suffer from its impact possibly related to the complicated, overcrowded measurement matrices of human body fluids. When national accreditation bodies assess EQA organizations for their ISO 17043 accreditation, their assessors become aware of these challenges in the dialogue between assessor and assessee. Equipped with such information and insights, assessors will bring such knowledge to their accreditation bodies which can apply these insights in the training of their assessors for ISO 15189 accreditation.

## National health organizations and policy makers

Health Technology Assessment (HTA) is a systematic, evidence-based process that examines and compares both clinical and non-clinical aspects of (new or existing) health technologies [69–71]. HTA acts as a link between science and politics by compiling findings from research or generating findings themselves and "translating" them so that they support decision-makers. The idea behind this is to lead to a more efficient use of resources in the healthcare sector and to ensure the highest level of security in the healthcare system. Although laboratory results may be decisive for the performance of health technologies, quality aspects seem to have not yet been fully recognized by HTA [72]. It should be noted that not all examination methods and measurands are harmonized, and therefore, "measuring" and "examining" do not necessarily mean obtaining reliable and interchangeable results regardless of the IVD-MD used. EQA results show the variability of results obtained by multiple identical and different IVD-MDs and thereby inversely show the extent of harmonization of results for a measurand [73]. In particular, the role of EQA as a unique comparison of examination procedures and IVD-MDs under routine conditions should be considered. In addition to the variability of quantitative examination results, EQA programs also compare rates of true positive and false negative results and, thus, the performance of IVD-MDs for pathogen detection used in the field [74–76].

## Public health authorities during public health emergencies

Quality laboratory and diagnostic data is critical in a public health emergency. Key epidemiological data like case counts and disease incidence are based on aggregated individual test results, and thus, the accuracy of these indicators depends on the performance of assays used in testing facilities, more precisely on their true positives and false negatives rates. The important role of EQA providers and their programs for public health authorities was clearly demonstrated during COVID-19 pandemic from 2020 to 2023. In this global health emergency, loosened national and international regulations allowed numerous new examination procedures and IVD-MDs to be brought onto the market within a short period of time without extensive validation. New manufacturers appeared just as quickly as new distributors and new diagnostic test facilities started operating for the first time where previously they had no experience in human medicine. EQA programs for SARS-CoV-2 pathogen detection were deployed early in the COVID-19 pandemic so that participants could obtain information about the performance of their examination procedures [77–80]. An early provision of EQA is definitely supported by existing experience with the establishment of EQA programs for the detection of emerging pathogens [79]. In order to provide laboratories with feedback on the performance of their analysis as early as possible, revealing the EQA results quickly after or even during the ongoing cycle was helpful [81]. In some countries, successful participation in EQA programs was required for the qualification of laboratories to carry out SARS-CoV-2 pathogen detection [82]. The results of the earliest cycles already showed that the $C_q$ values reported by different examination procedures for the same samples were highly variable and therefore, could not be compared with each other and cannot be used as a reliable indicator of the virus load [77, 78, 83–86]. In later cycles, the impact of converting $C_q$ values into an international unit system on the harmonization of results for SARS-CoV-2 quantification was examined and reported to be beneficial [87]. Furthermore, significant limitations of rapid antigen tests and the impact of testers' experience and training were highlighted [74, 75, 88], just as the disharmonic anti-SARS-CoV-2 antibody quantification by different examination procedures [89], the low sensitivity inherent in some SARS-CoV-2 pathogen detection assays [90], and the diluting effect of sample pooling procedures [91]. In addition, EQA providers used their expertise and their unique central position to provide numerous laboratories with national reference materials with which they could relate copy numbers in the samples to the $C_q$ values of their analysis systems [44]; they clarified the nonscientific public misinterpretation of the prevalence of SARS-CoV-2 infections reported as being based on false positive test results [92]; they pointed out that the mention of test performance, in particular the rate of incorrect negative test results, was missing in an otherwise comprehensive article about the lessons for the future from the COVID-19 pandemic [93, 94]; they showed that the overall performance of SARS-CoV-2 virus genome detection did not improve over the time of the pandemic; they pointed out the danger of incorrectly interpreting negative test results as ruling out an infection [95]; and based on experiences from the COVID-19 pandemic, recommendations were made to EQA providers for future epidemics [96] (Table 3).

Some particular examples of notable activities and findings of EQA providers and their programs are presented in Supplement 1.

**Table 3:** Recommendations to EQA providers for future epidemics.

(1) Seek early arrangements with public health authorities so that in the case of an outbreak, epidemic, or pandemic:
– All test facilities, ideally with each of their individual test systems, are obliged to participate in EQA
– Test facility participation is verified
– In return, participating in EQA should be free of charge for test facilities participating in public health-relevant analytics
– Preventative actions after a failure in EQA are reviewed by experts
(2) Provide EQA programs early. EQA should be available as soon as testing begins
(3) Be flexible in designing and adapting EQA programs so that they best accompany the epidemic and the participating laboratories and test facilities; done in coordination with public health authorities
(4) Prepare programs and reports to regularly report on:
– Types and numbers of registered examination procedures and IVD-MDs
– Counts and categories of test facilities enrolled
– Study time
– Rates of false-positive and false-negative results, and analytical sensitivity of assays
– Interassays and intratype variability
– If applicable, proportion of test systems compliant with relevant recommendations
– Sample specification in a commonly used unit
– Reporting on these categories will support participants, public health authorities, other EQA providers, and the scientific community
(5) Make the summary report available shortly after the end of a cycle, or give participants immediate feedback on their results
(6) Immediately report suspicious or alarming findings to health authorities
(7) Take the role as a contact for non-EQA inquiries and a network partner seriously:
– Use the central position to share up-to-date information with participants
– Support participants standardizing their assays
(8) Support concerted campaigns and expert information exchange on EQA through participation

Adapted from [96].

## EQA providers' networks

EQA providers are in close contact with all laboratories participating in their programs, although the extent of this contact depends upon the staff resources of the EQA provider. In a survey of EQALM in 2022, the majority of EQA providers stated that they regularly receive technical inquiries on a wide variety of topics about analytical issues and also that they have sufficient and competent staff available to be able to answer these inquiries satisfactorily (unpublished). This important service underlines the value of EQA providers who know local regulations and laboratory practices. EQA providers may partner with laboratories or countries to support the implementation of a comprehensive program of laboratory quality improvement, encompassing IQC, EQA, method harmonization and education, e.g., the Project of Laboratory Quality Improvement for Portuguese Speaking Countries (ProMeQuaLab) [97]. ProMeQuaLab began in 2015 and is coordinated by the National Health Institute of Portugal (INSA). It is a cooperation project that aims to improve the quality of medical laboratories within the scope of EQA and IQC based on education, training and the application of good laboratory practices in the proper diagnosis and treatment of patients.

Collaboration between EQA providers allows multifunctional opportunities. The ability to compare performance characteristics of individual examination procedures across multiple EQA provider programs provides confirmation of performance issues. A common criticism of EQA is that the EQA sample is "different" from patient specimens, and is, therefore, the cause of the performance issues observed by the EQA provider. Collaboration between EQA providers can confirm in commutable samples that method-related performance issues exist for the measurand and are not attributable to the EQA sample matrix. Such collaboration assists conversations with regulatory bodies and manufacturers and supports the prompt, effective resolution of analytical issues. The COMET project (Manufacturing of COMmutable calibrators and quality control materials for standardization and post-markET surveillance of IVD tests) funded by the European Partnership in Metrology aims at addressing these challenges by evaluating commutability of a large number of EQA materials for key measurands. Identifying the most suitable matrices associated with high commutability levels and assigning reference method assigned values to EQA materials of proven commutability will pave the road towards enhanced post-market surveillance and make it possible to aggregate EQA data with confidence, which will support the development of the EQALM central database. The EQALM central database aims to centralize EQA results from various EQA providers to answer questions that are hard to answer using data from a single EQA provider. The advantage of centralizing data from various EQA providers is that conclusions can be drawn from a multitude of EQA samples analyzed in a short time span on a global scale, and this helps to answer questions about post-market surveillance, performance assessment of examination procedures and harmonization between them.

Individual collaborative studies are supported by EQA providers circulating identical samples across multiple programs. An example is the INPUtS project of EQA organizers in Italy, the Netherlands, Portugal, the United Kingdom and Spain, in which the performance of 17 general chemistry measurands was investigated across countries and manufacturers [98]. A second project of the same group focused on the suitability of routine creatinine assays for clinical applications [99]. Another example is an international collaboration with EQA organizations from Australia, Germany and the UK, in which the same five samples were provided to the participating laboratories for quantitative examinations of the cytomegalovirus genome within a defined time window during the respective national EQA cycle [100].

Apart from *ad hoc* initiatives there can also be structural collaboration, e.g., EQA organizers in Australia, Belgium, France, Italy, Spain, and the Netherlands share a program on trace elements. Each organizer has too few participants but together they have a viable statistical basis, shared quality targets and a multilingual website for the submission of results and retrieval of reports [101, 102]. EQA organizations across Europe shared their experiences, initially through meetings of the Joint Commissions for Standardisation and later those convened by the Bureau Communautaire de Référence (BCR), leading to collaborations and international comparisons. A particular success story was for specific proteins, where UK-led comparisons demonstrated that inadequate calibration was the main source of variation, prompting the production and validation of a European Reference Material, CRM470 [103, 104]. A large-scale example is a collaborative project between the IFCC and 25 national EQA organizers in Europe, Asia and America on the determination of $HbA_{1c}$ [105]. Once a year, two commutable samples, targeted by the IFCC network of reference laboratories, are manufactured in one site and shipped in bulk to the national EQA organizers for distribution to their participants. The IFCC network coordinator aggregates the results to provide overviews (a) per country, (b) per manufacturer, and (c) per country per manufacturer (Figure 2). The assessment of reported results in such "super challenges" remains with the individual EQA provider, who forwards the anonymized results for further evaluation to the study coordinator. The large and

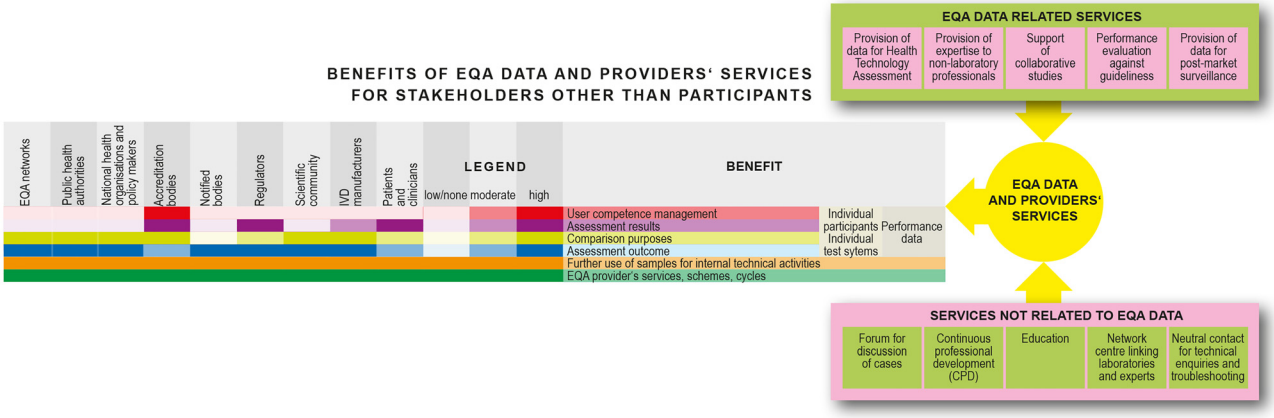


**Figure 1:** Benefits of EQA data and their providers' services to stakeholders other than participants. EQA data and providers' services offer benefit for participants as well as for other stakeholders; depending on the stakeholder, the benefit concerns six areas (EQA providers' services; further use of samples for internal technical activities; assessment outcome of individual test systems; for the purpose of comparing different test systems; assessment of results of individual participants; user competence management) that offer varying extent of benefits for them (high; moderate; low/none); >1 items per category (Table 1) or one extraordinary important item=high benefit; one moderately important item per category=moderate benefit.

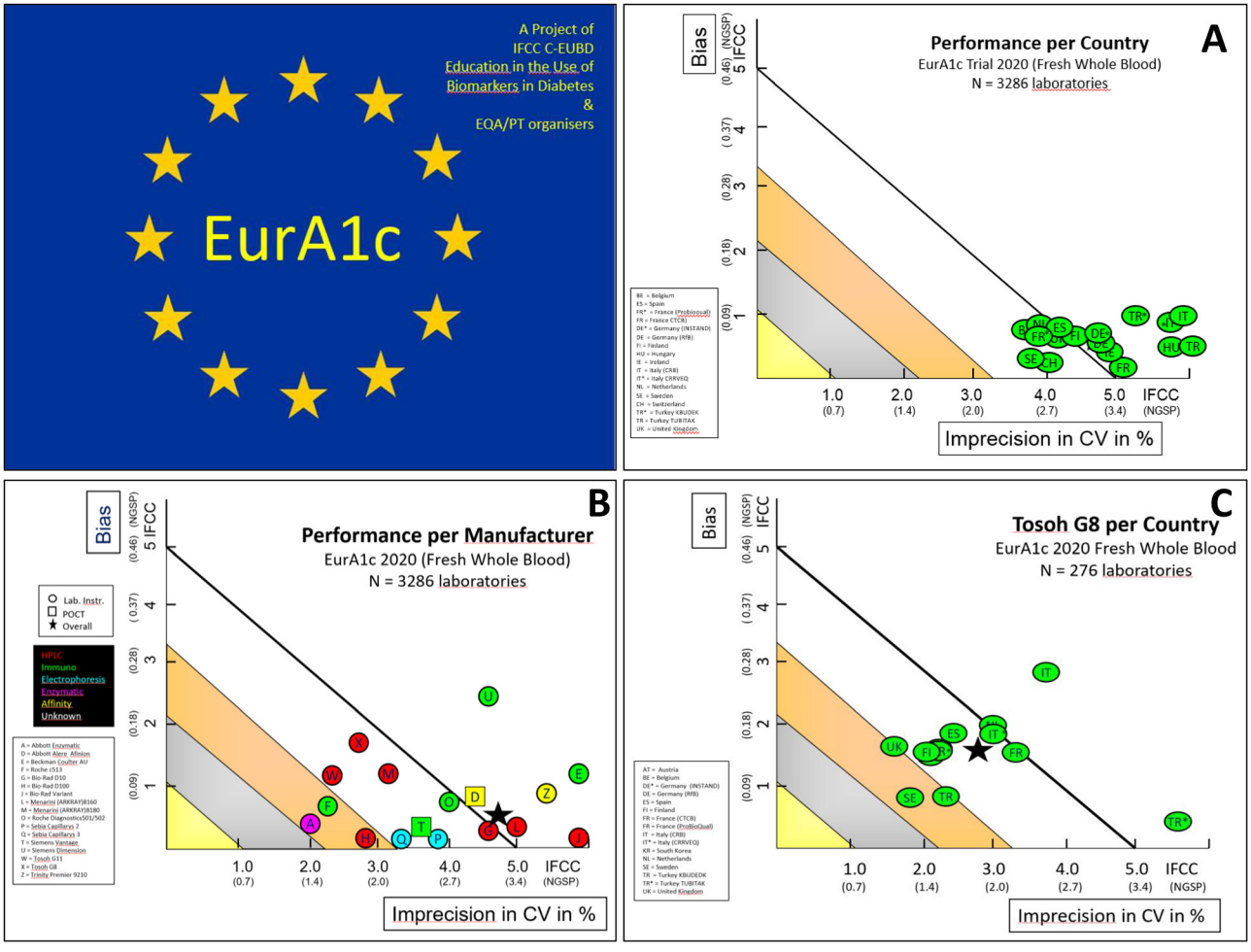


**Figure 2:** Overview of results of an EQA super-challenge including 3286 laboratories via 25 EQA providers. The Figure shows aggregations of the 3286 laboratories in the 2020 trial per country (A), per manufacturer (B) and per manufacturer per country (C) in the framework of the IFCC model for quality targets. The imprecision (between laboratory CV in %) is on the horizontal and the bias (difference from the target) on the vertical axis. The white, amber, gray and yellow triangles enclose areas for performances at a minimum, bronze, silver and gold level [104].

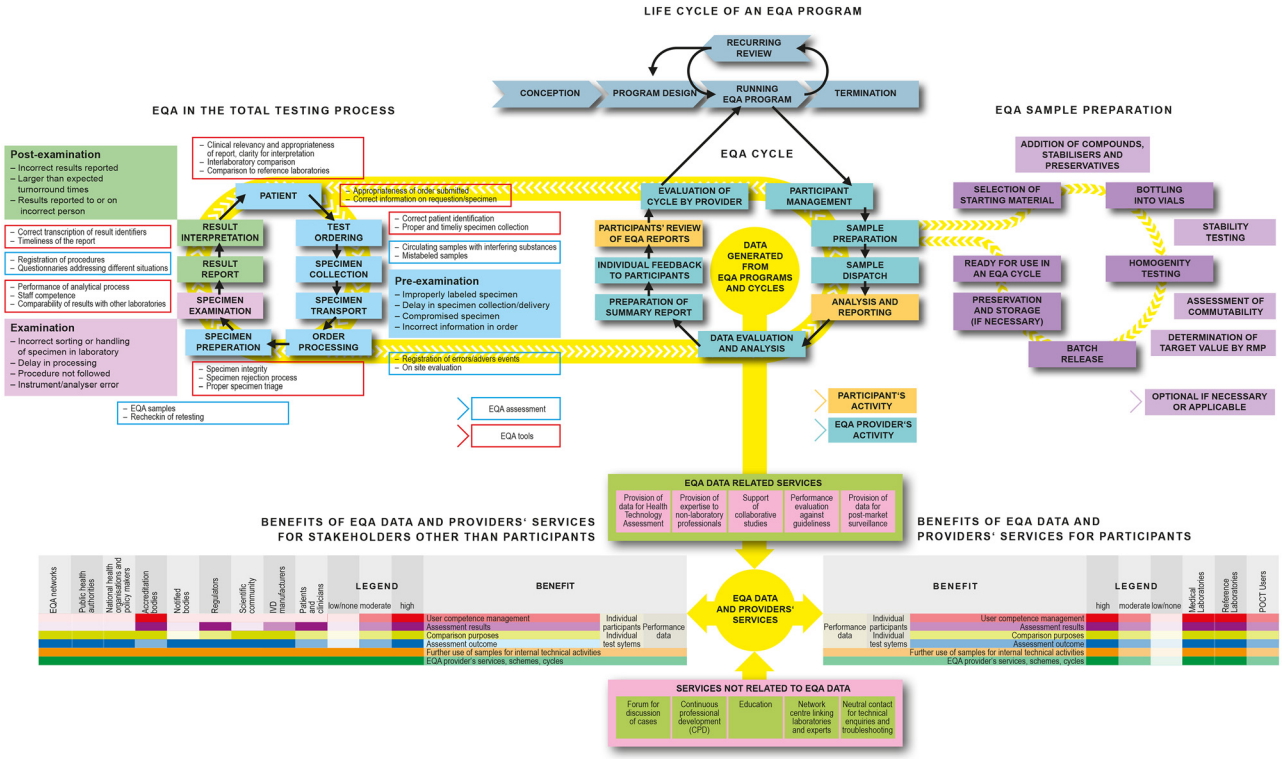


**Figure 3:** Laboratory total testing process, EQA programs, cycles and sample preparation, and benefits of EQA for participants and stakeholders other than participants. Relationship of the laboratory total testing process, EQA cycles including, the preparation of samples used in them, and EQA programs, and the benefits that EQA provides to participants and stakeholders other than participants.

international scale provides pressure to improve, when required. And it works: from year to year poor methods are removed from the market and replaced by improved systems. EurA1c demonstrates the power of collaboration between EQA organizers and might be a model for future development.

## Conclusions

After the properties of EQA programs, cycles and samples used in them, the benefits of EQA data and their providers' services for stakeholders other than participants were presented in this part of the article series (Figure 3). EQA data and the services of EQA providers enable many stakeholders to receive unique, important, and meaningful data that can only be obtained by aggregation of results that numerous participating laboratories have determined with many of the same and different test systems in identical samples. EQA providers, laboratories, the diagnostics industry and all other stakeholders should work together to maximize efficacy.

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