Review

Christoph Buchta*, Barbara De la Salle, Rachel Marrington, Stéphanie Albarède, Tony Badrick, Wolfgang Bicker, Andreas Bietenbeck, David Bullock, Vincent Delatour, Elisabeth Dequeker, Mira Flasch, Wolf-Jochen Geilenkeuser, Jaap van Hellemond, Jim F. Huggett, Viktoriia Ianovska, Patricia Kaiser, Martin Kammel, Anja Kessler, Nele Laudus, Peter B. Luppa, Pierre-Alain Morandi, Gavin O'Connor, Mauro Panteghini, Paola Pezzati, Jennifer Rosendahl, Sverre Sandberg, Heinrich Scheiblauer, Milan Skitek, Michael Spannagl, Anne Stavelin, Marc Thelen, Ursula Unterberger, Heinz Zeichhardt, Veronica Restelli and Lucy A. Perrone

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

Part IV – Benefits for participant laboratories

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Abstract: The main stakeholders in external quality assessment (EQA) programs are the participants, in whose interests these challenges are ultimately organised. EQA schemes in the medical field contribute to improving the quality of patient care by evaluating the analytical and diagnostic quality of laboratory and point-of-care tests (POCT) by independent third parties and, if necessary, pointing out erroneous measurement results and analytical or diagnostic improvement potential. Other benefits include the option of using EQA samples for other important laboratory procedures, such as the verification or validation of *in vitro* diagnostic medical devices (IVD-MDs), a contribution to the estimation of measurement uncertainty, a means of training and educating laboratory staff through educational EQA programmes or samples, or even for independent and documented monitoring of staff competence, such as on samples with unusual or even exceptional characteristics. Participation in an EQA scheme for beneficiaries like medical, microbiological and histo- and molecular pathology laboratories, users of POCT and self-testing systems as well as National Metrology Institutes, calibration laboratories and reference laboratories

***Corresponding author: Christoph Buchta**, Austrian Association for Quality Assurance and Standardization of Medical and Diagnostic Tests (ÖQUASTA), Hörlgasse 18/5, 1090, Vienna, Austria,
E-mail: christoph.buchta@oequasta.at. https://orcid.org/0000-0002-4153-8195
Barbara De la Salle, UK National External Quality Assessment Scheme (UK NEQAS) for Haematology, Watford, UK
Rachel Marrington, Birmingham Quality (UK NEQAS), Part of University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK. https://orcid.org/0000-0003-1045-8456
Stéphanie Albarède, Centre Toulousain Pour le Contrôle de Qualité en Biologie Clinique (CTCB), Toulouse, France
Tony Badrick, Royal College of Pathologists of Australasia Quality Assurance Program, Sydney, Australia. https://orcid.org/0000-0003-4846-9134
Wolfgang Bicker and Mira Flasch, FTC Forensic Toxicology Laboratory, Vienna, Austria
Andreas Bietenbeck, MVZ Ärztliche Laboratorien München-Land GmbH, Poing B, München, Germany. https://orcid.org/0000-0002-1228-0770
David Bullock, Former Director, Birmingham Quality, Former President, UK NEQAS, Sheffield, UK
Vincent Delatour, Laboratoire National de Métrologie et D'Essais (LNE), Paris, France
Elisabeth Dequeker and Nele Laudus, Department of Public Health and Primary Care, Biomedical Quality Assurance Research Unit, KU Leuven, Leuven, Belgium
Wolf-Jochen Geilenkeuser, Former, Reference Institute for Bioanalytics, Bonn, Germany
Jaap van Hellemond, Department of Medical Microbiology & Infectious Diseases, Erasmus MC University Medical Center, Rotterdam, Netherlands
Jim F. Huggett, National Measurement Laboratory, LGC, Teddington, UK; and School of Biosciences and Medicine, Faculty of Health & Medical Sciences, University of Surrey, Guildford, UK
Viktoriia Ianovska, NGO AQALM, Kyiv, Ukraine
Patricia Kaiser and Michael Spannagl, INSTAND E.V. Society for Promoting Quality Assurance in Medical Laboratories, Düsseldorf, Germany
Martin Kammel, INSTAND E.V. Society for Promoting Quality Assurance in Medical Laboratories, Düsseldorf, Germany; and GBD Gesellschaft für Biotechnologische Diagnostik MbH, Berlin, Germany
Anja Kessler, Reference Institute for Bioanalytics, Bonn, Germany
Peter B. Luppa, Institut für Klinische Chemie und Pathobiochemie, Klinikum Rechts der Isar, Technische Universität München, Munich, Germany

that are dedicated to specific tasks and have particular expectations of the EQA scheme are presented here.

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

Introduction

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

EQA's first and most important stakeholders are, of course, the participants, and only secondarily others, whose needs, benefits and wishes can be met if they do not conflict with those of the participants. As described below, participants benefit from having their examination results assessed by an independent third party, from having their results compared with those of other participants, and, if there are discrepancies or deviations between their results and those of others, from being advised to take appropriate corrective action. Furthermore, laboratories can use EQA samples to verify the suitability of IVD-MDs, utilise the complementary benefits of internal quality control and EQA, incorporate EQA results as a factor in estimating measurement uncertainty (MU), detect changes in performance over time, and develop and monitor staff competence with EQA samples and results. We also discuss the benefits of EQA for laboratories with special requirements or an unusual range of analyses, such as tests for rare diseases, infectious disease diagnostics, histo- and molecular pathology laboratories and users of point-of-care tests (POCT) and IVD-MDs for self-use. Finally, we discuss benefits of EQA for laboratories that are not directly involved in the routine analysis of patient samples, such as forensic toxicology laboratories and laboratories performing higher metrological order, rare or confirmatory analytical procedures that are unsuitable for routine use in clinical diagnostics, like National Metrology Institutes, calibration laboratories and the large and inhomogeneous group of reference laboratories. What all the different participants in EQA have in common is that they are interested in a global harmonisation of laboratory performance and examination results and support such developments through their participation. Such efforts are reflected in increased activity in various international laboratory benchmarking studies, such as those of the International Federation of Clinical Chemistry and Laboratory Medicine Working Group on Laboratory Errors and Patient Safety (IFCC WG-LEPS), the College of American Pathologists (CAP), and others [5] (Table 1, Figure 1).

EQA for medical laboratories

The International Standard ISO 15189:2022 requires laboratories to participate in interlaboratory comparison, usually through enrolment in appropriate EQA programs, and to use the outcome to improve future results and to correct past results where a significant impairment of results has been revealed [6] (Table 2).

EQA organisers should be aware of the ISO 15189:2022 requirements for laboratories. They must provide sufficient information about their programs to allow potential participants to select the program most appropriate to their needs. EQA programs should clearly identify the measurands, pre- and post-analytical aspects, define measurement ranges, document (limitations of) samples' commutability,

Pierre-Alain Morandi, Swiss Center for Quality Control (CSCQ), Chêne-Bourg, Switzerland
Gavin O'Connor, Physikalisch-Technische Bundesanstalt (PTB), Braunschweig, Germany; and Department of Biochemistry and Bioinformatics, Technische Universität Braunschweig, Braunschweig, Germany
Mauro Panteghini, Department of Laboratory Medicine, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Torun, Poland. https://orcid.org/0000-0002-7147-3433
Paola Pezzati, SOD Sicurezza e Qualità AOU Careggi Firenze, Florence, Italy
Jennifer Rosendahl, RISE Unit of Biological Function, Division Materials and Production, RISE Research Institutes of Sweden, Borås, Sweden
Sverre Sandberg and Anne Stavelin, The Norwegian Organization for Quality Improvement of Laboratory Examinations (Noklus), Bergen, Norway
Heinrich Scheiblauer, IVD Testing Laboratory, Paul-Ehrlich-Institut, Langen, Germany
Milan Skitek, University Medical Centre Ljubljana, Clinical Institute of Clinical Chemistry and Biochemistry, Ljubljana, Slovenia
Marc Thelen, Foundation for Quality Assessment in Laboratory Medicine (SKML), Nijmegen, The Netherlands; and Department of Laboratory Medicine, Radboud Medical Center, Nijmegen, The Netherlands. https://orcid.org/0000-0003-1771-669X
Ursula Unterberger, Center for Anatomy and Cell Biology, Medical University of Vienna, Vienna, Austria
Heinz Zeichhardt, INSTAND E.V. Society for Promoting Quality Assurance in Medical Laboratories, Düsseldorf, Germany; and IQVD GmbH, Institut für Qualitätssicherung in der Virusdiagnostik, Berlin, Germany
Veronica Restelli and Lucy A. Perrone, Canadian Microbiology Proficiency Testing Program (CMPT), Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, Canada. https://orcid.org/0000-0003-2185-688X (L.A. Perrone)

Table 1: Benefits of EQA data and EQA providers' services for participants.

Feature: Participant Group	Further use of samples for internal technical activities	EQA providers services, programs, cycles	Data on performance of			
			Individual examination procedures/IVD-MDs		Individual participants	
			Assessment outcome	Comparison purposes	Assessment results	User competence management
Medical laboratories and additional benefits for infection diagnostics, and histo- and molecular pathology	Verification of examination procedures and IVD-MDs Measurement uncertainty calculation	Fulfilment of obligation to participate in interlaboratory comparison Publications presenting and interpreting EQA data Independent technical advice Confidential handling of data and assessment results of the participants	Identification of IVD-MDs with suboptimal performance (unsafe, ineffective)	Comparison of performance of own with other IVD-MDs Extent of harmonisation between methods	Professional third-party evaluation of accuracy of results Objective quality indicator for analytical performance Monitoring laboratory performance over time	Education Means for checking employees competence
Additional benefits for national metrology institutes, calibration and reference laboratories	Basic research on sample materials	Joint processing of scientific questions	Evaluation and comparison of the methods	Comparison with peers Comparison with different methods	Proof of competence to third parties	Evaluation and comparison of methods, especially in the case of challenging samples
POCT users		Being part of the user community of such IVD-MDs	Recognizing the overall performance of the IVD-MD used	Comparison of the performance of the IVD-MD used with that of others	Evaluation of the accuracy of results	Recognizing major operational challenges that impact the reliability of results

EQA data and providers' services offer benefit for participants; the benefits concern six areas (further use of samples for internal technical activities; EQA providers' services, programs, cycles; assessment outcome of individual IVD-MDs; for the purpose of comparing different IVD-MDs; assessment of results of individual participants; user competence management) at varying extent (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.

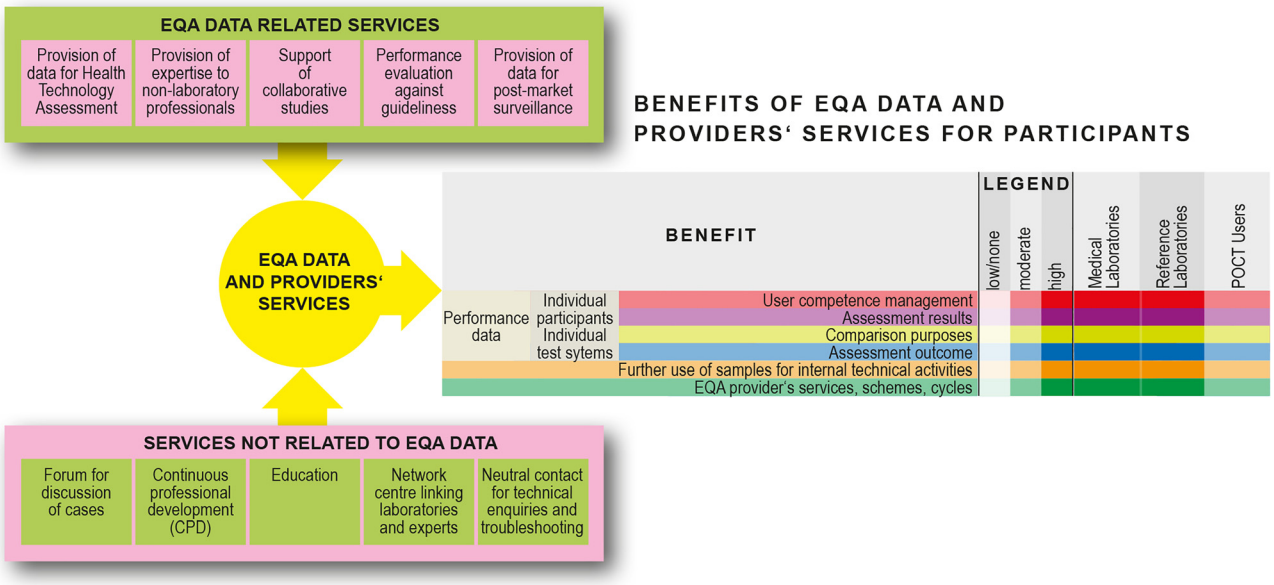

Figure 1: Benefits of EQA for participants. EQA data and providers' services offer benefit for participants; the benefits concern six areas (further use of samples for internal technical activities; EQA providers' services, programs, cycles; assessment outcome of individual IVD-MDs; for the purpose of comparing different IVD-MDs; assessment of results of individual participants; user competence management) at varying extent (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.

Table 2: Requirements in ISO 15189:2022 section 7.3.7.3 on external quality assurance.

The laboratory shall monitor its performance of examination methods, by comparison with results of other laboratories. This includes participation in EQA programmes appropriate to the examinations and interpretation of examination results, including POCT examination methods.
– This means that laboratories are required to participate in EQA for all activities and have to establish when they consider an EQA program 'appropriate'.
The laboratory shall establish a procedure for EQA enrollment, participation and performance for examination methods used, where such programmes are available.
– This means that laboratories are required to define criteria for selection of an EQA program/provider and performance evaluation in that EQA.
EQA specimens shall be processed by personnel who routinely perform pre-examination, examination, and post-examination procedures.
– This means that laboratories have to organise that their performance in EQA can be considered representative for that in patient care and should also cover non-examination phases.
EQA data shall be reviewed at regular intervals with specified acceptability criteria, in a time frame which allows for a meaningful indication of current performance.\
– This means that laboratories are required to evaluate their EQA performance and translate and evaluate the impact on patient care.
Where EQA results fall outside specified acceptability criteria, appropriate action shall be taken (see 8.7 nonconformities and corrective actions), including an assessment of whether the non-conformance is clinically significant as it relates to patient specimens.
– This requires laboratories to translate impact into both future (improvement actions) and history (correct prior patient results and communicate such corrections to requestors).
Where it is determined that the impact is clinically significant, a review of patient results that could have been affected and the need for amendment shall be considered and users advised as appropriate.
– This requirement is a further clarification of the previous one.
– There is also an important 'should' statement on EQA in 7.3.7.3. 'should' statements do not identify requirements, but directions to good practice.
– The notes in the quote from 7.3.7.3e make further explanation unnecessary.
When selecting EQA programme(s), the laboratory should consider the type of assigned value offered. Assigned values are:
1) Independently set by a reference method, or
2) Set by overall consensus data, and/or
3) Set by method peer group consensus data, or
4) Set by a panel of experts.
NOTE 1 when method-independent assigned values are not available, consensus values can be used to determine whether deviations are laboratory- or method-specific.
NOTE 2 where lack of commutability of EQA materials can hamper comparison between some methods, it can still be useful for comparisons to be made between methods for which it is commutable, rather than relying only on within-method comparisons.

specify the target values' type and source and have a documented rationale for the tolerance limits [7].

ISO 15189:2022 clearly explains that the purpose of interlaboratory comparison is not the comparison itself but the use of its results to check the validity of the laboratory results. That implies responsibility for both participants and EQA providers. When the results are acceptable, the laboratory can continue the current execution of the particular examination procedures, but corrective action should be considered when results are outside acceptable limits. However, before a laboratory embarks on corrective action, it needs to verify that the action is appropriate.

If an EQA provider considers an EQA suitable for trueness verification, the laboratory may employ the EQA samples and results for examination method verification and/or validation [8]. ISO 15189:2022 requires laboratories to verify claims of their validated examination methods and to validate their laboratory-developed tests (LDTs) as fit for the intended use. EQA, therefore, can have a role in method verification.

Using EQA for verification of IVD-MD suitability

Verification requires sufficient objective evidence to determine that a marketed IVD-MD fulfils the requirements as specified by the manufacturer [9], and EQA programs are essential to the post-market surveillance of IVD-MDs [10]. To fulfil this task, EQA must meet certain requirements [8].

Firstly, the EQA material commutability must be known [11]. Use of non-commutable EQA materials prevents the direct comparison of laboratory EQA performance to the measurement performance of patient specimens [12]. Using non-commutable EQA materials has been justified for demonstrating that the employed IVD-MD is similar to other IVD-MDs using the same measurement procedure. However, as healthcare professionals, we should expand our horizon to know whether the quality of laboratory measurement results is suitable for clinical use, independent of the IVD-MD type and the simple fulfilment of the manufacturer's specifications [13]. A working group of the European Federation of Laboratory Medicine (EFLM) has stressed the need that EQA providers should specify that material matrix and its commutability, because the interpretation of differences between results in an EQA program is strongly dependent on the nature of the survey material [7]. A recent publication by the WG-commutability in IFCC describes in detail how to assess the commutability of EQA material [14].

Assigning values to EQA materials with higher-order measurement procedures (MP) is the second requirement. For measurement results traceable to the International System of Units (SI) (as described in the three first calibration hierarchy models of ISO 17511:2020) [15], assigning values by the reference measurement procedure (RMP) to commutable EQA materials ensures the objective evaluation of performance through a trueness-based grading, therefore providing invaluable information about the correct implementation of metrological traceability and standardisation of results. It has been argued that this approach is not replicable for measurands where an RMP is lacking. The classic approach using the "peer group" EQA performance assessment is commonly used in this case. However, a drawback of this approach is the definition of "peer group", which may be heterogeneous between different EQA providers [16].

Finally, the EQA performance should be evaluated against clinically suitable limits. Defining analytical performance specifications (APS) regarding metrological traceability is a relatively new science. A consensus conference in 2014 concluded that APS derivation should be based on three models: clinical outcome, biological variation, or state-of-the-art [17] criteria for allocating measurands to these models were elaborated, and recommendations for MU APS were proposed [18].

EQA that meets metrological criteria has unique benefits that add substantial value to the practice of laboratory medicine (Table 3), e.g., the standardisation of glycated haemoglobin [19].

Table 3: Unique benefits of EQA meeting metrological criteria.

– Giving objective information about clinical suitability of laboratory performance
– Serving as management tool for the medical laboratory and IVD manufacturers, forcing them to investigate and eventually fix the identified problem
– Creating evidence about intrinsic harmonisation status of the examined IVD-MDs
– Helping those manufacturers that produce IVD-MDs to demonstrate the superiority of those products
– Identifying measurands that need improved harmonisation and stimulating and sustaining standardisation initiatives that are needed to support clinical practice guidelines
– Abandonment by users (and consequently by industry) of IVD-MDs with demonstrated insufficient quality

Adapted from Ferraro et al. [13].

The relationship between internal quality control and external quality assessment in laboratory medicine

Internal quality controls (IQC) are conducted at least daily for each analyte. A higher frequency is possible for measurements whose stability might otherwise pose a risk for the patients. Therefore, consumption and cost of IQC materials is considerable. Many laboratories use less expensive IQC materials supplied by the assay manufacturer or non-commutable control materials with assay specific target values [20]. In the chain of traceability, these types of IQCs are linked to the primary reference material or reference method through the same higher order measurements as the assay itself. An error at the assay manufacturer propagates to the IQC target values as well and cannot be detected. IQC is primarily used to monitor analytical stability in the laboratory only. EQAs with values assigned with a RMP can provide an independent link to the SI units and the primary reference material or reference method and guarantee traceable measurements over a longer time-period.

IQC results should be interpreted together with EQA performance of programs using commutable materials to detect lot-to-lot variation without any sophisticated statistical and mathematical evaluation [16, 21]. While commutability of EQA materials is required in category 1, 2, 3 and 4 EQAs, it is not a prerequisite to evaluate the stability of an examination procedure. However, IQC materials non-commutability should not result in a biased estimate of imprecision and therefore of MU [22]. The providers of reference and control materials for the next generation of *in-vitro* diagnostics should assess the commutability of those materials before their use. Origin of materials may influence the responsibility of assessing commutability. Certified reference material (CRM) suppliers are expected to assess the commutability of their products if they intended to serve as viable calibrators in a calibration hierarchy [15]. There are different responsibilities for control materials: The commutability of EQA materials should be assessed by the EQA provider, while the commutability of IQC materials (if the material is used for uncertainty estimation) is, at least nowadays, the responsibility of the end user [23–25].

Some data-driven quality control programs shift the boundaries between internal and external quality control. An example presented in part I of this manuscript series uses patient medians to monitor analytical quality [1].

Use of EQA results for the calculation of measurement uncertainty

Specification of MU of a laboratory examination method allows clinical laboratories and clinicians to evaluate the quality of test results based on an identifiable performance characteristic. High levels of trueness of laboratory results are required when sharp guideline-driven clinical decision limits are applied, as e.g. HbA1c in the diagnosis of diabetes and cholesterol in classification of low or high risk for coronary heart disease. It was shown that an analytical bias of 2 % resulted in a doubling of false positives in HbA1c and cholesterol screening [26]. To counteract this, recommendations have been made regarding the maximum tolerable measurement uncertainties [27].

Different approaches have been proposed to determine the MU mainly using imprecision (note: different coverage factors are in use), but some formulas also take into account the bias as a component of the MU. An essential requirement to properly evaluate bias is to use commutable EQA materials value assigned with a RMP. As both conditions are difficult to meet, bias estimation can be flawed. Whether bias is included or not in calculation of MU, bias needs to be taken into account in the overall communication of uncertainty of result to a clinician. This is where EQA plays a significant role in equipping the laboratory with such information. EQA schemes involve testing of identical samples with many laboratories using different established test systems. It is important to note that the observed variance of interlaboratory comparison results is relevant only when commutable EQA materials are used. However, this only allows conclusions to be drawn about the MU of a laboratory or an analysis method under certain conditions and with restrictions [28]. Although ISO 15189:2022 requires laboratories to consider the MU when verifying or validating a method and that the MU is regularly reviewed, it does not explicitly state how the MU should be calculated. However, guidance on this can be found in ISO/TS 20914:2019 [29].

Use of EQA results to monitor laboratory performance over time

EQA organisers accumulate large amounts of data, which have been used to demonstrate the improvement of laboratory analytical performance over time for specific parameters [30–33]. Several reasons could contribute to improvement:

(i) the awareness of the importance of providing high quality results, which is promoted by the accreditation of the laboratory according to ISO 15189:2022 [34], (ii) the approach of using state-of-the-art examination methods, (iii) the harmonisation of examination procedures [30], (iv) possible recognition that other laboratories have achieved better results with the same method, or (v) following comments or advice of the experts at the EQA provider. EQA data also show a correlation between the laboratory's good performance and regular participation in EQA programs [33, 35–37]. To assist participants in their long-term retrospective performance evaluation, some EQA providers plot the history of relative deviations of their results from the assigned value of past cycles so that any patterns (e.g. systematic or fluctuant biases) can be recognised and evaluated (Figure 2).

Use of EQA samples and results to develop and monitor staff competence

Participation in EQA, from sample preparation, examination and results submission to reviewing the report, can be used for continuous professional development (CPD) for laboratory professionals [1]. To monitor staff competence, EQA samples can be analysed by several laboratory employees. Each employee's results are collected by their supervisor and one person's results are selected to be reported to the EQA provider. Results obtained by other employees are compared with the targets once they are published at the end of the EQA cycle. Discussing the results and analysing any deviations and their causes is valuable for staff training and professional development. EQA programs are currently being developed that allow or even encourage group registration by an employer.

Benefits for participants in exceptional times

The role of EQA providers is crucial during military conflicts when medical laboratories face numerous challenges. For example, during the war in Ukraine, the country's infrastructure, including the medical sector, was severely damaged [38]. Laboratories in the affected regions faced a lack of power supply, a shortage of reagents, damaged equipment, and a lack of sufficient staff. Communication and logistics between institutions led to professional separation. However, conditions required prompt restructuring of laboratory tests and strengthening of rapid diagnostics, including for infectious diseases that can spread rapidly, bringing it closer to the combat zone and its unconditional quality. In such difficult conditions, the EQA provider continued its operation and united the professional laboratory community, ensuring the quality of laboratory tests, communication on various laboratory support, and unconditional moral support.

EQA for analyses for rare diseases

In addition to the requirements shared by all medical laboratories, laboratories performing analyses for rare diseases (i. e., diseases with a prevalence of less than 5 in 10,000 in Europe [39]) face particular challenges concerning EQA. A typical problem is the general scarcity of patients and, thus, limited availability of unadulterated samples that could be used as EQA materials. Indeed, EQA materials are often needed in relatively large quantities in many biological and immunological analyses. Patient specimens may then be in a less-than-ideal condition, e.g., due to non-standardized pre-examination processing. They may not be available in the quantities required by the laboratory, especially for infants and children. Furthermore, EQAs are not available for many diseases, even as international programs.

In general, frequent participation in EQA is desirable because positive patient diagnoses may be rare for many diseases and the functioning of an IVD-MD is only tested against specific positive controls. Also, LDTs are frequently used, and standardised methods are lacking. These issues are relevant in biochemical and immunological examination and genetic testing. Low annual test volumes for rare diseases or critical analyses, such as prenatal or preimplantation testing, require participation in many EQAs to maintain and demonstrate competency [40].

Finally, assessment of pre- and post-examination steps is beneficial in rare diseases, as there is often little or no specific knowledge of factors affecting the collection and transport of specimens, as well as the understanding, interpretation and efficient communication of results by the laboratory. EQA programs exist for rare diseases. A particular example is the EQA for porphyria supported by the International Porphyria Network (Ipnet) [41].

Additional benefits of EQA for infection diagnostics

The disciplines summarized under infection diagnostics–bacteriology, mycology, virology and parasitology–represent a very inhomogeneous field in terms of the types of

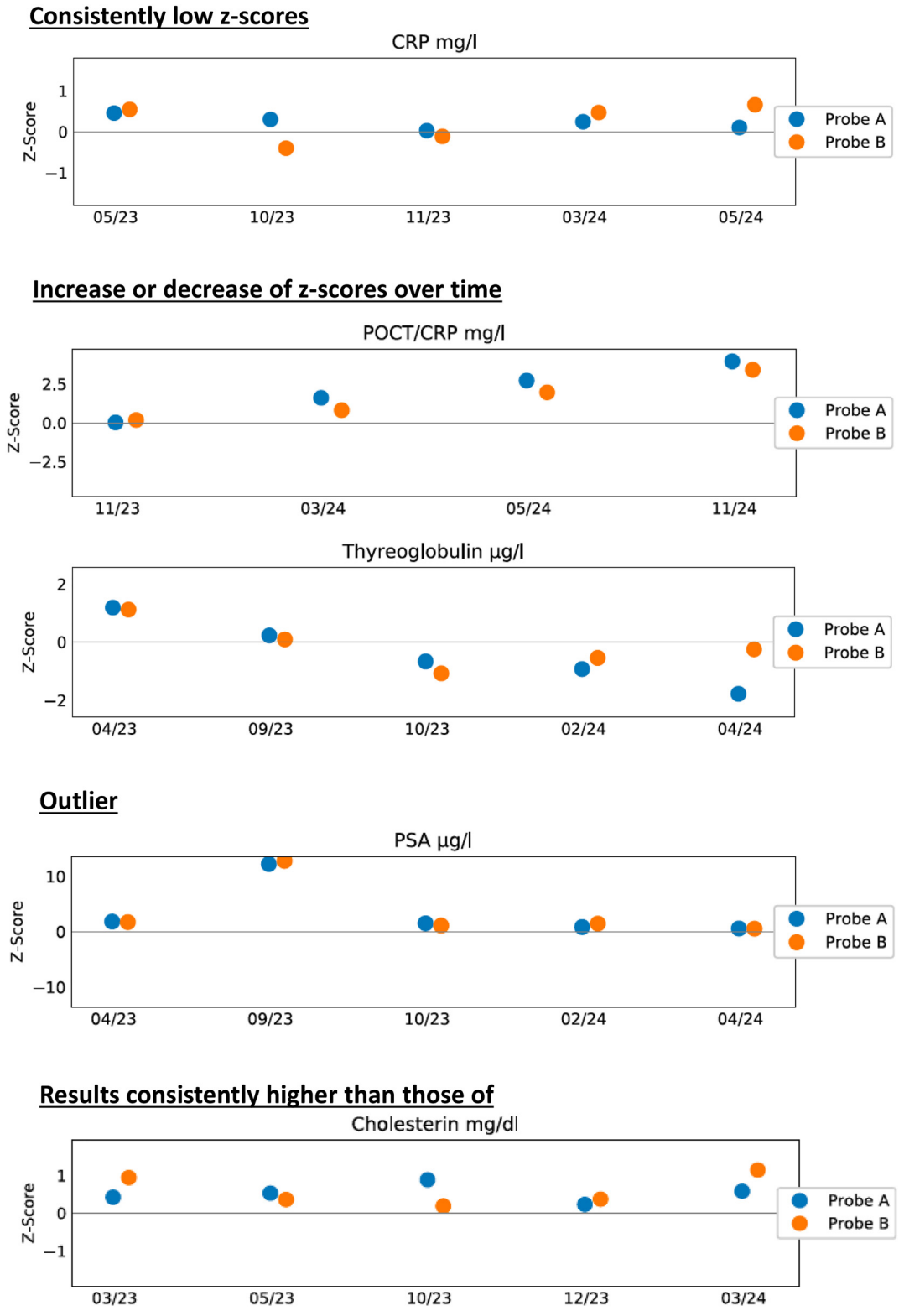

Figure 2: Development of z-scores of selected individual measurement results as reported by participants over several consecutive EQA cycles. EQA programs provide information on the deviation of a laboratory's results from the respective target value over time. The representation of the deviations as a z-score enables their evaluation independently of the respective level of the measurand in the EQA sample.

agents analyzed. Bacteria, fungi and parasites are living organisms with their own metabolism and the ability to replicate independently. Viruses, on the other hand, are not regarded as living organisms, but as 'close to life', as they are dependent on the metabolism of a host cell, but have the ability to control their replication and are capable of rapid evolution. In infection diagnostics, pathogens can typically be detected and specified, but their presence in the patient or in the sample provided by the patient cannot be completely ruled out by a laboratory test. Screening tests used in the examination of symptom-free individuals are often misinterpreted by the public as being suitable for ruling out an infection, a disease and infectivity. Due to the different nature of infectious agents, different laboratory diagnostic methods are used to detect them: Direct detection can be achieved by visual recognition under a microscope, by multiplication of the pathogens using culture methods or amplification of their RNA or DNA, by biochemical properties (color reactions due to the metabolism of the pathogen, resistance to antibiotics), while indirect detection uses reactions of the host's immune system as evidence of infection or to classify the state of the disease. According to the diversity of pathogens and their properties, EQA programs are designed with different goals and tasks for the participants. What they all have in common is that the benefit of the interlaboratory comparison for the participants lies in the fact that they are confronted with pathogens with which they may never or only very rarely come into contact in their everyday professional life. However, it may be challenging or even impossible for EQA providers to introduce all infectious agents into EQA programs and samples without exposing people to the risk of infection during transport or handling in the laboratory. Highly pathogenic pathogens can be inactivated in EQA samples for special diagnostic panels and can still be detected visually (parasites) or by DNA/RNA amplification methods or protein detection. An example of this is a report on a panel for the detection of a number of pathogens, none of which one would want to have in infectious form in the common diagnostic laboratory for microbiology: Chikungunya virus, Crimean-Congo hemorrhagic fever virus, dengue virus, Ebolavirus, Lassa virus, Marburg virus, West Nile virus, yellow fever virus, *Bacillus anthracis*, *Francisella tularensis*, *Leptospira* spp., and *Yersinia pestis* [42]. Therefore, inactivated EQA samples are of significant importance for verification, not least because they come from an independent third party and not from the manufacturer of the IVD-MD.

In the context of infection diagnostics, false negative test results or incorrectly identified pathogens can easily have serious consequences for un- or misdiagnosed individuals and their environment as they can spread the infection. Therefore, low positive EQA samples are desirable to fulfil the requirement of ISO 15189 to provide samples that mimic patient samples for clinically relevant challenges. The following describes the benefits of EQA for medical laboratories that perform infection diagnostics among other disciplines. They are required to at least identify samples as suspicious and, if necessary, to initiate further examinations. Such further examinations are carried out by specialized, expert or reference laboratories that are authorized, if necessary, to handle and examine infectious agents requiring Biosafety Levels 3 and 4 [43]. EQA and interlaboratory comparisons between these laboratories are described in the section *National Metrology Institutes, calibration and reference laboratories*.

Bacteriology and mycology

Reliable and accurate characterization and interpretation of microbiological specimens are impacted by many variables in a laboratory setting and the field of microbiology continues to evolve rapidly each year. EQA providers can start by supporting microbiology laboratory quality by including a patient case history with each EQA sample which should guide the laboratory's processing and interpretation of results. Evaluation of results then depends on the specific case and microorganism combination. This usually requires an interpretation of participant results and consensus of opinion on grading by expert committee review (composed by experienced and actively practising microbiologists) (Table 4). Samples and challenges are designed to ensure laboratories report normal flora or contamination as such, and that the final results report is clinically relevant. New organisms are frequently recognized and associated with new disease states, and new methods are developed for their detection or screening (e.g. *Candida auris*).

Challenges should also be designed to check laboratories' adherence to current guidelines and the appropriateness of participant antimicrobial susceptibility results reporting. New interpretation and reporting guidelines are published frequently by professional and standards organisations such as CLSI, EUCAST, and ISO and so it can be challenging for working laboratories to keep up to date with the flow of new information. For example, the Guidelines for the Detection and Identification of Group B *Streptococcus* were first published in 1996, updated in 2002, 2010, 2020 and 2021 directly impacting the role of the laboratory in the reporting of results [44]. By participating in EQA challenges that are designed to test the interpretation of results beyond the analytical aspect, laboratories make sure their interpretation of results are aligned with current guidelines, local regulations, and latest taxonomy changes.

Table 4: Example of a grading scheme for microbiology EQA.

Grade	Interpretation	Definition and examples
4	**Full value**	Accepted by the committee as the correct answer either in terms of current nomenclature or in terms of appropriate clinical relevance, including listing pathogen-specific negative results, correct antimicrobial profile reporting and/or descriptive reporting, e.g. MRSA, ESBL producer, VRE, and notification of public health, i.e., *Salmonella* from a stool sample.
3	**Essentially correct or acceptable**	A nomenclature or susceptibility error, generally at the species level, not technically correct but would have little or no clinical impact. A deviation from what is considered the most clinically relevant result, but one which would pose little difficulty in interpretation of the sample's report. For example: *Staphylococcus hominis* vs. *Staphylococcus epidermidis; Enterobacter aerogenes* vs. *Enterobacter cloacae; Plasmodium vivax* vs. *Plasmodium ovale;* susceptible vs. intermediate, and excessive over-reporting of susceptibility testing results (calculated as minus-1 from the full value).
2	**Separator**	To augment the difference between the two grading groups.
1	**Incorrect or unacceptable**	A nomenclature error that would be wrong at the species level, but by reporting may have an impact on clinical interpretation and potentially a treatment error. A major susceptibility error. A clinical relevant result that could lead to a diagnosis or treatment error. For example: *Corynebacterium jeikeium v*s. diphtheroids; *Staphylococcus aureus* vs. *Staphylococcus epidermidis.* Identify VSE as VRE. Reporting the presence of *Neisseria meningitidis* from a throat swab.
0	**Very incorrect or very unacceptable**	A nomenclature error that would be wrong at either the genus or species level or a very major susceptibility error that could result in a significant interpretation or treatment error. A clinical relevance result that could lead to a major diagnosis or treatment error. For example: *Salmonella* species vs. *Citrobacter* species; *Escherichia coli* vs. *Shigella dysenteriae; Burkholderia cepacia* vs. *Pseudomonas aeruginosa;* identify *Neisseria meningitidis* in a blood culture as a contaminant; identify VRE as VSE. Reporting *Staphylococcus aureus* and *Escherichia coli* in a mixed blood culture as 'probable contaminants'.

Although historically microbiology lagged behind other laboratory disciplines in the implementation of new technologies, this has changed dramatically with the implementation and saturation of MALDI-TOF instruments in medical laboratories and also the emergence of molecular technologies for genetic identification. Although these technologies are now used routinely in the laboratory, there are still pitfalls, and a thorough validation needs to be performed with each assay. Importantly in the field of microbiology, participation in EQA may be the only chance laboratories have to become familiar with a rare organism and to test their ability to isolate and identify organisms that are rarely isolated and may never reach a laboratory if not for a EQA sample. Microbiology laboratories and their personnel should not blindly trust results without EQA participation.

Virology

The focus in microbiological-bacteriological diagnostics is on pathogen and resistance determination, and serological diagnostics are of lesser importance. In virus diagnostics, however, pathogen detection is of equal importance as determination of specific immune responses. Accordingly, EQA programs for virological purposes are designed so that participants receive samples in which they can detect either one (or more) viral pathogens or specific antibodies against a particular virus. In addition to assessment of reported results, EQA for virus detection can also provide participants and manufacturers with information on sensitivity, specificity and linearity of their test systems [45]. Unpublished data indicate clinically relevant discrepancies between the results obtained by infection diagnostic IgG and IgM assays from different manufacturers. Even if EQA providers cannot offer a solution to this, they can still repeatedly draw the attention of participants (and manufacturers) to this fact in summary reports written in connection with completed EQA cycles and thus sensitise them to any strange constellations of results that inevitably occur in routine patient diagnostics. Several other features offered by virology EQA are described in Part V of this manuscript series [4].

Parasitology

Although DNA amplification techniques are increasingly used, manual microscopic examination is often used as an all-round method for the direct detection of parasites in clinical specimens because parasites are relatively large microorganisms and often difficult to culture. In addition, some serological assays are used to indirectly detect invasive parasitic infections. As discussed above, EQA is beneficial for all medical laboratories and for those that perform examinations to detect parasitic infections for the following two

specific reasons. (i) Although parasitic infections are worldwide very abundant, the large number of species and the differences in their endemic areas, pose a challenge for diagnostic laboratories as most parasite species will only be detected on rare occasions, and therefore, exotic EQA specimens are not only crucial for assessment of the competence of the laboratory staff but also to detect the knowledges gap that can subsequently be addressed by education [46]. The recent developments in virtual microscopy and its use in EQA provides new opportunities for detailed and personal feedback, which is of high educational value. (ii) Because the parasite load in clinical specimens is low compared to other pathogenic microorganisms, both the pre-analytical concentration methods and the subsequent DNA extraction methods are critical for optimal parasite detection by DNA amplification techniques. EQA schemes for the detection gastro-intestinal protozoa and helminths in stool as well as for *Acanthamoeba* spp. in corneal scrapings, have demonstrated an enormous difference in detection efficiency between laboratories and not only notifies medical laboratories on their poor efficiency performances but can also provide information on which part of their examination process should be improved (DNA isolation or DNA amplification) [47, 48]. (iii) Due to the immune regulatory properties of parasites and their complex antigenicity, most serological assays to detect invasive parasites cannot use a single or small set of recombinantly expressed proteins as antigen(s) as this will result in a poor sensitivity. Instead, serological assays to detect invasive parasites are often based on antigens prepared from purified fractions of parasites. Therefore, serological assays to detect parasitic infections not only differ in technological set up (e.g. agglutination, ELISA, western-blot, etc.), but also on the type of antigens used and the procedure by which these fractions are produced. Since EQA schemes are in fact a longitudinal inter-laboratory comparison study, EQA is the most powerful tool to evaluate the performance of distinct serological assays.

Additional benefits of EQA for histo- and molecular pathology laboratories

Histopathological, immunohistochemical and molecular genetic testing play a crucial role in enabling personalised medicine and it is therefore common practice to use all available means to ensure the reliability of results, including EQA. To cover pre-analytical, analytical and post-analytical processes, it may be necessary to subscribe to several EQA programs [49].

Since the performance of pre-analytic procedures, like cutting, extraction and staining, is crucial for further examination, the suitability of the sample material for the intended purpose of the EQA program or the individual sample should be verified. If the program is focused on the examination of biomarkers, liquid samples with extracted DNA/RNA may be used. However, if the performance of nucleic acid extraction methods should be assessed, formalin-fixed paraffin-embedded (FFPE) tissues should be used, which also should be used for the assessment of technical parts of the pre-examination process, like cutting sections or staining methods. In such cases, the participants cut and stain the samples or extract nucleic acid from them according to their routine procedures. The processed samples may be returned to the EQA provider for assessment.

Research has shown that participation in an appropriate EQA program soon after the introduction of a new biomarker in the laboratory improves performance by aiding the detection of assay errors, pitfalls, or weaknesses of the new biomarker [50]. As new biomarkers are continuously evolving, EQA can support laboratories in the examination part of their testing process by incorporating such newly established biomarkers promptly. Even though it is a challenge for EQA providers to integrate these into their proficiency testing programs at an early stage, it is still a great benefit for the participants.

In addition to new biomarkers, new developments and trends should also be quickly implemented in EQA programs. One such challenge is the introduction of machine learning and artificial intelligence into routine practice and the management of the associated big data. The current shift in pathological diagnostics from a laboratory-based to an individual approach should be reflected in EQA programs.

The development in digital pathology should also be reflected in the EQA in order to be able to identify challenges and abnormalities of this technique at an early stage. Some providers no longer include wet samples but solely provide digital samples, which allows them to present the identical original cases to all participants. This is beneficial for rare cases and for large EQA programs since it is often impossible to provide each participant with samples of the same tissue block.

EQA programs support the competence management of staff in a pathology laboratory. A clear advantage of EQA in pathology is the possibility to evaluate the uniformity of the interpretation of the results by several pathologists. This can involve both uniformity of the description of the tissue and,

in particular, possible different semi-quantitative information, such as staging in oncological diagnostics or the description of the extent of the dysplasia. Findings from such EQA programs can be translated into training sessions later on and contribute to (inter)national guidelines.

In summary, EQA offers a comprehensive range of benefits for histo- and molecular pathology laboratories regarding pre-examination, examination and post-examination processes. International collaboration projects between EQA providers, like the updated EQA guideline for biomarker examination in medical oncology by Dufraing et al., support harmonisation between EQA programs [51].

Benefits for users of point-of-care testing (POCT) devices

Point-of-care (POCT) testing devices (or near-patient (NPT) testing devices as specified in the European *In-vitro* Diagnostic Medical Device Regulation (IVDR)) may be electronic devices or manual tests, including rapid tests that use e.g. lateral flow technology [52]. As the users of POCT systems are usually not laboratory technicians, the IVDR requires such devices to be unaffected by external influences and independent of maintenance and calibration activities by operators, so that they can be used even without laboratory-specific training and the responsibility for the accuracy of the results is assigned exclusively to the POCT IVD-MD [52–55].

POCT systems are used both in hospitals for analyses outside the central laboratory and in healthcare facilities outside hospitals. As required by ISO 15189, central laboratories are increasingly assuming responsibility for the operation of POCT applications in hospitals and provide POCT coordination teams of technicians for this purpose. However, the integration of POCT applications in healthcare facilities outside hospitals into a network with a POCT coordinator, expert advice available and a quality management system is not yet widespread. EQA providers may therefore be the only competent contact for these POCT users besides the manufacturer and they may have an additional role for them, see "*EQA providers networks*" in [4].

Just as manufacturers of IVD-MDs intended for POCT use must design the analysis systems so that they can be operated without in-depth laboratory training, EQA providers must also design their schemes so that they can be carried out by healthcare personnel other than laboratory experts and the reports are presented in an understandable manner. For example, it should be easy to understand whether an unacceptable EQA result is due to the poor performance of the system or the user [56]. To ensure high quality EQA programs, commutable samples and assigned values obtained by reference methods should be used also in EQA for POCT [57]. However, some POCT-IVD MDs require customised EQA materials and for certain other device types it may even not be possible to provide suitable materials. A first attempt has already been made to deal with situations where commutable EQA sample materials cannot be made available [58]. Also, if appropriate, a note on the possible influence of different reagent batches on the accuracy of the results may be helpful information for participants, as this may explain differing EQA results [59].

A recent systematic review has concluded that adoption of quality management for POCT, including participation in IQC and EQA, with the support of laboratory medicine professionals, will improve the quality of the patient results [60]. There is limited evidence on the ideal frequency of IQC and EQA also for POCT, and even different EQA frequencies for different types of POCT instruments have been suggested. In this regard, a recent study has developed an IVD-MD-specific easy to use scoring system to determine the frequency of IQC in primary healthcare [61].

For POCT applications to function properly, it is important to establish and maintain a quality management system that includes IQC and EQA as well as training, education and professional development appropriate to the competence of the users [53, 62]. The support of laboratory experts, such as POCT coordinators, is essential to ensure high quality patient outcomes, event-related root cause analysis and appropriate corrective and preventive measures, regulatory compliance and promotion of continuous improvement [60, 63–66].

EQA for IVD-MDs intended for self-use

Besides IVD-MDs for professional use and POCT use, devices for self-testing are the third category of IVDs defined by IVDR [52]. These IVD-MDs are intended for use by non-professionals. They must be designed and manufactured to perform appropriately, considering the skills and means available to the intended user and the variation that can be reasonably anticipated in the intended user's technique and environment [52]. From 2001 to 2004 a pilot EQA for blood glucose self-testing was provided. Due to a lack of further financing, this EQA program was not adopted into routine, although the results in terms of analytical quality clearly indicated the benefits of participation [67]. We do not have any information about the currently offered EQA programs for self-use IVD-MDs.

Forensic toxicology laboratories

Successful participation in EQA programs is an important aspect when arguing the competence of a forensic toxicological laboratory to deliver reliable and defensible analysis results in legal cases. Comprehensive proficiency testing in forensic toxicology requires the coverage of an extensive number of analytes (not all of them being available as CRM) and, compared to routine clinical laboratories, special sample types such as *post-mortem* material. In practice, it is not possible to mimic all analytical scenarios in forensic toxicology through interlaboratory testing, and commercially available programs are mostly limited to plasma, serum, whole blood, urine, saliva and hair, as well as analytes of broad (international) relevance such as alcohol, common illicit drugs, and psychoactive medications [68, 69]. In this regard, proficiency testing in forensic hair analysis is particularly challenging owing to sample homogeneity issues and the need for authentic consumer samples instead of spiked samples to monitor the efficiency of analyte extraction during sample processing [70]. Despite the challenges associated with proficiency testing in forensic toxicology, its growth in recent decades, both in terms of available parameters and sample types, reflects its practical value in quality management processes of this analytical field.

Benefits of EQA for national metrology institutes, calibration and reference laboratories

National Metrology Institutes (NMIs) and calibration laboratories usually are not involved in the analysis of clinical samples. In contrast, among the heterogeneous group of reference laboratories, some may (e.g., National Reference Laboratories (NRLs)), and others may also be not involved in the analysis of patient specimens (e.g., European Union Reference Laboratories (EURLs)). Characteristics of different types of reference laboratories and their characteristics are described elsewhere [71]. As the laboratories described in this section routinely perform higher metrological order, rare or confirmatory analytical procedures that are unsuitable for routine use in clinical diagnostics, they welcome quality assurance measures of all kinds, including EQA schemes.

National metrology institutes

The “metre convention”, first signed in 1875, is an international treaty which created an international organisation called the Bureau International des Poids et Mesures (BIPM). Since its inception the BIPM has been tasked with facilitating the standardisation of measurements worldwide by coordinating the activities of member states on activities related to measurement science. On its inception, the treaty was focused on the unification and improvement of the metric system. This mainly focused on physical measurements vital for the industrial revolution and intercontinental communications and trade. Therefore, historically many of the national institutes that engaged with the BIPM were devoted to physics (e.g. national physics laboratories such as NPL (National Physical Laboratory) in the UK or PTB (Physikalisch-Technische Bundesanstalt) in Germany). However, as the measurement needs for trade and other areas of where the international comparability of measurement results using the international system of units (SI) expanded such as environmental monitoring and measurements in the heath sector, the activities of the BIPM and its members expanded to include these activities. In 1995 the first meeting of the Consultative Committee for the amount of substance (CCQM) took place. The major focus of this committee was to improve the comparability of chemical measurement across the different application areas. In 1999 the mutual recognition agreement (MRA) of national measurement standards and calibration and measurement certificates issued by national metrology institutes was drawn up. The objectives of this agreement are to: (i) establish the degrees of equivalence of national measurement standards maintained by NMIs; (ii) provide for the mutual recognition of calibration and measurement certificates of NMIs; (iii) provide governments and other parties with a sound technical basis to conduct wider agreement related to trade and regulatory affairs. This agreement stipulates the nomination of one NMI per member state. In many countries the national physical laboratory was nominated to fulfil this role. However, for many countries this laboratory did not possess the range of measurement activities covered by the MRA. Therefore, many countries have designated institutes (DI), such as LGC in the UK or BAM in Germany, where measurements for specific sectors or activities are delegated by the NMI to these institutes. The role of the NMI is to coordinate the actives within their country to assure their national and international needs are met. Under the MRA the consultative committees or sometimes regional metrology organisations organise office comparisons of the services and/or measurement services offered by the NMIs/DI. These comparisons are referred to as key or supplementary comparisons. They have very strict rules and all methods and their associated uncertainty estimates are rigorously peer reviewed. These comparisons lead to calibration measurement capability claims which are listed on an online BIPM database

[72]. In the clinical sector these normally take place via two different mechanisms. Where NMIs have CRMs for the same measurand, all participants can send their CRM to a single laboratory where a comparison of the materials and their assigned values is undertaken. However, more commonly materials are sent from one coordinating laboratory to participating NMIs who provide estimates and their associated uncertainties for the measurands in the materials received. The NMIs normally use a primary method or primary ratio method of analysis, which for pure materials normally incorporates quantitative NMR supported by mass balance approaches, while for matrix materials this normally involves isotope dilution mass spectrometry-based methods. While the measurement and calibration approaches remain the same, no two materials are samples are identical, therefore the NMIs will often have to alter the extraction, chromatographic or mass spectrometry conditions for the sample received. Effectively this requires the method to be revalidated on the sample as received. This approach enables the NMIs to assess and quantify the individual uncertainty contributors for the material received. This is one of the reasons why the procedures and approaches are not suitable for high throughput analysis and why these procedures may not readily identify commutability issues if the materials are to be used as CRMs.

On the one hand, while the key comparison could be considered a sort of EQA, NMIs benefit from participating in broader based EQA from a number of factors. (i) If an NMI participates in key studies and maintains Calibration and Measurement Capabilities (CMCs) by participating in the same EQA as its national reference or calibration laboratories it can assess the agreement of reference values between reference laboratories and assure their link to SI; (ii) cooperation with expert laboratories allows the exchange of knowledge and experience of the NMIs regarding the establishment of higher metrological order examination procedures and the expertise of the expert laboratories on specific properties of certain measurands and matrices [73, 74]; and (iii) as unknown bias can be introduced by change of methods and technology, participation in EQA enables an unbiased assessment of the current state of the art. On the other hand, NMIs can use EQA challenges to (iv) test suitability of newly developed CRMs; this provides extra confidence in the NMI assigned value and may quickly identify commutability issues with the material (this should never substitute a complete and thorough assessment of commutability). Finally, (v) NMIs can assist in obtaining comparable measurement results for a particular sector; this can be done by engaging with a whole community (e.g. infection diagnostics) where the specific measurands need both harmonisation and standardisation activities. In these and other areas it is essential that NMIs engage with stakeholders to help provide solutions. This is best done in a collaborative manner and with early intervention to prevent the development of SI traceable measurement with small uncertainties for a different measurand than is intended by the community.

Calibration laboratories

Laboratories may be listed as so-called *calibration laboratories* in the Joint Committee on Traceability in Laboratory Medicine [75] (JCTLM) database as reference measurement services providers qualified to perform JCTLM-listed RMPs [76]. Inclusion of reference measurement procedures and calibration services in the JCTLM database is directly linked to participation in interlaboratory comparisons like RELA-IFCC, the IFCC EQA program for reference laboratories in laboratory medicine [77]. The applicable international standard ISO 15195 also requires accredited calibration laboratories to demonstrate their competence to carry out calibration work correctly through interlaboratory comparisons, and ISO 17025 even requires them to ensure the validity of results [78, 79]. The RELA interlaboratory comparison process uses target value assignment by RMPs, and transparency of the program and information to third parties are particularly important. Results to be reported by participants for two different samples include measured values and associated MU estimate according to the Guide to the Expression of Uncertainty in Metrology (GUM) [80]. A draft of the final report, in which the participants are anonymised, is distributed to the participants at the end of the submission period. Participants may request that their results be removed from the report before the results and the disclosed identities of the other laboratories are made freely available on the IFCC-RELA website [77]. In addition to the results, limits of equivalence (LoE) as set by the RELA advisory board and the IFCC Committee for Traceability in Laboratory Medicine (C-TLM), are disclosed in the report. LoE are not considered as a “grading” system and have no regulatory impact, but they may be used for educational purposes to compare and monitor the performance of the procedures at the highest metrological order. Since the introduction of RELA in 2003, the number of participants has increased continuously, which underlines the utility for reference laboratories to compare their respective results.

Interlaboratory comparisons are also an important tool for validation during the development of new calibration procedures. Target values assigned by calibration laboratories are used for the evaluation of EQA schemes for routine laboratories or for calibrators to establish the metrological

traceability of measurement results in the framework of IVDR. This places calibration results at a high level in the metrological traceability chain. Therefore, the direct link from the calibration results to the patient results helps to continuously increase measuring accuracy and therefore also patient safety. Also, other networks, such as the IFCC network for HbA1c, or intercomparison measurements organised by NMIs, support this concept of quality assurance for calibration laboratories as part of the metrological traceability of measurement results.

Reference laboratories

Several competent organizations have designated reference laboratories for their interests, like the European Union (EU) and national governments [71]. Tasks, required competences and authorizations assigned to these reference laboratories are defined in regulations or contracts and may include the requirements for participation in EQA. Even if the client does not explicitly request this, the objective proof of passed EQA challenges can serve the contractor as objective proof of his analytical competence and good laboratory performance. It is also quite possible that the standard according to which the reference laboratory is accredited requires participation in interlaboratory comparisons anyway. Reference laboratories may have a different analytic portfolio than routine medical laboratories, but they also may employ different examination procedures, e.g. for confirmatory tests. For these two reasons, as described below, they participate in customized EQA programs that either include the required measurands and/or allow comparison with other laboratories using the same test systems.

European union reference laboratories

Two types of EURLs are currently being established, namely those for IVD-MD performance assessment and those for monitoring of infectious agents in both human medicine and environmental and food analysis. A total of five EURLs started operations in October 2024 to be involved in the conformity assessment of highest risk (class D) IVD-MDs [81]. In January 2025, six EURLs started operations according to Regulation (EU) 2022/2371 in public health microbiology surveillance [82]. These are currently not the same reference laboratories that are active in the field of IVD-MD assessment. Requirements regarding their participation in EQA

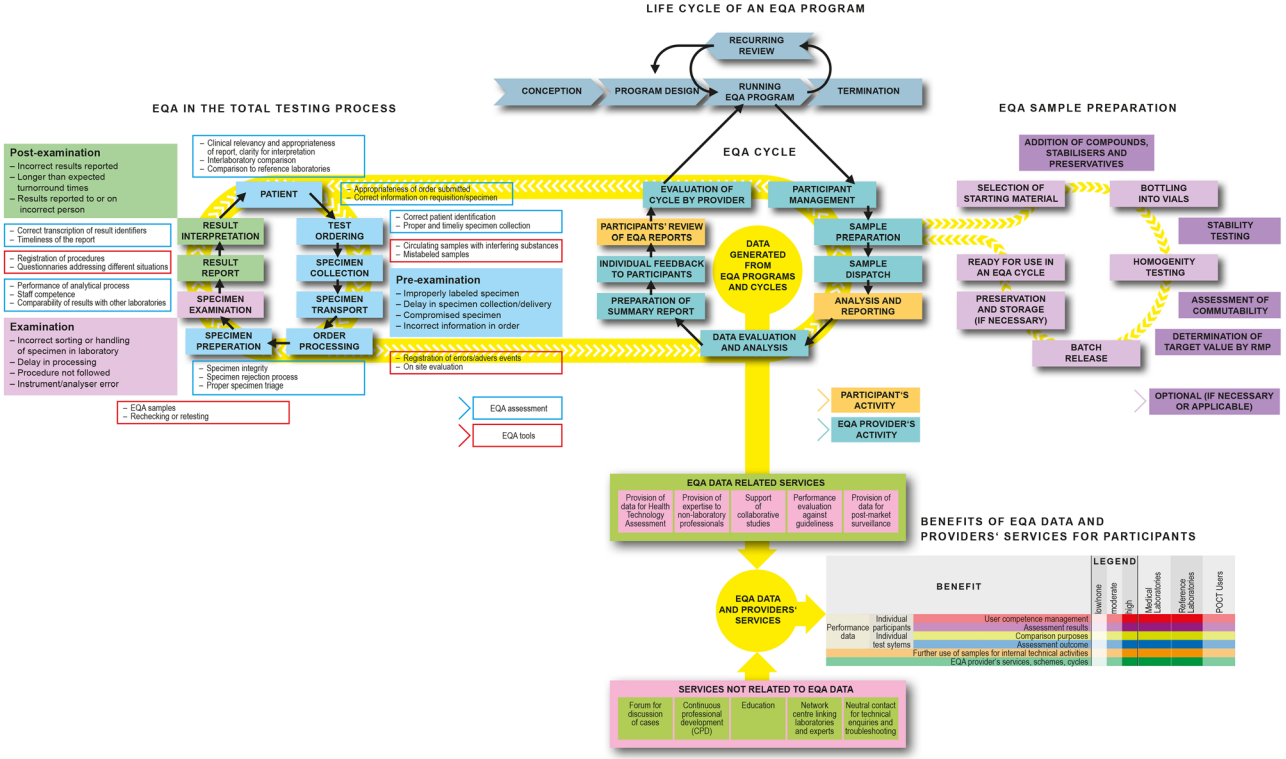

Figure 3: Laboratory total testing process, EQA programs, cycles and sample preparation, and benefits of EQA for participants and stakeholders other than participants. Relationship of the laboratory total testing process, EQA cycles including, the preparation of samples used in them, and EQA programs,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

have not yet been defined. However, as EURLs are required to be accredited according to a standard (e.g. ISO 17025), the requirements for EQA of the respective standard apply. In any case, a lively exchange of information and samples between specialised laboratories in the sense of an inter-laboratory comparison is to be expected, if only for the professional interest of the EURLs.

National reference laboratories

NRLs and their networks are expected to be in networks with EURLs [83]. They are responsible for public health microbiology surveillance at national level, but may also be active as referral laboratories or reference laboratories for specialised infection diagnostics. The European Centre for Disease Prevention and Control (ECDC) [84] regularly organises EQAs for NRLs, in which participation is voluntary but only possible with an invitation. These challenges include both clinical specimens and environmental samples, but they appear to be more focused on bacteriology than virology.

Conclusions

After the properties of EQA programs, cycles and samples used in earlier parts, the benefits of EQA participation were presented in this part of the article series (Figure 3). Participants may perceive EQA a chore, as professional third-party feedback on the performance of their examination procedures and the competence of their staff, as a means of comparing the performance of different examination and measurement procedures, as an objective quality indicator, as a contribution to continuous professional development, or as a technical enrichment of their examination processes and thus as a noble contribution to the pursuit of excellence. EQA will always be a central requirement of quality management systems and the pursuit of harmonisation to ensure equivalent results, while laboratory diagnostics play a crucial role in patient care, diagnosis, follow-up and research.

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