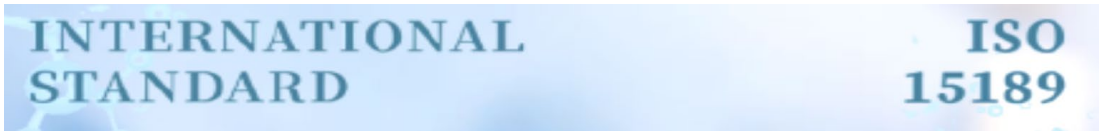
A Guide on How to Implement Internal Quality Control (IQC)

Supplementary to A Practical Guide to IQC published by HKAML in 2015

With references to the most updated edition of ISO 15189: 2022



ISO 15189:2012	ISO 15189:2022 (this document)
5.6.2 Quality control 5.6.2.1 General 5.6.2.2 Quality control materials 5.6.2.3 Quality control data	7.3.7.2 Internal quality control (IQC)

Edited by

Richard Pang, PhD, FADLM
Senior Consultant
Pro Q Consulting Services
Hong Kong

For
Hong Kong Association of Medical Laboratories Limited

March 2024

香港醫務化驗所總會
Educational Material

(This page is intentionally left blank)

Disclaimer

The guidelines are compiled based, in most cases on published professional recommendations from national or international expert bodies or individuals. The guidelines are not intended to be a complete primer or guidance for the best internal quality control (IQC) practice in medical laboratories. Most importantly, neither the Editor nor the Hong Kong Association of Medical Laboratories (HKAML) Ltd. assumes responsibility for the accuracy of, errors or omissions in these guidelines.

Editor: Richard Pang
Managing Editor: Denise Hou

Coordinators:
Jason Lam
Marianne Leung
Adrian Li
Alex Li
Jacky Ng
Cybil Wong

http://www.hkaml.org

The Editor welcomes comments on this document which may be addressed to:
ProQ@live.hk

HKAML gratefully acknowledges the help of Qualab Biotech. Co., Shanghai, China for their invaluable assistance in creating an abridged Chinese version of this book.

编者鸣谢上海昆涞生物科技有限公司质量控制工作组老师对中文版本文章摘要翻译提供的协助。

Preface

In a fast-changing world, people get used to having quick results. Efficiency is often emphasized in the workplace. Technology enables the transformation of many manual duties to become fully automatic, this happens to our profession. Apart from getting faster, tests are getting more and more sensitive, and measuring units getting smaller and smaller. To achieve fast and sensitive testing reliably depending on state-of-the-art management skills on all related parameters. Quality control is a collective term for monitoring all the factors involved.

With the kind initiative from Dr. Richard Pang, the first formal educational material (A Practical Guide to Internal Quality Control (IQC) for Quantitative Tests in Medical Laboratories) from the Hong Kong Association of Medical Laboratories Limited (HKAML) was borne in September 2009. Six years later, in February 2015, Version 2.0 was published. Certainly, it is not a textbook to be studied every day, instead, it is a sourcebook that hopefully can offer help when you are required. That's what HKAML hopes to be.

Thanks, Dr. Pang for the kind contribution all through this time. Here it comes, "A Guide on How to Implement Internal Quality Control (IQC)" is made available. It is taken as a supplement to the 2015 version regarding the updated edition of ISO 15189: 2022.

On behalf of all members of HKAML, thank you Dr. Pang for the unfailing support and contribution. Knowledge is power, hopefully, all members are equipped with the extra strength to overcome the ever-changing environment.

Alex Li
Chairman, HKAML

Foreword

The Hong Kong Association of Medical Laboratories (HKAML) is delighted to present the "Guide on How to Implement Internal Quality Control (IQC)" to its members and colleagues.

The ISO 15189 international standard has been updated to its fourth edition in December 2022. The new version emphasizes the need for more detailed monitoring of the IQC policy and procedures. To fulfill the internal quality control requirements listed in Clause Section 7.3.7.2 of the updated standard and ensure the validity of examination results, a supplementary document has been provided by Dr. Richard Pang and his Editorial Board members. This document describes the necessary processes that must be followed.

The new supplementary document and its appendices may be helpful additions to the previous guidelines published in 2015 for those planning to apply or transition to the new ISO 15189:2022 accreditation.

HKAML intends this guide for HKAML member laboratories and interested non-member colleagues to use for their day-to-day internal QC decisions. It's important to note that this guide is not a substitute for any laboratory's expert or published opinions, and we do not claim any overriding authority on the subject matter.

We would like to express our gratitude to Dr. Pang for contributing to HKAML's mission of advancing Hong Kong's laboratories and good laboratory practices.

Marianne Leung
Founder Chairman, HKAML

Contents

1. Aims

The Hong Kong Association of Medical Laboratories (HKAML) is issuing a revision or supplementary edition of the Practical Guidelines to Internal Quality Control (IQC) that aims to address the shortcomings of the current guidelines published in 2015 [1]. The goal of the revision is to provide "more up to date" guidance to requirements according to the most recently released ISO 15189: 2022 edition [2] that emphasizes the applications of risk management principles leading to "fewer quality defects and recalls" according to a risk management plan in the laboratory.

The revised guideline will introduce new clause requirements of ISO 15189 that "*The Intended Quality and Consistent Validity Pertinent to Clinical Decision Making*" is achieved.

References

1. A Practical Guide to Internal Quality Control (IQC) For Quantitative Tests in Medical Laboratories, Version 2.0 February 2015, HKAML.
2. International Organization for Standardization (ISO). ISO/IEC 15189:2022 Medical laboratories requirements for quality and competence. Geneva (Switzerland), December 2022.

1.1 Objectives

- To provide healthcare professionals in the private sector with clear guidance on the management of internal quality control for quantitative tests in the laboratory.
- To provide information and suggestions for good laboratory practice and for producing reliable results, regardless of where the test is performed.
- It is recommended that guidance on QC issues should be sought from consensus statements and/or publications of relevant national or international professional associations or societies.

1.2 Complementary

Requirements for the basic IQC policies and procedures are not included. This document should be read in conjunction with the previous edition of the Practical Guidelines to Internal Quality Control published in February 2015 [1].

1.3 Background

The International Organization for Standardization (ISO) has established standard requirements for medical laboratories (ISO 15189) to ensure the quality of their analytical processes. One such requirement is the Internal Quality Control (IQC) procedure, which monitors the ongoing validity of examination results according to specified criteria. The IQC procedure is designed to ensure that the intended quality is achieved and that the results are consistent and valid for clinical decision-making.

ISO standards are intended to standardize practices globally. Unfortunately, ISO implementation is frequently accompanied by misunderstandings. This How-to Guide discusses the pros, cons, and some myths regarding the new 2022 edition of ISO 15189 standards.

1.4 The previous version of ISO 15189:2012 Clause 5.6.2 regarding the IQC.

ISO 15189:2012 Medical Laboratories – Requirements for Quality and Competence

5.6.2 Quality Control

5.6.2.1 General Provision "*Laboratories shall design quality control procedures to verify the quality of results that are expected*."

Quality data and accurate information are essential to decision-making. Internal quality control (IQC) involves analyzing samples to find out if they meet the criteria for acceptability. IQC procedures are essential in laboratories to ensure reliable results and patient safety. Independent quality control material is recommended to help safeguard patient safety in laboratory medicine. Comprehensive quality assurance programs are in place to verify the expected results, and every step of producing results is monitored to ensure the correct tests are performed, reliable results are produced, and these are communicated to the appropriate clinician promptly.

Statistical quality control (SQC) is a crucial monitoring tool that helps identify bias and imprecision in the analytical system, thereby reducing the risk of erroneous results and ensuring patient safety. SQC is widely used in clinical laboratories during routine testing processes, and it plays a significant role in ensuring the accuracy and precision of test results. Since its introduction in the 1950s, Shewhart's industrial Statistical Process Control (SPC) procedures have undergone several decades of development, and the process has continuously improved to become an important way to guarantee the quality of laboratory testing. To keep up with the latest management methods and

standards like ISO 15189, laboratory staff should adopt the best practices and improve IQC procedures to enhance testing quality in clinical laboratories.

Remember, IQC is not just about compliance; it's about managing quality effectively. Implementing IQC in a medical laboratory is essential to ensure accurate and reliable test results. The process can be broken down into three steps according to ISO requirements:

1) Select the Appropriate IQC Procedure:
- Choose the right IQC procedure based on the specific test method used in your laboratory.
- Consider statistical criteria or control rules, as well as the number of control measurements required e.g., according to sigma-metrics.
- Align these choices with the quality standards expected for the test.

2) IQC Implementation Strategies:
- Use graphical tools such as power function or critical-error graphs to plan the IQC process.
- Create charts that define acceptable performance limits for your test.
- Follow a three-stage design to ensure high error detection, low false rejection, and the right length of the analytical run.

3) Total QC Strategy:
- Formulate a strategy that balances cost and quality.
- Ensure that your IQC process aligns with overall laboratory goals.
- Regularly review and update your strategy based on performance data.

Bibliography:

International Organization for Standardization (ISO). ISO/IEC 15189:2012 Medical laboratories requirements for quality and competence. Geneva (Switzerland), February 2017.

James O Westgard. Internal quality control: planning and implementation strategies. Ann Clin Biochem 2003; 40: 593–611.

2. What's New?

The IQC procedure should consider the intended clinical application of the examination and allow for the detection of either lot-to-lot reagent or calibrator variation or both. The procedure should also be able to identify trends and non-conforming results and investigate identified failures and trends. The laboratory should assess and mitigate the risks to the extent possible and communicate the residual risk to the users.
The structure and content of ISO 15189:2022 have been revised. The IQC section has been expanded from three subclauses to seven (a-g).

The other major change in this version is the inclusion of requirements relating to point-of-care testing (POCT). The new standard contains Annex A – Additional Requirements for Point of Care Testing (POCT) which is a one-page outline of the main focus of the POCT element of the standard. Responsibility of the laboratory to the organization (departments/personnel) for POCT will include device selection, training, quality assurance, and management review.

A Gentle Reminder

ISO 15189 only specifies laboratory requirements without detailing how to fulfill them or prepare the necessary documentation. ISO has recently developed new standards, including risk management (ISO 22367:2020) and metrological traceability (ISO 17511:2020), which complete the documentation systems. The new version ISO15189 replaces many CLSI guidelines with ISO documents. It's important to read related ISO documents to understand the requirements fully.

Below are those point-to-point practical approaches (compliance vs practicality) to the ***NEW*** clauses and subclauses (in *Italics*):

3. ***7.3.7.2 Internal quality control (IQC)***

a) The laboratory shall have an IQC procedure for monitoring the ongoing validity of examination results, according to specified criteria, that verifies the attainment of the intended quality and ensures consistent validity pertinent to clinical decision-making.

The IQC procedure is designed to detect variations in reagents or calibrators and ensure that the results are reliable enough to be released. The procedure considers the intended clinical application of the examination and verifies the attainment of the intended quality. The laboratory should also monitor and evaluate the risks and effectiveness of their mitigation according to the potential harm to the patient.

Compliance vs Practicality

The performance specifications for the same measurand can differ in different clinical settings, and the intended clinical application of the examination should be considered. The European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) has published a consensus statement on defining analytical performance specifications, which provides a framework for setting analytical performance specifications based on the intended clinical application of the examination. The statement suggests three different models to set analytical performance specifications, with each model being better suited for certain measurands than for others. The models are as follows:

- Model 1: Based on the effect of analytical performance on clinical outcomes.
- Model 2: Based on components of biological variation of the measurand.
- Model 3: Based on state-of-the-art analytical performance.

The statement also highlights that the performance specifications for the pre- and post-analytical laboratory processes should follow the same models as for analytical performance specifications.

Bibliography:

Sverre Sandberg, Callum G. Fraser , Andrea Rita Horvath , Rob Jansen , Graham Jones , Wytze Oosterhuis , Per Hyltoft Petersen , Heinz Schimmel , Ken Sikaris and Mauro Panteghini. Defining analytical performance specifications: Consensus Statement from the 1st Strategic Conference of the European Federation of Clinical Chemistry and Laboratory Medicine. Clin Chem Lab Med 2015; 53(6): 833–835.

4. ***7.3.7.2 Internal quality control***

a1) The intended clinical application of the examination should be considered, as the performance specifications for the same measurand can differ in different clinical settings;

See Appendix A
Analytical Performance Specifications (APS)

Compliance vs Practicality

The choice of model to use for your clinical application depends on the nature of the measurand and the intended clinical application of the examination. The EFLM consensus statement provides a detailed description of each model and the measurands for which they are best suited. You may find it helpful to consult the statement to determine which model is most appropriate for your specific clinical application.

Model 1 is based on the effect of analytical performance on clinical outcomes. It is best suited for measurands that have a direct impact on patient care and clinical decision-making. An example of a measurand for which Model 1 would be appropriate is troponin, which is a protein released into the bloodstream when the heart muscle is damaged. Troponin is used as a diagnostic biomarker for acute myocardial infarction (AMI), and the analytical performance of troponin assays has a direct impact on patient care and clinical decision-making. Therefore, Model 1 can be used to set analytical performance specifications for troponin based on the effect of analytical performance on clinical outcomes.

The measurement of analytical performance specifications (APS) depends on the model used to set the specifications.

The EFLM consensus statement provides detailed guidance on how to measure APS for each model. For example, Model 2 is based on the components of biological variation of the measurand. The APS for Model 2 can be measured by calculating the total allowable error (TEa), which is the maximum permissible difference between the true value of the measurand and the measured value that is consistent with the biological variation of the measurand. The TEa can be calculated using the following formula:

$$TEa = 1.65 \times CVi \times (\mu + CVg)$$

where CVi is the within-subject biological variation, μ is the analytical measurement uncertainty, and CVg is the between-subject biological variation. The EFLM consensus statement provides detailed guidance on how to calculate the TEa for different measurands.

Bibliography:

Graham R.D. Jones*, Stephanie Albarede, Dagmar Kesseler, Finlay MacKenzie, Joy Mammen, Morten Pedersen, Anne Stavelin, Marc Thelen, Annette Thomas, Patrick J. Twomey, Emma Ventura and Mauro Panteghini, for the EFLM Task Finish Group – Analytical Performance Specifications for EQAS (TFG-APSEQA). Clin Chem Lab Med 2017; 55(7): 949–955.

Federica Braga, Sara Pasqualetti, Francesca Borrillo*, Alessia Capoferri, Mariia Chibireva, Leila Rovegno and Mauro Panteghini. Definition and application of performance specifications for measurement uncertainty of 23 common laboratory tests: linking theory to daily practice. Clin Chem Lab Med 2023; 61(2): 213–223.

The Royal College of Pathologists Australasia Quality Assurance Programs, RCPAQAP has used analytical performance goals to assess the quality of results. These goals, called Analytical Performance Specifications (APS), are quality standards to allow participating laboratories to assess their performance and respond accordingly.

Bibliography:

RCPA Data Analysis and Assessment Criteria Handbook (Accessed 2 January 2024).

Model 3 is designed to provide cutting-edge analytical performance. It is particularly useful for measuring quantities that are new or lack adequate biological variation data. For instance, SARS-CoV-2 antigen testing is an appropriate example of such a quantity. This test is utilized to detect the presence of the SARS-CoV-2 virus in individuals. Since it's a relatively new test, there is limited biological variation information available for it. Therefore, Model 3 can be used to establish analytical performance specifications for SARS-CoV-2 antigen testing based on state-of-the-art analytical performance.

4.1 ***7.3.7.2 Internal quality control***

a2) The procedure should also allow for the detection of either lot-to-lot reagent or calibrator variation, or both, of the examination method. To enable this, the laboratory procedure should avoid lot change in IQC material on the same day/run as either lot-to-lot reagent or calibrator change, or both;

Lot-to-lot verification is an integral component for monitoring the long-term stability of a measurement procedure. The practice is challenged by the resource requirements as well as uncertainty surrounding experimental design and statistical analysis that is optimal for individual laboratories, although guidance is becoming increasingly available. Collaborative verification efforts as well as the application of patient-based monitoring are likely to further improve the identification of any differences in performance in a relatively timely manner. Appropriate follow-up actions for failed lot-to-lot verification are required and must balance potential disruptions to clinical services provided by the laboratory. Manufacturers need to increase transparency surrounding release criteria and work closer with laboratory professionals to ensure acceptable reagent lots are released to end users. A tripartite collaboration between regulatory bodies, manufacturers, and laboratory medicine professional bodies is key to developing a balanced system where regulatory, manufacturing, and clinical requirements of laboratory testing are met, to minimize differences between reagent lots and ensure patient safety.

See Appendix B
Lot-to-Lot Reagent Verification

Compliance vs Practicality

Lot-to-lot variation affecting calibrators and reagents is a frequent challenge that limits the laboratory's ability to produce consistent results over time. This variation is not without clinical consequences and there are several well-documented examples of adverse clinical outcomes. Laboratories must have procedures in place for quantification of this inaccuracy, and for determining whether the amount of variation is acceptable for the release of patient results. Various approaches have been taken to the assessment of new lots, including the evaluation protocol published by the Clinical and Laboratory Standards Institute (CLSI). Internal quality control and external quality assurance materials are often not commutable, so the use of native patient samples is preferred. Published evaluation protocols differ significantly in ease of use and statistical rigor, and some may be underpowered to detect a clinically meaningful change between lots. Furthermore, current protocols (including the CLSI protocol) will

not detect cumulative shifts between reagent lots. This shortcoming may at least partly be addressed by laboratories adopting moving patient averages or similar quality procedures. Collaboration and data-sharing between laboratories and manufacturers also have an important role to play in the detection of lot-to-lot variation. While the laboratory may take steps to evaluate and detect variation, the ideal is to reduce variation between lots at the point of manufacture. Using appropriate acceptance criteria based on medical needs or biological variation requirements instead of some arbitrary percentage may go some steps toward achieving this. Laboratories need to ensure that there is no significant shift in reagent performance or reporting of patient data.

Bibliography:

Tze Ping Loh, Sverre Sandberg and Andrea Rita Horvath. Lot-to-lot reagent verification: challenges and possible solutions. Clin Chem Lab Med 2022; 60(5): 675-680.

Simon Thompson, Douglas Chesher. Lot-to-Lot Variation. Clin Biochem Rev 2018; 39 (2): 51-60.

4.2 ***7.3.7.2 Internal quality control***

a3) The use of third-party IQC material should be considered, either as an alternative to or in addition to, control material supplied by the reagent or instrument manufacturer.

NOTE Monitoring of interpretations and opinions can be achieved through regular peer review of examination results.

The use of third-party IQC material should be considered. In-kit control materials, although produced independently of the instrument or reagent, are often supplied or recommended by the instrument/reagent manufacturer. It is this manufacturing relationship between the two that requires scrutiny when considering if these controls are fit for purpose. Although the control material is not directly produced by the instrument manufacturer, they are often produced according to their exact specifications and therefore, optimized to work with a specific test system.

See Appendix C
Independent or Third-party Quality Control (QC) Materials

Compliance vs Practicality

There are inherent differences between the QC materials provided by the system manufacturer and third-party providers. If the manufacturer's (in-kit) QC material is made from the same material as the end-user calibrators, or if a different lot of end-user calibrators is utilized as QC, then the results obtained from the QC tests do not offer any new information concerning the traceability of the end-user calibrator or the measurement system. In such cases, all the results are self-referential. The implementation of robust IQC practices is crucial for ensuring the trueness and precision of the results produced by a laboratory. Used correctly, IQC can monitor variability caused by instrumentation and lot changes as well as various other sources of analytical error. Third-party IQC material can provide an independent check of the whole testing system, which can be beneficial in ensuring the accuracy and reliability of the results.

It is important to conduct thorough research and compare the offerings of different providers before making a decision.

The QC materials should meet the following specifications:

1) **Analytical Range**:
   - Cover the entire analytical range of our testing systems.
   - Include low, normal, and high concentration levels and functional sensitivity, where appropriate.
2) **Stability and Shelf Life**:
   - Clearly state the stability period (e.g., shelf life after reconstitution).
   - Provide storage conditions (temperature, light exposure, etc.).
3) **Matrix Compatibility**:
   - Ensure compatibility with our specific sample matrices (e.g., serum, plasma, urine).
   - Minimize matrix effects.
4) **Traceability and Accuracy**:
   - Document traceability to certified reference materials, where applicable.
   - Specify accuracy targets (e.g., $\leq \pm 2\%$ deviation).
5) **Documentation**:
   - Include certificates of analysis (CoA) for each lot.
   - Provide user manuals and handling instructions.

Bibliography:

Matthew W Rosenbaum, James G Flood, Stacy E F Melanson, Nikola A Baumann, Mark A Marzinke, Alex J Rai, Joshua Hayden, Alan H B Wu, Megan Ladror, Mark S Lifshitz, Mitchell G Scott, Octavia M Peck-Palmer, Raffick Bowen, Nikolina Babic, Kimia Sobhani, Donald Giacherio, Gregary T Bocsi, Daniel S Herman, MD, Ping Wang, John Toffaletti, Elizabeth Handel, Kathleen A Kelly, Sami Albeiroti, Sihe Wang, Melissa Zimmer, Brandon Driver, Xin Yi, Clayton Wilburn, Kent B Lewandrowski. Quality Control Practices for Chemistry and Immunochemistry in a Cohort of 21 Large Academic Medical Centers. Am J Clin Pathol 2018; 50 (2): 96–104.

5. ***7.3.7.2 Internal quality control***

b) The laboratory shall select IQC material that is fit for its intended purpose. When selecting IQC material factors to be considered shall include:

1) stability with regard to the properties of interest;

Compliance vs Practicality

Stability: Choose stable materials that remain reliable over prolonged periods without interfering with preservatives, at least for the intended period of use. The stability of the material should be evaluated under the same conditions as the samples being analyzed.

2) the matrix is as close as possible to that of patient samples;

Compliance vs Practicality

When using third-party IQC material, it is important to ensure that the material is stable concerning the properties of interest for the intended period of use. The matrix of the IQC material should be as close as possible to that of patient samples.

3) the IQC material reacts to the examination method in a manner as close as possible to the patient samples;

Compliance vs Practicality

IQC materials are used to monitor the performance of instruments and reagents in the laboratory. The IQC material is tested using the same examination method as the patient samples to ensure that the results obtained are as close as possible to the actual patient results. This helps to identify and correct any errors in the testing process and ensure the accuracy of the results.

4) the IQC material provides a clinically relevant challenge to the examination method, has concentration levels at or near clinical decision limits, and when possible, covers the measurement range of the examination method.

Compliance vs Practicality

IQC material is designed to provide a clinically relevant challenge to the examination method. Including analytes at clinical decision levels will not only eliminate the need to purchase additional controls but also ensure that the results provided are accurate and reliable to prevent potential misdiagnosis or inappropriate treatment. The IQC material

is also designed to cover the measurement range of the examination method, which helps to ensure that the results provided are accurate and reliable across the entire range of the examination method. The concentration levels of the IQC material are set at or near clinical decision limits to ensure that the results provided are clinically relevant and can be used to make informed decisions about patient care.

Functional Sensitivity

Functional sensitivity is the minimum detectable concentration of an analyte with a certain level of confidence. It plays a critical role in determining the lower limit of detection of hormones, especially those in extremely low concentrations like TSH. Factors affecting it include assay design, reagent quality, and detection method. Note that analytical sensitivity is not equivalent to functional sensitivity.

The functional sensitivity of an assay is a crucial factor in determining the lower limit of detection of a hormone. This is important in diagnosing and monitoring endocrine disorders. For instance, the functional sensitivity of TSH assays has improved significantly from 1.0 mIU/L with first-generation immunoassays to 0.01 mIU/L with third-generation immunoassays, and ultra-sensitive assays with 0.001 mIU/L. However, it is important to keep in mind that the functional sensitivity of an assay is not the only factor that determines its clinical usefulness. Other factors, such as the assay's specificity, accuracy, and precision, also play a critical role in determining its clinical utility.

Bibliography:

C A Spence, M Takeuchi, M Kazarosyan, F MacKenzie, G J Beckett, E Wilkinson. Inter-laboratory/inter-method differences in functional sensitivity of immunometric assays of thyrotropin (TSH) and impact on reliability of measurement of subnormal concentrations of TSH. Clin Chem 1995;41(3): 367-74.

In summary

How to select IQC materials? To be fit for purpose!

- Stability concerning properties of interest
- Matrix as close as possible
- Reaction to the examination method as close as possible to the patient sample
- Concentration levels at/near the clinical decision limits and, when possible, covering the measurement range

6. ***7.3.7.2 Internal quality control***

c) If appropriate IQC material is unavailable, the laboratory shall consider using other methods for IQC. Examples of such other methods may include:

1) trend analysis of patient results, e.g., with moving average of patient results, or percentage of samples with results below or above certain values or associated with a diagnosis;

A patient-based quality control (QC) system that utilizes trend analysis comprises several components, such as a calculation algorithm, block size, truncation limits, and control limits. It is crucial to establish the relationship of these components with the analyte being controlled. To optimize the patient-based QC system and identify systematic errors with minimal false alarms, patient data from the testing laboratory must be utilized.

See Appendix D
Patient-based Real Time Quality Control (PBRTQC)

Compliance vs Practicality

Trend analysis of patient results can be performed using various statistical methods. Two such methods are moving average and percentage of samples with results below or above certain values or associated with a diagnosis.

- Moving average (MA) is a statistical method that uses the mean patient results to continuously monitor assay performance. It involves developing sensitive moving average protocols that rapidly detect systematic error (SE). Moving averages may detect SE in advance of the next quality control (QC) event, minimizing the number of unreliable patient results reported.
- The percentage of samples with results below or above certain values or associated with a diagnosis is another statistical method that involves tracking how the distribution of results changes over time. This can help identify shifts in patient health or treatment effectiveness.

It has been experimentally confirmed that it is possible to perform the selection, optimization, and validation of MA procedures using the bias detection simulation method. Also, it is possible to define MA procedures as optimal for a laboratory with a small daily testing volume.

Bibliography:

Vera Lukić, Svetlana Ignjatović. Optimizing moving average control procedures for small-volume laboratories: can it be done? Biochem Med (Zagreb) 2019; 29(3): 030710

Daren Kiat How Poh, Chun Yee Lim, Rui Zhen Tan, Corey Markus, Tze Ping Loh. Internal quality control: Moving average algorithms outperform Westgard rules. Clinical Biochemistry 2021; 98: 63-69.

2) *comparison of results for patient samples on a specified schedule to results for patient samples examined by an alternative procedure validated to have its calibration metrologically traceable to the same or higher order references as specified in ISO 17511;*

Compliance vs Practicality

The statement or requirement is related to the comparison of results for patient samples on a specified schedule to results for patient samples examined by an alternative procedure validated to have its calibration metrologically traceable to the same or higher order references as specified in ISO 17511. Some web search results might help understand this topic better. Here are some links to explore below:

i. ACB Method Comparison - Patient Samples Instructions Document provides a spreadsheet program primarily designed for estimating the difference between two methods by comparing the results of measured patient samples. It allows input of single or duplicate results. With duplicate measurements, the imprecision of the methods can also be estimated. Differences between the means of the reference and measured samples are evaluated with parametric and non-parametric methods, in addition to ordinary and Deming regression analyses. Results are displayed in a scattergram and absolute and relative difference diagrams. Differences are demonstrated in an error grid comprising A, B, and C zones. The data set can be partitioned to facilitate a detailed evaluation depending on relevant threshold values.

ii. EP31-A-IR: Verification of Comparability of Patient Results Within One … provides a practical, statistically valid approach that laboratories of varying sizes and resources can use to satisfy this quality.

iii. Method comparison in the clinical laboratory - Wiley Online Library discusses studies comparing a new method with an established method, to assess whether the new measurements are comparable with existing ones, frequently conducted in clinical pathology laboratories.

iv. EP09-A3: Measurement Procedure Comparison and Bias Estimation Using … involves the comparison of results from patient samples from two measurement procedures intended to measure the same component (e.g., the concentration of a measurand) with the key determination being the estimate of bias between them. Several different scenarios exist in which measurement procedure comparison studies are indicated.

3) retesting of retained patient samples.

Patient blood samples are suitable for quality control. Although stability is a concern, they are stable enough for short-term control of systematic errors.

Compliance vs Practicality

To ensure the accuracy of initial test results, it is advisable to perform a retest of retained patient samples. Shyamali Pal conducted a study that provides an analytical approach to retesting retained sample results. According to ISO 15189:2012, accredited medical laboratories should follow a sample retention policy of 24 hours for Clinical Chemistry analytes. In this study, 22 common analytes were retested based on the time lag, and the deviation from the first observation was evaluated. The results were used to establish and implement a sample retention policy. The study involved testing the analytes in the Cobas Integra 400 plus system which were performed as routine tests and considered as the first observation. The second observation values were obtained after the specified time lag, and the results were compared using statistical software. To eliminate personal bias, a single test was repeated in the same method and system by two different laboratory personnel. Electrolytes were excluded from the study as they preferred to be retested from freshly collected samples. Similarly, labile parameters like L-lactate, ammonia, and bicarbonate were not considered for the same reason.

Bibliography:

Shyamali Pal. An Analytical Study of Retesting of Retained Sample Results. BJMMR 2015; 6(3): 265-277.

7.3.7.2 Internal quality control

d) IQC shall be performed at a frequency that is based on the stability and robustness of the examination method and the risk of harm to the patient from an erroneous result.

The frequency of internal quality control (IQC) testing should be determined based on the stability and reliability of the examination method and the potential harm that could be caused to patients from an incorrect result. The frequency of IQC testing should be optimized based on the estimated number of unreliable final patient results. The risk of harm to patients from incorrect results should be the main factor in determining the frequency of IQC testing.

Compliance vs Practicality

The Clinical and Laboratory Standards Institute (CLSI) has issued a new guideline for statistical quality control (SQC; C24-Ed4) which recommends implementing risk-based SQC strategies. The guideline outlines a planning process for risk-based SQC strategies and describes two applications for examination procedures that provide 6-sigma and 4-sigma quality. The selection process for traditional SQC, which uses power function graphs to select control rules and the number of control measurements, can be expanded to determine the frequency of SQC testing using a run-size nomogram. Such practical tools are necessary for planning risk-based SQC strategies.

Bibliography:

The Clinical and Laboratory Standards Institute (CLSI) C24-A4 Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions, 4th Edition. September 2016. Clinical and Laboratory Standards Institute 950 West Valley Road, Suite 2500 Wayne, PA 19087 USA.

Huub H van Rossum. When internal quality control is insufficient or inefficient: Consider patient-based real-time quality control! Ann Clin Biochem 2020, 57(3): 198–201.

The Hong Kong Association of Medical Laboratories (HKAML) has suggested a set of guidelines for internal quality control (IQC) related to quantitative tests conducted in medical laboratories. These guidelines prescribe the required levels of quality control materials to be used each day, how frequently QC should be performed, what

types of QC materials should be used, and the acceptance criteria for QC customized for each examination procedure based on the specific capabilities of the procedure.

Bibliography:

A Practical Guide to Internal Quality Control (IQC) For Quantitative Tests in Medical Laboratories, Version 2.0 February 2015, HKAML. (Accessed 2 January 2024).

7.1 IQC Frequency for POCT

Internal quality control (IQC) plays a crucial role in ensuring the accuracy and reliability of laboratory test results. However, there is no universal consensus or guideline on when and how IQC should be analyzed on point-of-care testing (POCT) devices.

See also Appendix E
Internal Quality Control in Point-Of-Care Testing (POCT)

Compliance vs Practicality

A study in Clinical Chemistry and Laboratory Medicine (CCLM) proposed a scoring system for determining the IQC frequency of POCT devices in primary healthcare. The system considers analyte importance, device type, user-friendliness, and the number of patient samples. Scores for each factor determine recommended IQC frequency. Adjustments may be needed based on patient samples. Consult a professional for specific needs.

Many risk factors should be considered when designing the stringency and frequency of any POCT QC strategy. The greater the risk, the more stringent the QC procedure should be. When designing an appropriate QC strategy several risk factors need to be taken into consideration:

- high-risk tests with a large impact on the wrong result,
- tests used to support the clinician's decision in isolation,
- tests acted upon immediately, and
- tests performed on specimens that are difficult to collect.

Examples of IQC Frequency for POCT:

Devices analyzing high-risk analytes (e.g., blood-cell counters, glucose meters) typically undergo daily or weekly IQC. For instance, all blood-cell counters should have daily IQC, while glucose meters may have weekly IQC.

Important

Remember that the proposed scoring system provides differentiated and device-specific recommendations for IQC frequency in primary healthcare. It's just a practical tool to ensure quality while balancing care efficiency.

Bibliography:

Gro Gidske, Sverre Sandberg, Anne L. Fossum, Stein Binder, Eva C. Langsjøen, Anne E. Solsvik and Anne Stavelin. Point-of-care testing in primary healthcare: a scoring system to determine the frequency of performing internal quality control. Clin Chem Lab Med 2022; 60(5): 740–747.

Helen Holt and Danielle B Freedman. Internal quality control in point-of-care testing: where's the evidence? Ann Clin Biochem 2016; 53(2): 233–239.

8. ***7.3.7.2 Internal quality control***

e) The resulting data shall be recorded in such a way that trends and shifts are detectable and, where applicable, statistical techniques shall be applied to review the results.

Remember that the application of statistical techniques should align with the specific context of the laboratory and the type of data handled. Emphasize risk management and identify potential sources of error or variation that could affect trends or shifts. Most importantly, continuously monitor data trends. Set up regular reviews to identify shifts or unusual patterns, and regularly review and analyze data to detect patterns or deviations.

To identify trends and shifts, consider the following practices:

- Graphical Representation: Plot data over time using line charts or control charts. Visual patterns can reveal trends or shifts.
- Moving Averages: Calculate moving averages (e.g., 3-day or 7-day averages) to smooth out fluctuations and highlight underlying trends.
- Run Charts: Create run charts to display data points sequentially. Look for patterns, sudden changes, or gradual shifts.
- Control Charts: Implement control charts (e.g., Shewhart charts or CUSUM charts) to monitor process stability. Detect deviations from expected behavior.
- Statistical Process Control (SPC): Consider using SPC methods to detect trends over time. Apply SPC techniques to assess variation, identify outliers, and track process performance.

Compliance vs Practicality

A historical overview of internal quality control models that have been used in the medical field from the latter half of the 20th century up to the present day has indicated that initially, models relied on testing control materials and utilizing multiples of the analytical procedure's standard deviation as control limits. Later, these limits were replaced with values based on the intended use of the test, which were primarily derived from biological variation. For measurands without any available QC material, methods based on replicating the analysis of patients' samples were developed, and they have been continuously improved in recent years. Additionally, sigma metrics that relate the desired quality with laboratory performance have resulted in a highly efficient QC model. Presently, risk management constitutes an essential component of the Quality Management System (QMS) of medical laboratories, the trend is to modulate IQC by considering the workload and the impact of analytical failure on patient safety. By

adhering to those practices, the laboratory can enhance the detectability of trends and shifts in the recorded data.

Bibliography:
Carmen Ricós, Pilar Fernandez-Calle, Carmen Perich and James O. Westgard. Internal quality control – past, present and future trends. Adv Lab Med 2022; 3(3): 243–252.

The results of IQC and their management play a crucial role in improving Total Quality Management. However, a survey showed that there is a lot of variability in the responses received. Only 56.4% of countries expressed their interest in participating in an IQC pilot training program organized by the IFCC. Although global best practices in IQC can differ, most literature and ISO 15189 assessments suggest that results should be assessed daily by those who are responsible for conducting the tests. At less frequent intervals, supervisory personnel should review the results to ensure that the assays are working correctly. Surprisingly, only 42.5% of respondents indicated that bench-level personnel reviewed IQC. Even though 76.2% of respondents mentioned that IQC was reviewed on a daily basis, it was observed that supervisors and laboratory directors were the most common reviewers. This may indicate that the question was interpreted as who performs the final review of IQC or that some countries rely on supervisors or directors to review QC before reporting patient results. Despite variations in IQC review intervals and reviewers, 97.6% of respondents reported that their medical laboratories take corrective action in the event of IQC failure. However, without appropriate policies and procedures in place, these corrective actions and result remediations may not be consistent between personnel.

Bibliography:
Sarah E. Wheeler, Ivan M. Blasutig , Pradeep Kumar Dabla , Jean-Marc Giannoli , Anne Vassault , Ji Lin , Kandace A. Cendejas , Armand Perret-Liaudet , Renze Bais , Annette Thomas , Egon P. Amann and Qing H. Meng. Quality standards and internal quality control practices in medical laboratories: an IFCC global survey of member societies. Clin Chem Lab Med 2023; 61(12): 2094–2101.

9. ***7.3.7.2 Internal quality control***

f) IQC data shall be reviewed with specified acceptability criteria, at regular intervals and in a time frame, which allows a meaningful indication of current performance.

The specifications for quality based on biological variation are the best fit for the analytical and clinical purposes of laboratory tests. The laboratory needs to be aware that the manufacturer's method specifications and control ranges should be used with caution when compared with results and analytical goals in the field.

Compliance vs Practicality

To ensure that the process of reviewing IQC data is effective, it is crucial to establish a review schedule that permits the timely identification of any issues. The review schedule should be based on the frequency of testing and the stability of the test system. Moreover, it is essential to establish acceptability criteria for the IQC data review process. These criteria should be based on the performance characteristics of the test system and should be established in consultation with the laboratory director, ensuring that the review process is efficient and effective.

Furthermore, the IQC data review process should be conducted at regular intervals with specified acceptability criteria to ensure that the current performance is meaningful. The review schedule should be based on the frequency of testing and the stability of the test system, and the acceptability criteria should be established in consultation with the clinical users.

Bibliography:

Jean-Marc Giannoli, Stéphanie Albarede, Thierry Avellan, Jean-Pierre Bouilloux, Régine Cartier, Richard Cohen, Nathalie Colard, Luc Essemilaire, Jean-Louis Galinier, Mathieu Kuentz, Mickaël Paris, Henri Portugal, Florian Scherrer, Jean-Pascal Siest, Anne Vassault, and Jean-Michel Vialle. Recommendations for the application and follow-up of quality controls in medical laboratories. Biochem Med (Zagreb) 2021;31(2):020501.

10. ***7.3.7.2 Internal quality control***

g) The laboratory shall prevent the release of patient results in the event that IQC fails the defined acceptability criteria.

Laboratory has a responsibility to ensure that patient results are accurate and reliable. To achieve this, it must have a procedure in place to monitor the validity of results and record data in a way that allows trends and shifts to be identified. Statistical techniques should be used where possible. The laboratory should also assess and mitigate risks, communicate them to users, and monitor and evaluate their effectiveness to improve patient care. To ensure the validity of results, IQC data must be reviewed at regular intervals against defined acceptability criteria. If the criteria are not met, no results will be released. Instead, the results will be rejected, and patient samples will be re-examined after correction.

See Appendix F
Defined Acceptability Criteria

Compliance vs Practicality

Clinical laboratories need to manage risks effectively to ensure accurate test results and patient safety. A practical tool for managing risks in clinical laboratories involves five cyclical steps: identifying risks, quantifying them, prioritizing them, mitigating them, and surveillance. To identify risks, a questionnaire is used that evaluates five major components of laboratory processes: specimens, test systems, reagents, environment, and testing. The questionnaire helps quantify all risks using the risk priority number (RPN), calculated through failure modes and effects analysis (FMEA). Based on the calculated RPN, identified risks are then prioritized and mitigated to ensure patient safety.

1) When IQC-defined acceptability criteria are not fulfilled and indicate results are likely to contain clinically significant errors, the results shall be rejected and relevant patient samples re-examined after the error has been corrected (see 7.5);

Compliance vs Practicality

Based on ISO 15189 clause 7.5, if the acceptability criteria defined by IQC are not met and indicate that the results may have clinically significant errors, then the results are to be rejected. The relevant patient samples should be re-examined only after the error has been corrected. If the IVD measuring system's performance is deteriorating compared to appropriate analytical specifications, then prompt corrective actions

should be taken to ensure the clinical validity of test results. Cause analysis takes a top-down approach, first identifying the deficiency, and then taking small steps to dig deeper and determine the root of the nonconformity.

2) The results from patient samples that were examined after the last successful IQC event shall be evaluated.

Compliance vs Practicality

The ISO management system requirements that form the basis for ISO 15189:2022 emphasize the importance of corrective action, which involves conducting a cause analysis. This standard is designed to encourage a thoughtful and deliberate approach to understanding how a nonconformance occurred and to prevent it from recurring in the future. By conducting a thorough cause analysis, organizations can also identify potential issues and prevent deficiencies from happening. It's worth noting that a single problem can often be the root cause of multiple nonconformities, so resolving one issue can significantly reduce the risk of others occurring.

The QC frequency shall be decided based on the stability and robustness of the examination method and the risk of harm to the patient

- Data shall be recorded
- IQC data shall be reviewed with defined acceptability criteria at regular intervals
- No release of results if IQC fails the criteria; the results are rejected, and patient samples are re-examined after correction
- The results after the last successful IQC shall be evaluated

Bibliography:

Ensuring Validity of Examination Results. What is new in the new ISO 15189
(Accessed 2 January 2024).

Appendix A
Analytical Performance Specifications (APS)

Analytical Performance Specifications (APS) are numerical criteria that specify the quality required to deliver laboratory test information that would achieve the best possible health outcomes for patients. External Quality Assessment (EQA) organizers provide APS that indicate whether the deviation from the target value achieved by the laboratory is acceptable. APS is generally expressed as several units or a percentage deviation from a specified target, creating upper and lower acceptance limits.

Below is a published article that describes the definitions and descriptions of analytical performance specifications for external quality assessment. One can access the paper by clicking on the following link:
https://www.degruyter.com/document/doi/10.1515/cclm-2017-0151/html
(Accessed 2 January 2024).

Note 1:
The ISO standard for clinical laboratories, ISO 15189:2022, mandates that laboratories validate or verify the performance of a measurement procedure for its 'intended use'. However, since a participant may use a test for a different purpose than what was envisioned by the EQA provider, the APS of a particular scheme may not apply to their situation. For example, if a laboratory uses a certain glucose test only to differentiate hypoglycemic from hyperglycemic comatose patients in the Accident and Emergency (A&E) department or intensive care unit of the hospital, a wider APS might be applicable than for other applications such as the diagnosis of diabetes. As EQA organizers cannot have APS for every possible intended use of a test, laboratories are advised to document their own required response to results if their use of the assay differs from the generally expected use.

Note 2:
To determine if your lab meets the APS requirements, you can participate in EQA programs. EQA organizers provide APS that indicate whether the deviation from the target value achieved by the laboratory is acceptable.

To verify the performance specifications of your laboratory, your laboratory director is responsible for determining the appropriate selection of samples to permit the laboratory to verify performance specifications and have confidence in test results, while being aware of the resources expended.

EQA programs are designed to objectively check the performance of medical laboratories using an external agency or facility to evaluate participant performance against pre-established criteria through interlaboratory comparison. According to ISO/IEC 17043:2023, the EQA provider reports the findings to the participants in a way that facilitates the verification of trueness, establishes the corrective actions needed, and assesses the success of prior corrective actions.

There are two types of EQA schemes: regulatory and educational:

1) Regulatory EQA schemes have wider analytical performance specifications (APS) but severe consequences for failure.
2) Educational EQA schemes aim to improve the quality of laboratory testing, and therefore not all laboratories will achieve the performance goals at the time of implementation. Educational programs may also offer support to participants in the form of additional troubleshooting advice, webinars on the interpretation of QC and EQA, and workshops on addressing measurement problems identified in the EQA program.

The structure of an EQA program is defined by the EQA samples, the frequency of samples, the APS, and how the target values are established. The sample may be verified commutable with clinical samples, have a range of concentrations, and be repeated during the EQA cycle.

The laboratory can download the Data Analysis and Assessment Criteria Handbook from the Royal College of Pathologists of Australasia Quality Assurance Programs (RCPAQAP) website. The handbook contains information on Analytical Performance Specifications (APS), which are quality standards that participating laboratories can use to assess their performance in all RCPAQAP disciplines and respond accordingly.

https://rcpaqap.com.au/resources/chemical-pathology-analytical-performance-specifications/

(Accessed 17 May 2024).

The handbook provides the following definitions for the terms mentioned:

- Optimal: The analytical performance specification (APS) that is desirable for a laboratory to achieve. It is defined as 0.125 $(CVi^2 + CVg^2)^{1/2}$ + 2.33 x 0.5 CVi for total error (TE) and 0.25 $(CVi^2 + CVg^2)^{1/2}$ + 2.33 x 0.25 CVi for imprecision.
- Desirable: The APS that is achievable by most laboratories. It is defined as 0.25 $(CVi^2 + CVg^2)^{1/2}$ + 2.33 x 0.5 CVi for TE and 0.5 $(CVi^2 + CVg^2)^{1/2}$ + 2.33 x 0.25 CVi for imprecision.
- Minimal: The APS that is the minimum acceptable level of performance. It is defined as 0.375 $(CVi^2 + CVg^2)^{1/2}$ + 2.33 x 0.75 CVi for TE and 0.75 $(CVi^2 + CVg^2)^{1/2}$ + 2.33 x 0.25 CVi for imprecision.

Permissible Bias (pB%)

Several concepts have been suggested to deal with analytical bias and minimize it. The ultimate goal is to eliminate it. If the bias is within permissible limits (pB%) and occurs within one control cycle, it should be treated as a random error. On the other hand, long-term bias should be eliminated either by estimating interlaboratory reference limits (RLs) or by circumventing them. This will reduce analytical uncertainty to permissible imprecision (pCV). Once this is done, models that combine imprecision and bias will become irrelevant, and the numerical value of total analytical error will be identical to imprecision. To simplify quality assurance schemes considerably, bias can be disregarded by estimating RLs or verifying the applied reference limits (checking the transferability), as requested by ISO and CLSI.

pB% = 0.7 pCV (Permissible CV: <1/3 TEa)
= 0.7 x 1/3 TEa
= 0.233 TEa
(Approximately 1/4 TEa)

Bibliography:

Rainer Haeckel, Eberhard Gurr, and Torsten Hoff, on behalf of the working group Guide Limits of the German Society of Clinical Chemistry and Laboratory Medicine (DGKL). Bias, its minimization or circumvention to simplify internal quality assurance. J Lab Med 2016; 40(4): 263–270.

Appendix B
Lot-to-Lot Reagent Verification

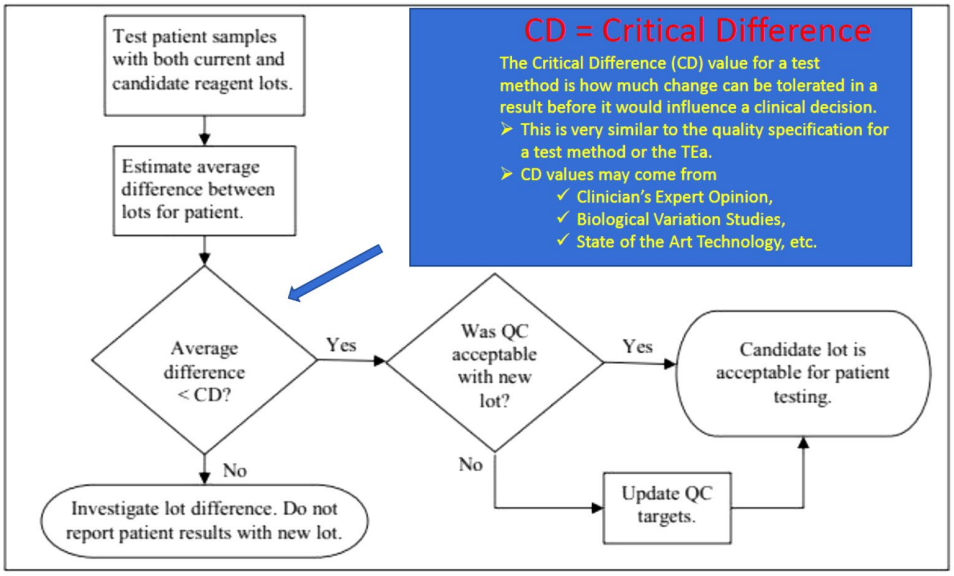
Lot-to-lot variation is a phenomenon that occurs when reagents or calibrators manufactured in batches under similar conditions, are assigned the same manufacturers' reference number (or 'lot number') but may not always be identical between different batches. This may produce reagents and/or calibrators that interact differently with patient samples, subsequently altering analytical performance. The practice of lot-to-lot verification is an integral component for monitoring the long-term stability of a measurement procedure. The practice is challenged by the resource requirements as well as uncertainty surrounding experimental design and statistical analysis that is optimal for individual laboratories, although guidance is becoming increasingly available. Collaborative verification efforts and the application of patient-based monitoring are likely to improve further the identification of any differences in performance in a relatively timely manner. Appropriate follow-up actions for failed lot-to-lot verification are required and must balance potential disruptions to clinical services provided by the laboratory. Manufacturers need to increase transparency surrounding release criteria and work closer with laboratory professionals to ensure acceptable reagent lots are released to end users. A tripartite collaboration between regulatory bodies, manufacturers, and laboratory medicine professional bodies is key to developing a balanced system where regulatory, manufacturing, and clinical requirements of laboratory testing are met, to minimize differences between reagent lots and ensure patient safety.

A research paper titled "Lot-to-lot variation and verification" by Tze Ping Loh et al., was published in Clinical Chemistry and Laboratory Medicine. The paper emphasizes the significance of lot-to-lot verification to ensure the long-term stability of a measurement procedure. It also highlights the challenges faced by individual laboratories in terms of resource requirements, uncertainty surrounding experimental design, and statistical analysis that is optimal for individual laboratories. The paper suggests that collaborative verification efforts and the application of patient-based monitoring are likely further to enhance the identification of any differences in performance promptly. The paper also recommends appropriate follow-up actions for failed lot-to-lot verification and urges manufacturers to increase transparency surrounding release criteria and work closely with laboratory professionals to ensure acceptable reagent lots are released to end users.

In addition, another publication by the Clinical and Laboratory Standards Institute (CLSI) titled "EP26-A User Evaluation of Between-Reagent Lot Variation". This publication provides clinical laboratories with a standardized protocol for reagent lot verification.

The protocol involves two phases:

- The first phase involves determining the number of patient samples to be tested, the acceptance criteria, and the rejection limit.
- The second phase involves verification of the new reagent lot by testing the determined number of patient samples with both lots of reagents, calculating the average concentration differences between the two lots, and analyzing the acceptability of the new lot based on the rejection limit established during the first phase.



Clin Biochem 2016 Nov;49(16-17):1211-1212. doi: 10.1016/j.clinbiochem.2016.04.003. Epub 2016 May 6.

For Hematology (Coagulation)

To perform lot-to-lot verification of calibrators, it is recommended to follow the guidelines provided by the International Council for Standardization in Hematology (ICSH). The ICSH has published a new guideline for new lot verification of coagulation reagents, calibrators, and controls. This guideline provides a framework and provisional guidance for clinical laboratories for evaluating and verifying the performance of new lot reagents used for coagulation testing.

It is important to ensure that there is no significant shift in reagent performance or reporting of patient data before implementing new reagent lots for clinical use. The guideline recommends that laboratories determine the performance of the new reagent lot by evaluating the magnitude of change in analytical characteristics between an existing (in-use) lot and a new (candidate) lot of reagents to ensure they meet predefined acceptance limits.

It is recommended to perform calibration verification with each new lot when initiating a new test in the laboratory until you are satisfied with the consistent performance lot-to-lot. However, it is generally unnecessary to perform calibration verification while introducing a new lot number of reagents unless the manufacturer requires it.

Bibliography:

International Council for Standardization in Hematology Guidance for New Lot Verification of Coagulation Reagents, Calibrators, and Controls
https://www.thieme-connect.com/products/ejournals/pdf/10.1055/s-0043-1776405.pdf
(Accessed 2 January 2024).

Appendix C
Independent or Third-party Quality Control (QC) Materials

Independent or third-party quality control materials are manufactured outside the quality system used to manufacture the instrument, kit, or method they are intended to monitor. They are designed to deliver an unbiased and independent assessment of performance with any instrument or method, enabling laboratories to gain accreditation and ensure optimum performance and accuracy in clinical laboratory testing.

Third-party QCs offer a better solution compared to in-house QCs, as values are assigned using a large number of independent laboratories, thus ensuring statistically valid targets. The use of highly consolidated controls allows for significant space, time, and cost savings. Additionally, boosted shelf life ensures continuity of supply and reduced costs, while reducing preparation times by eliminating the need for multiple instrument controls.

Currently, third-party QCs are becoming increasingly popular across the globe, with more and more laboratories incorporating them into their daily QC strategy. The benefits of using such controls are widely accepted and recommended by both key opinion leaders and regulatory bodies in the field of Quality Control.

To purchase third-party QC materials, the laboratory can contact the manufacturers directly or reach out to a distributor that specializes in laboratory supplies. Some of the popular distributors include Bio-Rad Laboratories, Randox Laboratories, Technopath, and ThermoFisher Scientific, as well as Qualab Biotechnology in China.

When selecting a third-party IQC material provider for clinical laboratories, it is important to consider "*the intended quality and consistent validity pertinent to clinical decision-making*" is achieved and the successful provider or supplier should provide the following QC materials:

- Quality: The provider should offer high-quality products that are reliable, accurate, and consistent. It is recommended to choose a provider that has a proven track record of producing quality products and adheres to international standards.

- Range of products: The supplier should offer a wide range of products that cater

to different laboratory needs. This includes products that cover a range of analytes, methods, and formats.

- Flexibility: The supplier should offer flexible options that can be customized to meet the specific needs of the laboratory. This includes options for assayed/unassayed, liquid/lyophilized, and human/bovine formats.
- Cost-effectiveness: The supplier should offer cost-effective solutions that provide value for money. It is recommended to choose a provider that offers competitive pricing and delivers cost savings through consolidation.
- Regulatory compliance: The supplier should comply with all relevant regulations and guidelines. It is recommended to choose a provider that has a strong reputation for regulatory compliance and adheres to international standards.

Problems Associated with Quality Control Materials

- The use of non-human based materials and additives of animal origin, the physical and chemical characteristics of QC materials that differentiate such samples from those from patients
- Attempts to generate QC materials with extreme levels of particular analytes
- The difficulties in handling and storage of QC materials, the dangers of hepatitis, and the stability of QC materials both during storage in the laboratory and after their reconstitution.

Concentrations, Activities, or Levels

Many manufacturers 'cut corners' or take shortcuts in an attempt to keep costs down. This often results in unrealistic values, parameter imbalances, a frequent lack of differentiation between levels, and ultimately in controls that do not completely cover the clinical range. In many situations, these inadequacies force laboratories to purchase additional and often expensive low or high-level controls. For example, Troponin levels in the low-level control from some manufacturers do not adequately cover the cut-off levels used in diagnosis. This often results in the need for additional controls to cover these lifesaving concentrations. The levels of Troponin I and Troponin T should be in line with internationally recommended levels.

The functional sensitivity of Troponin I assays is an important characteristic that determines the lowest concentration of troponin I that can be detected with a certain degree of confidence. It is defined as the concentration at which the coefficient of variation (CV) is less than or equal to 10%. The functional sensitivity is important because it determines the ability of the assay to detect small changes in troponin I concentration over time. This is particularly important in the diagnosis of acute

myocardial infarction (AMI), where the detection of small changes in troponin I concentration is critical for early diagnosis and treatment. High-sensitivity troponin assays have been developed to improve the detection of small changes in troponin I concentration, which can lead to earlier diagnosis and treatment of AMI.

Bibliography:

Fred S Apple, Yader Sandoval, Allan S Jaffe, Jordi Ordonez-Llanos for the IFCC Task Force on Clinical Applications of Cardiac Bio-Markers. Cardiac Troponin Assays: Guide to Understanding Analytical Characteristics and Their Impact on Clinical Care. Clin Chem 2017; 63(1): 73–81.

Medical Decision Levels (MDLs)

It is recommended to run the Quality Control (QC) material at a concentration close to the Medical Decision Level (MDL) of the assay. The MDL is the concentration of the substance being measured that is used to make a clinical decision. By running the QC material at the MDL, the laboratory can ensure that the assay is accurately and precisely performed at the concentration that is most relevant to patient care. This helps to maintain the quality of the test results, which are crucial for providing accurate diagnosis and treatment for patients.

Bibliography:

For General Clinical Chemistry

Distinguishing reference intervals and clinical decision limits – A review by the IFCC Committee on Reference Intervals and Decision Limits. https://doi.org/10.1080/10408363.2018.1482256

For Hematological parameters

Analytical Performance Evaluation of Hematology Analyzer Using Various TEa Sources and Sigma Metrics. https://doi.org/10.2147/PLMI.S414693

Measurand	Unit	Reference Interval	Decision Levels				
			1	2	3	4	5
Metabolites							
Creatinine	mg/dL	0.7-1.5	0.6	1.6	6.0		
Glucose	mg/dL	60-95	45	120	180		
Cholesterol	mg/dL	150-275	90	240	260	350	
HbA1c	%	<6.5	4	6.5	8		
Troponin I (cTnI)	ng/mL	0-0.04	0.01	0.1	0.5	1	10
Hormones							
Cortisol In Urine	ug/24h	20-90	50	100			
Cortisol In Plasma	ug/dL	7-20 (@8am)	5	10	18	25	
Prolactin	ng/mL	1-20 (Male)	30	100	300		
TSH	mIU/L	0.5-5.0	0.05	0.5	1.0	5.0	20
Hematology							
Partial Thromboplastin Time	sec	30	35	45	90		
Hemoglobin	g/dL	14-17.8 (Male) 12-15.6 (Female)	4.5	10.5	17	23	
Platelet Count	K/uL	150-400	10	50	100	600	1000

Examples of Medical Decision Levels (MDLs)

Appendix D
Patient-based Real Time Quality Control (PBRTQC)

Patient-based Real Time Quality Control (PBRTQC) is a statistical method laboratories use to ensure the quality of their testing processes. It involves analyzing the statistical characteristics of a specific patient population served by the laboratory using certain analytical platforms. The method is patient-centric and can help detect bias in an assay using the specific characteristics of the population served.

According to a review article published in Clinical Chemistry, PBRTQC is a next-generation quality control instrument for clinical laboratories that allows continuous quality control with greater error detection capabilities for many important analytes and thereby a reduction in patient risk. Traditional quality control methods, on the other hand, rely on the measurement of stabilized control samples. PBRTQC avoids the limitations of traditional quality control methods and needs to be adapted to individual laboratories with parameters such as algorithm, truncation, block size, and control limit.

PBRTQC can help improve Internal Quality Control (IQC) by providing a more sensitive detection of changes in bias, which are not impacted by non-commutability issues. Once set up, it is low-cost to maintain, but it requires knowledge of the characteristics of the laboratory's patient population(s) and the analytical methods used. Each measurand in a population needs to be tailored to PBRTQC, but this is not a major limitation. Optimization requires access to simulation software and patient data from the Laboratory Information System (LIS).

Besides providing an effective QC system, PBRTQC can also be used to provide an external quality assessment (EQA) and has a role in post-market surveillance of in vitro diagnostics. Monitoring the population medians and the flagging rates (i.e., the number of patients who fall outside the reference intervals) over time allows the identification of bias. These rates can also be compared across different laboratories with method-specific data such as calibrator and reagent lot numbers. These data allow the identification of bias introduced by a change in calibrator or lot number across many laboratories.

According to an article published in Clinical Chemistry, PBRTQC is a next-generation quality control instrument for clinical laboratories that allows continuous quality

control with greater error detection capabilities for many important analytes and thereby a reduction in patient risk. PBRTQC is implemented in the following way:

- The laboratory information system (LIS) extracts patient data from the laboratory database.
- The LIS then applies the PBRTQC algorithm to the patient data to calculate the median and standard deviation of the patient population.
- The LIS then compares the patient results to the median and standard deviation of the patient population.
- If the patient result falls outside the median ± 3 standard deviations, the result is flagged as an outlier.

Bibliography:

Tony Badrick, Andreas Bietenbeck, Alex Katayev, Huub H van Rossum, Mark A Cervinski, Tze Ping Loh on behalf of the International Federation of Clinical Chemistry and Laboratory Medicine Committee on Analytical Quality. Patient-Based Real Time QC. Clinical Chemistry 2020; 66(9): 1140–1145.

Rui Zhou , Wei Wang , Andrea Padoan , Zhe Wang , Xiang Feng , Zewen Han , Chao Chen , Yufang Liang , Tingting Wang , Weiqun Cui , Mario Plebani and Qingtao Wang. Traceable machine learning real-time quality control based on patient data. Clin Chem Lab Med 2022; 60(12): 1998–2004.

Optimizing the parameters for moving mode PBRTQC is a difficult task. The metrics used are not mathematically independent as they are recalculated on almost the same set of patient results. To overcome this, optimization approaches have shifted from simple statistical models to computer simulations. Ng et al. used a simulated annealing algorithm to optimize block size and truncation limits for moving averages. Fleming et al. evaluated 10 different PBRTQC algorithms, however, with only 4 block sizes. Van Rossum presented validation charts that demonstrate exponentially weighted moving averages with various weights and biases for 3 analytes.

Bibliography:

Ng D, Polito FA, Cervinski MA. Optimization of a moving averages program using a simulated annealing algorithm: the goal is to monitor the process not the patients. Clin Chem 2016; 62(10): 1361–71.

Fleming JK, Katayev A. Changing the paradigm of laboratory quality control through implementation of real-time test results monitoring: for patients by patients. Clin Biochem 2015; 48(7-8): 508–13.

van Rossum HH, Kemperman H. Optimization and validation of moving average quality control procedures using bias detection curves and moving average validation charts. Clin Chem Lab Med 2017; 55(2): 218–24.

Xincen Duan, Beili Wang, Jing Zhu, Chunyan Zhang, Wenhai Jiang, Jiaye Zhou, Wenqi Shao, Yin Zhao, Qian Yu, Luo Lei, Kwok Leung Yiu, Kim Thiam Chin, Baishen Pan, Wei Guo. Regression-Adjusted Real-Time Quality Control. Clinical Chemistry, 2021; 67(10): 1342–1350.

Rui Zhou , Wei Wang , Andrea Padoan, Zhe Wang , Xiang Feng , Zewen Han , Chao Chen , Yufang Liang , Tingting Wang , Weiqun Cui , Mario Plebani, Qingtao Wang. Traceable machine learning real-time quality control based on patient data. Clin Chem Lab Med 2022; 60(12): 1998–2004.

Dongliang Man, Runqing Mu, Kun Zhang, Zhiwei Zhou, Hui Kang. Patient-based pre-classified real-time quality control (PCRTQC). Clin Chim Acta 2023; 549: 1 September 2023, 117562.

Real-time QC including delta checking (Δ) is an important issue. A method of monitoring optimized R-values "the positive Δ value ratio minus 0.5." is referred to as the even-check method (ECM) and was compared with QC testing in terms of error detection. The ECM is a practical real-time QC method, controlled by setting R-value conditions, that quickly detects bias values.

Bibliography:

Noriko Hatanaka, Yoshikazu Yamamoto, Yuya Shiozaki, Eiji Kuramura, Naoharu Nagai, Akira Kondo, Mikio Kamioka. Development and Evaluation of "The Delta Plus-Minus Even Distribution Check": A Novel Patient-Based Real-Time Quality Control Method for Laboratory Tests. JALM 2024; 9(2): 316-328. https://doi.org/10.1093/jalm/jfad116
(Accessed 8 March 2024)

Performance Verification and Documentation

It is crucial that the verification process accurately reflects the performance of PBRTQC in the laboratory environment, enabling the lab to assess risks effectively. The configuration settings of the PBRTQC can be categorized into three parts:

(a) criteria for inclusion and exclusion,

(b) calculation algorithm (including block size or weighting factor), and

(c) control limits.

After finalizing PBRTQC parameters and completing the verification process, document both sets of parameters properly. Alternative strategies have been proposed for verifying PBRTQC performance, but methods that provide patient risk information are preferred. Specialized simulation software, such as https://www.huvaros.com, can be a convenient way for this. Running the algorithm in the production environment without activating alarms can also help to obtain a realistic picture of the number of alarms generated and to decide whether they can be managed before going live.

PBRTQC Algorithms for Multiple Instruments

It is currently unclear how to best apply the patient-based real-time quality control (PBRTQC) algorithm when multiple instruments are involved. One simulation study compared using the PBRTQC algorithm separately for each instrument versus using it for all instruments combined. Although combining data from multiple instruments can increase the data stream and speed up error detection, it can also widen control limits and potentially decrease the probability of detecting errors. Additionally, if an error only affects one instrument, the presence of multiple instruments in the data stream may make it more difficult to detect.

Bibliography:

Qianqian Zhou, Tze Ping Loh, Tony Badrick Chun Yee Lim. Impact of combining data from multiple instruments on performance of patient-based real-time quality control. Biochem Med (Zagreb) 2021;31(2):020705.

Appendix E
Internal Quality Control in Point-Of-Care Testing (POCT)

Internal Quality Control (IQC) plays an important role in quality assurance in laboratory medicine. However, there is no universal consensus or guideline on when and how IQC should be analyzed on point-of-care testing (POCT) devices despite the Clinical Laboratory and Standards Institute (CLSI) has produced documents relating to the development of quality control plans (QCP), including IQC protocols, based on risk management. A published article in the Clinical Chemistry and Laboratory Medicine (CCLM) journal proposed a scoring system to determine the frequency of performing IQC on POCT devices at sites for clinical users of primary healthcare. The scoring system takes into account four factors:

1) The importance of the analyte in diagnosing and monitoring patients,
2) type of POCT device,
3) user-friendliness, and
4) number of patient samples.

The scoring system can be easily adapted to the QCP and IQC protocols of other local environments and is easy to use.

Bibliography:

Gro Gidske , Sverre Sandberg , Anne L. Fossum , Stein Binder , Eva C. Langsjøen , Anne E. Solsvik and Anne Stavelin. Point-of-care testing in primary healthcare: a scoring system to determine the frequency of performing internal quality control. Clin Chem Lab Med 2022; 60(5): 740–747.

It is crucial to establish appropriate quality control protocols for point-of-care testing outside of the central laboratory. These protocols should be based on risk management, which means they need to take into account things like the complexity of the analyzer being used, any built-in system checks that are available, the risk associated with releasing inaccurate patient results, and how often the testing is being done. The goal should be to design an effective protocol, rather than just introducing frequent QC checks. Typically, a pass/fail criterion is used to determine whether IQC results fall within acceptable ranges.

It is also suggested that the IQC protocols should be tailored to the complexity of the POCT device. The major difficulty in IQC for POCT lies in finding appropriate QC materials that can accurately reflect the instrument's performance on patient samples. Getting commutable control materials for POCT is challenging since the matrix is often whole blood.

An example of the minimal requirements for IQC monitoring of a POCT system (i-STAT, a portable blood gas analyzer) is given below:

1) Within individual clinical user units, operators (Medical Officers or Nursing Officers) use the i-STAT electronic simulator on each analyzer DAILY to simulate actual test cycles, testing the functionality and continuity of the analyzer to determine if the analyzer is performing accurately. Results from the electronic simulator are documented and transmitted to the PC (Central Data Station) located in the ward.

2) The laboratory will provide a WEEKLY performance check on the instrument by sending control solutions to individual clinical user units to ensure the proper operation of the system, and maintaining a log, documenting each quality control test for record-keeping in the laboratory.

3) To verify the integrity of a new shipment of cartridges. A MONTHLY (or on the day of delivery of cartridges to the hospital) performance verification which consists of three levels of controls covering the normal, acidosis, and alkalosis ranges will be performed on-site to document that cartridges have been received and are functioning properly.

4) Regular i-STAT user meetings involving the laboratory, clinical users, and representatives from the manufacturer would be desirable.

Bibliography:

Richard WC Pang. Point-of-care testing (POCT): Whose responsibility? JHKMTA 1997/98; 7: 9-13.

Appendix F
Defined Acceptability Criteria

In laboratory medicine, it's crucial to have predefined analytical quality goals to assess the quality of an assay accurately. The Total Allowable Error (TEa) is the maximum error that a laboratory can allow. The Association for Diagnostics and Laboratory Medicine (ADLM), formerly AACC, has published an article on TEa, which explains how much error laboratories can permit. One can find the article below:
https://www.aacc.org/cln/articles/2021/december/total-allowable-error-tea-how-much-error-can-your-laboratory-allow
(Accessed 2 January 2024).

Calculating the Total Allowable Error (TEa) for the laboratory requires a few steps:

- Determine the analytical method you will use for the assay.
- Identify the sources of error that can occur during the assay, such as imprecision and bias.
- Calculate the total error for each source of error.
- Combine the total errors to calculate the TEa.

For example, the sources of error for an assay include imprecision and bias. The laboratory can calculate the total errors for each source of error by using the following formulas:

Imprecision: CV% x mean concentration
Bias: (mean observed value - true value) / true value x 100
Once you have calculated the total errors for each source of error, you can combine them to calculate the TEa. The formula for TEa is:

$$TEa = 1.65 \times (\text{sqrt}[(CV\%)^2 + (bias\%)^2])$$

To determine the quality specifications for an analyte, the inherent biological variation is evaluated by measuring the imprecision and bias that can be tolerated before they mask significant biological changes. The TEa values can be calculated using the

equation based on biological variation. The allowable imprecision is based on within-individual variation, while allowable bias is based on within-individual and between-individual biological variation. If you want to calculate the TEa value using this formula, you can refer to the book by Dr. Callum Fraser (Biological Variation: From Principle to Practice. Washington: The Association for Diagnostics & Laboratory Medicine (ADLM) Press; 2001) for more details. Alternatively, one can use the published values for biological variation, which can be found at the following link:

https://www.qcnet.com/resources/technical-documents
(Accessed 17 May 2024). Courtesy of Bio-Rad Laboratories, CA, USA.

Alternatively, one can download the Defined Acceptability Criteria or the database of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) biological variations for medical laboratory testing from the EFLM official website. The website provides a comprehensive list of biological variation estimates for various measurands, along with analytical performance specifications and reference change values. The website also offers meta-analysis-derived BV estimates for over 100 measurands.

https://biologicalvariation.eu/
(Accessed 2 January 2024).

Please note that the data on the website is copyrighted by EFLM, and you may not distribute or commercially exploit the content without their express written permission.

Criteria for Clinically Acceptable Analytical Performance Specifications (CAAPS)
The *CAAPS* models pose a new tool for assessing *APS* in a clinical laboratory. Their usability depends on the relevance of clinically significant differences (*CD)* limits, required statistical power, and the feasibility of repeated measurements. Clinical guidelines were used to calculate *CAAPS* by converting them to *CD* for six common clinical chemistry measurands with variable characteristics, as listed in Table 1 of the link and reference below:

https://doi.org/10.1016/j.cca.2023.117233
(Accessed 2 January 2024).

Bibliography:

Emmi Rotgers, Solveig Linko, Elvar Theodorsson, Timo T. Kouri. Clinical decision limits as criteria for setting analytical performance specifications for laboratory tests. Clin Chim Acta 540 (2023) 117233.

(This page is intentionally left blank)

如何满足新版 ISO 15189:2022 对 IQC 的要求

编者鸣谢上海昆涞生物科技有限公司质量控制工作组老师对中文版本文章摘要翻译提供的协助。

注 1：笔者申明此文讲述的是工作组老师对于新版 ISO 15189:2022 关于 IQC 部分内容的认知和理解，并不代表任何实验室、认证机构或评审员的建议。

注 2：如有异议一切以英文版本为准。

新版 ISO 15189 室内质量控制体系应该如何建立

首先我们看一下内容上的变更

原 ISO15189: 2012 版室内质控要素包含三个方面，程序设计，质控品，质控数据。

5.6.2 质量控制

5.6.2.1 总则

实验室应设计质量控制程序以验证达到预期的结果质量。注：在某些国家，本条款所指的质量控制也称为“内部质量控制”。

5.6.2.2 质控物

实验室应使用与检验系统响应方式尽可能接近患者样品的质控物。应定期检验质控物。检验频率应基于检验程序的稳定性和错误结果对患者危害的风险而确定。

注 1：只要可能，实验室宜选择临床决定值水平或与其值接近的质控物浓度，以保证决定值的有效性。

注 2：宜考虑使用独立的第三方质控物，作为试剂或仪器制造商提供的质控物的替代或补充

5.6.2.3 质控数据

实验室应制定程序以防止在质控失控时发出患者结果。当违反质控规则并提示检验结果可能有明显临床错误时，应拒绝接受结果，并在纠正错误情况并验证性能合格后重新检验患者样品。实验室还应评估最后一次成功质控活动之后患者样品的检验结果。应定期评审质控数据，以发现可能提示检验系统问题的检验性能变化趋势。发现此类趋势时应采取预防措施并记录。

注：宜尽量采用统计学和非统计学过程控制技术连续监测检验系统的性能。

新版 ISO 15189 标准以风险管理为基础，以患者为中心，鼓励医学实验室持续改进。新标准的一些变化：结构进行了调整；结构和管理要求中取消“质量主管”的称谓；不再强调必须编制“质量手册”；强调“风险管理”相关要求。

对于质量控制，新标准有哪些变化呢？ISO 15189:2012 版中 5.6.2 为质量控制条款，注中提到在某些国家将质量控制也称为“内部质量控制”。每一检验程序的规定要求应与该检验的预期用途有关，质量控制程序以验证达到预期的结果质量。ISO 15189:2022 版中，7.3.7.2 为室内质量控制（IQC）条款，要求制定室内质量控制程序以验证达到预期质量，并确保与临床决策相关的有效性。

从 2003 版发展至 2022 版，ISO 15189 均提到质量控制要验证达到预期质量。众所周知，统计质量控制（SQC）是一种重要的监测工具，用于检测分析系统的不正确度和/或不精密度，并降低因错误结果而导致的患者风险。新版增加了要确保临床决策相关的有效性，若在质量控制过程中，不考虑人为差错导致的失控，SQC 足以满足质量控制的要求。但实际工作中不可避免会有人为差错，需加入风险管理才能降低患者风险。因此新标准以风险管理为基础，才能确保与临床决策相关的有效性。

新版中 IQC 条款新增标准包括考虑项目在不同临床科室的应用、试剂或校准品批号更换、使用第三方质控品。笔者认为旧版中使用第三方质控品仅在注解中提到，新版已正式写入条款正文中，这无疑是对第三方质控品使用要求的加强。下面将讲解新版 ISO 15189:2022 对 IQC 的要求，实验室该如何理解及应对。

新版 ISO 15189：2022 版在结构和内容上有所调整，IQC 部分也由原来三个小节调整为 a-g 七个小节

A: 质控程序设计

7.3.7.2 a) 实验室应制定室内质量控制程序，根据规定的标准监测检验结果的持续有效性，以验证达到预期质量，并确保与临床决策相关的有效性。

如何制定室内质量控制程序，实验室可参考《WS/T641-2018 临床检验定量测定室内质量控制》，内容包括但不限于:

1) 定义质量目标；
2) 质控规则；
3) 质控品类型、浓度和检测频率；
4) 质控物位置；
5) 质控记录；
6) 评估患者风险。

7.3.7.2 a)

1) 宜考虑检验的预期临床用途，因为同一被测量的性能特征在不同的临床情况下可能不同。

实验室需要考虑项目的预期用途，是由于同一项目在不同的临床科室有不同的应用，如雌二醇是一个激素项目，同时也是一个肿标项目。同一项目不同基质，其允许总误差也是不同的，如葡萄糖血液基质 TEa 为 7%，尿液基质 TEa 为 20%。

参考附录 Appendix A 分析性能规范 （APS）

7.3.7.2 a)

2) 质量控制程序宜能监测检验方法的试剂或/和校准品的批号变化；为此，在更换试剂或/和校准品批号的同一天/批时，宜避免改变室内质控品的批号。

质量控制程序能监测试剂或校准品批号间变化，因此实验室要避免更换试剂/校准品批号时，更换质控品批号。CLSI EP26-A 对更换试剂或校准品的性能评价有指导意见，但执行较为困难；也有相关文献提出对于试剂/校准品批号更换可进行病人样本比对计算其偏差是否超过可接受要求。

为此实验试剂批号或（和）校准品批号同一天/批发生改变时，宜（应）避免质控批号发生改变。

注解：可以通过定期的比对，对解释和意见进行监控

参考附录 Appendix B 批次间试剂验证

7.3.7.2 a)

3) 宜考虑使用第三方室内质控品，作为试剂或仪器制造商提供的质控物的替代或补充。

笔者认为在新版中提到的是“宜”考虑使用第三方质控，而不是“应”，可能是由于在实际工作中并不是所有项目都有第三方质控：

1) 质控物可为商品化质控物或自制质控物；

2) 若使用自制质控物，需要评估其均匀性和稳定性。

这里是宜还是（应）英文版原文为 should，具体翻译参考 CNAS-CL02:2023

不同的临床情况下同一测量程序，可能存在浓度或样本类型不同，临床应用不同应如何选择质控品呢？

参考 CLSI C24-A4 5.2 部分内容：

- 基质通常应与患者标本的基质相似；例如：当患者标本为血清时，血清基质的质控品是合适的。当使用相同的测量程序同时进行测量，例如血清、血浆、尿液和脑脊液标本时，拥有一组不同的质控品基质并不总是实用的。
- 质控品的主要目的在于确定测量程序按预期执行，以确认患者标本的结果适合用于提供医疗服务。当不同的患者标本基质使用相同的测量区间时，且具有合适浓度的单一基质的 QC 样品可能足以监测性能。
- 在患者标本基质需要不同于其它患者标本使用的测量区间的情况下，有必要确保 QC 策略中包含具有适用于该测量区间的基质和浓度的 QC 样品。
- 考虑浓度时，也需考虑不同的临床情景，如 PSA 不同浓度应对常规检测和术后的监测。
- 同样质控规则和频率也应考虑不同的临床风险

同样在 CNAS CL02-A001:2023 中也有所强调遵守国家和行业标准要求

增加：试剂批间差或者校准品批间的差异应当被检测出来，

选择质控品时，容易走入误区，认为是 CV 越做小越好，或不反映出 BIAS 差异越好，这里我们强调质控品的选择应当能正确反映出样本随监测系统所发生的变化，且这一点，现已纳入质控程序设计要求。

第三点内容与原来要求相同，原 ISO15189：2012 版本中，第三方质控的推荐只是写在“注解“中，在新版中可以看到已经正式写入室内质控程序设计要求中，这也是第三方质控使用要求进一步加强，并可参考第一点与第二点来选择质控品。

参考附录 Appendix C 独立或第三方质量控制 （QC） 材料

B: 质控品选择

7.3.7.2 b) 实验室应选择符合预期用途的室内质控品。当选择室内质控品时，应考虑以下因素：

1) 相关性能的稳定性；

2) 基质尽可能接近患者样品；

3) 室内质控品对检验方法的反应方式尽可能接近患者样品；

4) 室内质控品满足检验方法的临床适宜用途，其浓度处于临床决定限水平或与其接近，可能时，覆盖检验方法的测量范围。

在原有稳定性，基质、浓度的要求下，新增了覆盖测量范围的可能，这里也参见 CLSI C24-A4 中对于浓度覆盖测量范围的举例，例如，接近测量区间下限或上限的性能对于验证测量系统在整个测量区间的保持稳定可能很重要。

风险无处不在，为了降低风险，医学实验室应该慎重选择独立的第三方质控品，不仅要考虑稳定性，也要考虑成本效益，其浓度水平是否有临床决策水平，最后该质控品厂商的售后服务，是否能够提供统计分析和总结分析等。

实验室在选择时，质控品有一个长期的稳定性，可以更好地监测检测系统的质量。质控品与患者样本基质接近，反应方式与患者样本接近。若质控品使用的是非人类材料和动物源性添加剂，结果可能会出现干扰或偏差。在 ISO 15189:2012 版中要求宜选择接近临床决定水平的质控品浓度；2022 版中要求实验室应选择符合预期用途的室内质控品，满足检验方法的临床适宜用途，其浓度处于临床决定限水平或与其接近。笔者认为新版对于选择接近临床决定水平的质控品不止是建议，若不满足要求可能会是一个不符合项。但在实际中，实验室大都只做 2 个质控水平，可能无法与临床决定限水平相一致。同时由于来自现有市场的质控品复合程

度高，可能无法满足每个项目的浓度都达到预期。但实验室仍不能忽视一些重要项目的有意义浓度是临床所需要的。若是由试剂厂商提供质控品，最好有不同于校准品浓度的质控，可以更好监测项目在定标时出现问题。

C: 替代质量控制程序方法

新增了没有合适 IQC 质控品时可采用方法，在之前通常为一些特殊项目没有合适的商品化质控品，自制质控品又要评价均一性和稳定性，这里可以作为一些参考。

7.3.7.2 c) 当无法获得合适的室内质控品时，实验室应考虑使用其他方法进行室内质量控制。

IFCC 在 2020 年提出基于患者数据的实时质量控制（PBRTQC），它包括多种运算程序，如正态均值法（AON）、BULL 法、移动中位数法、移动均值法和指数加权移动均值法等。但其实该方法早在 1965 年就已提出，BULL 法被广泛应用于血细胞分析质量控制。在 2016 年 CLSI 更新了室内质控标准，提出 PBRTQC 可在不额外增加人力和物力成本的情况下即时检测检测系统的稳定性和判断有误“失控”情况。

7.3.7.2 c)

1) 患者结果的趋势分析，例如：患者结果的浮动均值，或结果低于或高于特定值的样品的百分比，或结果与诊断相关的样品的百分比。

《WS/T 641-2018 临床检验定量测定室内质量控制》提出应用患者数据的质量控制方法包括正态均值法和移动均值法。PBRTQC 可以在一定程度上弥补 IQC 的

不足。PBRTQC 特点是实时监测失控情况，一旦发现失控可及时处理。传统的质量控制方式不足包括无法监测到长期的系统偏差、低浓度质控水平中不精密度的临床意义、不能在分析灵敏度下限检测到小的正偏倚以及不能及时发现检测系统分析性能的重大变化等、质控失控时处理较难。PBRTQC 可以在每个病人样本结果生成后进行计算，可即实时监测检测系统。由于 PBRTQC 需要强大的病人结果数量支持，因此国外对其的应用较少。近期有研究引入一种扩展方法，即回归调整质量控制（RARTQC），以提高即时质量控制协定的性能，回归调整后可以提高敏感度。在 2023 年 9 月 Clinica Chimica Acta 发表一篇文章关于 PCRTQC，其重点在于 Pre-classified（预分组）。它摆脱了过去 PBRTQC 的做法，引入临床视角，将有临床内在联系的不同检验项目联合起来，从而大大提升 PBRTQC 的效能。实验室在 PBRTQC 系统投入使用前务必进行验证。

参考附录 Appendix D 基于患者的实时质量控制 （PBRTQC）

7.3.7.2 c)

2) 按照规定方案，将患者样品结果与另一替代程序检测结果比较，该程序经确认可计量溯源至 ISO 17511 规定的同级或者更高级别的参考标准。

7.3.7.2 c)

3) 患者样品留样再测。

对于患者样品留样再测的方法存在一个较大的限制是样本中该物质本身的储存条件及稳定性是否可以接受。在样本留样时还需考虑医学决定水平附近浓度，评价其关键性变化。

7.3.7.2 室内质量控制（d-g）主要讲述质控频率与质控数据管理，基本上与上一版要求一致

7.3.7.2 d) 室内质量控制的检测频率应基于检验方法的稳定性和稳健性，以及错误结果对患者危害的风险而确定。

CLSI C24-A4 建议的质控频率有分批运行模式、连续运行模式和关键控制点质控。质控频率与校准频率是密切相关的。笔者认为如果实验室校准频率越高，那么相对的失控几率可能就越少。目前对于多久做一次质控没有直接的答案，取决于出现失控时项目发生高风险的概率、处理失控的能力等。Alan Wu 提出项目的失控率越高，则需要使用更多的质控规则来控制。

7.3.7.2 e) 记录结果数据的方式应能检查出趋势和漂移，适用时，应采用统计学技术审核结果。

《医学实验室质量控制实践基础》中建议每个质控数据应有日期和时间，可使用 LJ 图或 Z 分数图以及柱状图等数据分析工具进行分析；记录所有可能引起检测系统稳定性的重要变量，如试剂批号更换、仪器维修、项目定标、更换操作者、更换检测程序等。

7.3.7.2 f) 应按照规定的可接受标准定期评审室内质量控制数据，在某一时段内能够有效提示当前性能。

《WS/T 641-2018 临床检验定量测定室内质量控制》建议每个月或者规定时间内进行统计分析；GB/T 22576 建议绘制室内质控图，可使用 LJ 质控图或 Z 分数图，质控图应标注质控品名称、浓度、批号、效期、检测结果、中心线和控制界线、分析仪器名称和唯一标识、检验方法名称、检验项目名称、试剂和校准物批号、每个数据点的日期和时间、干预行为的记录、检测人员及审核人员的签字。

7.3.7.2 g) 室内质量控制不符合可接受标准时，实验室应避免发布患者结果。

1) 当室内质量控制不符合可接受标准，并提示检验结果可能有明显临床意义的错误时，应拒绝结果，并在纠正错误后重新检验相关患者样品。

2) 实验室应评估最后一次在控的室内质控之后的患者样品结果。

有很多网站、文献及标准文件中都有相应的标准，那哪个才是最好符合规定的可接受标准？其实最好的标准是根据临床要求来制定或选择 TEa。

CLSI C24-A4 的主编 Curtis Parvin，PhD 还提出一些不需要复杂计算的质控策略，可供大家参考使用。

1) 在一批病人样本检测完成时进行一次质控。

2) 缩短两次 QC 时间短于纠正结果所需的时间。

3) 对等组中本实验室 CV 表现，让自己处于前 20%。

4) 设置 QC 靶值在不同的仪器间。

5) 了解 QC 之间患者样本检测数量。

6) 在纠正前评估此次失控的程度。

7) 选择一个合理的 TEa。

8) 当出现失控后，可以复测，但仅复测一次。

9) 高 Sigma 规则目标：降低误拒绝率；低 Sigma 规则目标：增加 QC 频率。

参考附录 Appendix E 即时检测 (POCT)中的内部质量控制

CNAS CL02-A001:2023 补充内容应符合 ISO 15189，7.3.7.2 条款及下列要求：

1) 宜参考相关国家/行业标准建立质量控制程序，如 WS/T 641，内容包括：质控规则（质控规则应确保试验的稳定性和检验结果的可靠性）；质控物的类型、浓度和检测频度；质控物位置（如酶联免疫试验，适用时，用质控物应随机放置且应覆盖检测孔位）；质控记录。

2) 质控物可为商品化质控物或自制质控物。

3) 定量检测项目：应至少使用两个浓度水平（正常和异常水平）的质控物。可利用质控图对质控数据进行统计分析，包括失控时的分析处理 程序和纠正措施等。

4) 定性检测项目：每次实验应设置阴性、弱阳性和/或阳性质控物，并对质控数据进行分析，包括阴、弱阳性和/或阳性结果是否符合预期。

5) 病理实验室：

a) 应制定科内疑难病例讨论制度，每月至少 1 次；

b) 应监测检查结果与既往病理诊断的符合率、术中冰冻和石蜡切片诊断的符合率；

c) 应定期随机抽取病理报告进行内部同行复阅；

d) 应建立细胞和组织学病理报告结果对照的统计分析制度。

e) 应建立妇科细胞学结果统计分析制度，如不满意、阴性、非典型、 低级别及高级别病变的比例等各种病变的比例。

6) 分子诊断实验室：

a) 若开展核酸提取，适当时，应评价核酸的含量和质量（如纯度和完 整性）并保留评价记录。

b) 若开展基因变异、基因多态性或基因型检测，质控物应宜包括临床常见的或者是最具临床价值的变异类型或者基因型。

c) 若开展肿瘤组织分子病理检测应评估样品中肿瘤细胞的含量并记录。

7) 微生物实验室：应至少对使用中的染色剂、凝固酶、过氧化氢酶、氧化酶及抗菌药物敏感性试验等进行质量控制。应贮存与诊断相配套的质控物，以便在染色、试剂、试验、鉴定系统和抗菌药物敏感性试验中使用。药敏用标准菌株种类和数量应满足工作要求，保存其来源、 传代等记录，并有证据表明标准菌株性能满足要求。

2024 年国家卫生健康委临床检验中心室间质量评价标准及 2024 年新增 EQA 计划汇总

国家卫生健康委临床检验中心自 1982 年开始开展全国临床检验室间质量评价活动。40 多年来，室间质量评价计划检验项目范围不断扩大，目前涵盖临床生物化学、免疫学、血液体液学、微生物学、分子生物学、临床输血等主要检验专业的 399 项重要常规检验项目(见参考文献 9)。

参考附录 Appendix F 定义的可接受性标准

大家也可以参考大中华区其他地区发布的关于质量控制设计、质量控制材料选择和替代质量控制程序的指南。

"...定量检验报告已从提供临床诊断、筛检、治疗与预后的参考，逐渐变转换成医療处置的依据。报告是否值得信赖有兩项极为关键的核心工作，其一是采用优良的分析系统，其二就是执行有效的质控程序。质控程序的宽松或严紧，取决于其所服务的医院病人属性。简言之即是临床的需求，才是质控程序订定的最终目的。质控最重要的功能就是确保量测结果的一致性。以科学的途径选择最适宜的质控策略，并且能预测所选择质控策略的执行目标达成率。实验室如何应用已建构完整的质控统计学，订定定量检验质控程序。期望实验室重视分析批次长短 (时间) 或大小 (检体數) 及质控物上机顺序等作法，因为它们都可能影响到错误侦测的能力。对质控规则有更清楚的认知，才能了解错误的類型大小，能更适切的处理品管失效事件"。

摘自

定量检验品管指引 TSLM-MG-AA-08(3), 2019 社团法人台湾医事检验学会 Taiwan Society of Laboratory Medicine (TSLM)

https://www.labmed.org.tw (Accessed 28 February 2024)

重要提示

新版 ISO 15189 依然只是解决“要去做”的问题，没有给出“怎么做”的答案。

正如其标题，ISO 15189 只是规定了医学实验室质量能力的 “requirements”，也就是该文件只关心实验室“要去做”哪些工作，至于“怎么做”，ISO 15189 是没有答案的，新版的也是如此。尤其是厂商和实验室如何准备相应的文件，这在 ISO 15189 是没有任何具体信息的。

之前 ISO 有关医学实验室的各种标准严重缺乏，无法闭环，形成一套完整的文件体系。但是自从 2015 年之后，ISO 开始明显发力，颁布了一系列新标准，诸如：风险管理（ISO 22367:2020）、量值溯源（ISO 17511:2020）等，开始逐步闭环，渐渐独立成一套体系文件。新版 ISO15189 放弃了许多 CLSI 指南的使用，并将他们重新定向到自己的 ISO 文档。随着新版 CNAS-CL02:2023 的启用，那 CNAS-CL02:2023 涉及的 ISO 文件到底有多少？

这也提醒大家，如果想真正理解 ISO 15189，不能只看 ISO 15189 文件，其它相关的 ISO 文件也要一并阅读，才有助于理解其中真意。

https://mp.weixin.qq.com/s/4CmG8aAn1cLIDHCZmmWjfA

(Accessed 25 January 2024)

总结

最后简单总结新版 15189 对室内质控的要求，新版 ISO 15189：2022 版在结构和内容上有所调整，IQC 部分也由原来三个小节调整为 a-g 七个小节。实验室应制定 IQC 程序，根据规定的标准检测结果的持续有效性，以验证达到预期质量，并确保与临床决策相关的有效性。

- 结合 ISO 15189:2022 和 CNAS CL02-A001:2023 的要求
- 考虑不同的临床应用场景，也是对质控的进一步细化要求
- 考虑试剂批间差，校准品批间差的检出，增加线性范围的建议
- 无合适质控品时，比对方法的可以参考，类似于简化版的 PBRTQC
- 遵守并参考我国现有法规行业标准，在 CNAS CL02-A001:2023 中，对分子，病理，微生物的质量要求
- 理解并结合于基础篇室内质量控制体系的基本建立，可以进一步细化即可

参考文献

1. International Organization for Standardization. ISO/IEC 15189:2022 Medical laboratories requirements for quality and competence. Geneva (Switzerland): International Organization for Standardization. 12/2022.
2. WS/T 641-2018 《临床检验定量测定室内质量控制》 http://www.nhc.gov.cn/.....pdf (Accessed 25 January 2024)
3. The Clinical and Laboratory Standards Institute (CLSI) C24-A4 Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions, 4th Edition. September 2016. Clinical and Laboratory Standards Institute, Wayne, PA 19087 USA.

4. CNAS CL02-A001：2023《医学实验室质量和能力认可准则的应用要求》
https://lab.cti-cert.com/static/upload/file/20230830/1693378303792764.pdf
https://www.cnas.org.cn/zxtz/images/2023/08/01/1690872875466098898.pdf
5. The Clinical and Laboratory Standards Institute (CLSI) EP26-A User Evaluation of Between-Reagent Lot Variation; Approved Guideline. September 2013. Clinical and Laboratory Standards Institute, Wayne, PA 19087 USA.
6. GB/T 22576.4-2021 《医学实验室质量和能力的要求》
https://img.antpedia.com/standard/files/.....2021.pdf
7. CNAS GL0-XX1: 202x《医学实验室基于患者数据实时质量控制方法建立及评估指南》（征求意见稿）
https://www.cnas.org.cn/zxtz/images/2023/05/29.....pdf
8. 质控编年史 CNAS- CL02:2023 涉及的 ISO 文件到底有多少？ISO15189 认可纳入的这些 ISO 文件你真的都读了么？
https://mp.weixin.qq.com/s/4CmG8aAn1cLIDHCZmmWjfA
(Accessed 25 January 2024)
9. 《国家卫生健康委临床检验中心室间质量评价标准》
https://mp.weixin.qq.com/s/oWKsx9KdJIJGUr7hGt0DrA
(Assessed 5 February 2024)
10. 定量检验品管指引 TSLM-MG-AA-08(3), 2019 社团法人台湾医事检验学会 Taiwan Society of Laboratory Medicine (TSLM)
https://www.labmed.org.tw (Accessed 28 February 2024)

(This page is intentionally left blank)

如何滿足新版 ISO 15189:2022 對 IQC 的要求

編者鳴謝上海昆涞生物科技有限公司質量控制工作組老師對中文版本文章摘要翻譯提供的協助。

注 1：筆者申明此文講述的是工作組老師對於新版 ISO 15189:2022 關於 IQC 部分內容的認知和理解，幷不代表任何實驗室、認證機構或評審員的建議。

注 2：如有異議一切以英文版本爲准。

新版 ISO 15189 室內質量控制體系應該如何建立

首先我們看一下內容上的變更

原 ISO15189: 2012 版室內質控要素包含三個方面，程序設計，質控品，質控數據。

5.6.2 質量控制

5.6.2.1 總則

實驗室應設計質量控制程序以驗證達到預期的結果質量。注：在某些國家，本條款所指的質量控制也稱爲“內部質量控制”。

5.6.2.2 質控物

實驗室應使用與檢驗系統響應方式盡可能接近患者樣品的質控物。應定期檢驗質控物。檢驗頻率應基於檢驗程序的穩定性和錯誤結果對患者危害的風險而確定。

注 1：只要可能，實驗室宜選擇臨床決定值水平或與其值接近的質控物濃度，以保證決定值的有效性。

注 2：宜考慮使用獨立的第三方質控物，作爲試劑或儀器製造商提供的質控物的替代或補充

5.6.2.3 質控數據

實驗室應制定程序以防止在質控失控時發出患者結果。當違反質控規則幷提示檢驗結果可能有明顯臨床錯誤時，應拒絕接受結果，幷在糾正錯誤情況幷驗證性能合格後重新檢驗患者樣品。實驗室還應評估最後一次成功質控活動之後患者樣品的檢驗結果。應定期評審質控數據，以發現可能提示檢驗系統問題的檢驗性能變化趨勢。發現此類趨勢時應采取預防措施幷記錄。

注：宜儘量采用統計學和非統計學過程控制技術連續監測檢驗系統的性能。

新版 ISO 15189 標準以風險管理爲基礎，以患者爲中心，鼓勵醫學實驗室持續改進。新標準的一些變化：結構進行了調整；結構和管理要求中取消“質量主管”的稱謂；不再强調必須編制“質量手册”；强調“風險管理”相關要求。

對於質量控制，新標準有哪些變化呢？ISO 15189:2012 版中 5.6.2 爲質量控制條款，注中提到在某些國家將質量控制也稱爲“內部質量控制”。每一檢驗程序的規定要求應與該檢驗的預期用途有關，質量控制程序以驗證達到預期的結果質量。ISO 15189:2022 版中，7.3.7.2 爲室內質量控制（IQC）條款，要求制定室內質量控制程序以驗證達到預期質量，幷確保與臨床決策相關的有效性。

從 2003 版發展至 2022 版，ISO 15189 均提到質量控制要驗證達到預期質量。衆所周知，統計質量控制（SQC）是一種重要的監測工具，用于檢測分析系統的不正確度和/或不精密度，幷降低因錯誤結果而導致的患者風險。新版增加了要確保臨床決策相關的有效性，若在質量控制過程中，不考慮人爲差錯導致的失控，SQC 足以滿足質量控制的要求。但實際工作中不可避免會有人爲差錯，需加入風險管理才能降低患者風險。因此新標準以風險管理爲基礎，才能確保與臨床決策相關的有效性。

新版中 IQC 條款新增標準包括考慮項目在不同臨床科室的應用、試劑或校準品批號更換、使用第三方質控品。筆者認爲舊版中使用第三方質控品僅在注解中提到，新版已正式寫入條款正文中，這無疑是對第三方質控品使用要求的加强。下面將講解新版 ISO 15189:2022 對 IQC 的要求，實驗室該如何理解及應對。

新版 ISO 15189：2022 版在結構和內容上有所調整，IQC 部分也由原來三個小節調整爲 a-g 七個小節

A: 質控程序設計

7.3.7.2 a) 實驗室應制定室內質量控制程序，根據規定的標準監測檢驗結果的持續有效性，以驗證達到預期質量，幷確保與臨床決策相關的有效性。

如何制定室內質量控制程序，實驗室可參考《WS/T641-2018 臨床檢驗定量測定室內質量控制》，內容包括但不限于:

1) 定義質量目標；
2) 質控規則；
3) 質控品類型、濃度和檢測頻率；
4) 質控品位置；
5) 質控記錄；
6) 評估患者風險。

7.3.7.2 a)

1) 宜考慮檢驗的預期臨床用途，因爲同一被測量的性能特徵在不同的臨床情況下可能不同。

實驗室需要考慮項目的預期用途，是由於同一項目在不同的臨床科室有不同的應用，如雌二醇是一個激素項目，同時也是一個腫標項目。同一項目不同基質，其允許總誤差也是不同的，如葡萄糖血液基質 TEa 爲 7%，尿液基質 TEa 爲 20%。

參考附錄 Appendix A 分析性能規範 （APS）

7.3.7.2 a)

2) 質量控制程序宜能監測檢驗方法的試劑或/和校準品的批號變化；爲此，在更換試劑或/和校準品批號的同一天/批時，宜避免改變室內質控品的批號。

質量控制程序能監測試劑或校準品批號間變化，因此實驗室要避免更換試劑/校準品批號時，更換質控品批號。CLSI EP26-A 對更換試劑或校準品的性能評價有指導意見，但執行較爲困難；也有相關文獻提出對於試劑/校準品批號更換可進行病人樣本比對計算其偏差是否超過可接受要求。

爲此實驗試劑批號或（和）校準品批號同一天/批發生改變時，宜（應）避免質控批號發生改變。

注解：可以通過定期的比對，對解釋和意見進行監控

參考附錄 Appendix B 批次間試劑驗證

7.3.7.2 a)

3) 宜考慮使用第三方室內質控品，作爲試劑或儀器製造商提供的質控物的替代或補充。

筆者認爲在新版中提到的是“宜”考慮使用第三方質控，而不是“應”，可能是由于在實際工作中幷不是所有項目都有第三方質控 ：

1) 質控品可爲商品化質控物或自製質控物；

2) 若使用自製質控物，需要評估其均匀性和穩定性。

這裏是宜還是（應）英文版原文爲 should，具體翻譯參考 CNAS-CL02:2023

不同的臨床情況下同一測量程序，可能存在濃度或樣本類型不同，臨床應用不同應如何選擇質控品呢？

參考 CLSI C24-A4 5.2 部分內容：

- 基質通常應與患者標本的基質相似；例如：當患者標本爲血清時，血清基質的質控品是合適的。然而， 當使用相同的測量程序同時進行測量，例如血清、血漿、尿液和腦脊液標本時，擁有一組不同的 質控品基質幷不總是實用的。
- 質控品的主要目的在於確定測量程序按預期執行，以確認患者標本的結果適合用于提供醫療服務。當不同的患者標本基質使用相同的測量區間時，且具有合適濃度的單一基質的 QC 樣品可能足以監測性能。
- 在患者標本基質需要不同于其它患者標本使用的測量區間的情況下，有必要確保 QC 策略中包含具有適用于該測量區間的基質和濃度的 QC 樣品。
- 考慮濃度時，也需考慮不同的臨床情景，如 PSA 不同濃度應對常規檢測和術後的監測。
- 同樣質控規則和頻率也應考慮不同的臨床風險

同樣在 CNAS CL02-A001:2023 中也有所强調遵守國家和行業標準要求

增加：試劑批間差或者校準品批間的差異應當被檢測出來，

選擇質控品時，容易走入誤區，認爲是 CV 越做小越好，或不反映出 BIAS 差异越好，這裏我們强調質控品的選擇應當能正確反映出樣本隨監測系統所發生的變化，且這一點，現已納入質控程序設計要求。

第三點內容與原來要求相同，原 ISO15189：2012 版本中，第三方質控的推薦只是寫在“注解“中，在新版中可以看到已經正式寫入室內質控程序設計要求中，這也是第三方質控使用要求進一步加强，幷可參考第一點與第二點來選擇質控品。

參考附錄 Appendix C 獨立或第三方質量控制 （QC） 材料

B: 質控品選擇

7.3.7.2 b) 實驗室應選擇符合預期用途的室內質控品。當選擇室內質控品時，應考慮以下因素：

1) 相關性能的穩定性；

2) 基質盡可能接近患者樣品；

3) 室內質控品對檢驗方法的反應方式盡可能接近患者樣品；

4) 室內質控品滿足檢驗方法的臨床適宜用途，其濃度處于臨床决定限水平或與其接近，可能時，覆蓋檢驗方法的測量範圍。

在原有穩定性，基質、濃度的要求下，新增了覆蓋測量範圍的可能，這裏也參見 CLSI C24-A4 中對于濃度覆蓋測量範圍的舉例，例如，接近測量區間下限或上限的性能對于驗證測量系統在整個測量區間的保持穩定可能很重要。

風險無處不在，爲了降低風險，醫學實驗室應該慎重選擇獨立的第三方質控品，不僅要考慮穩定性，也要考慮成本效益，其濃度水平是否有臨床决策水平，最後該質控品廠商的售後服務，是否能够提供統計分析和總結分析等。

實驗室在選擇時，質控品有一個長期的穩定性，可以更好地監測檢測系統的質量。質控品與患者樣本基質接近，反應方式與患者樣本接近。若質控品使用的是非人類材料和動物源性添加劑，結果可能會出現干擾或偏差。在 ISO 15189:2012 版中要求宜選擇接近臨床决定水平的質控品濃度；2022 版中要求實驗室應選擇符合預期用途的室內質控品，滿足檢驗方法的臨床適宜用途，其濃度處于臨床决定限水平或與其接近。筆者認爲新版對于選擇接近臨床决定水平的質控品不止是建議，若不滿足要求可能會是一個不符合項。但在實際中，實驗室大都只做 2 個質控水平，可能無法與臨床决定限水平相一致。同時由於来自现有市场的質控品複合程

度高，可能無法滿足每個項目的濃度都達到預期。但實驗室仍不能忽視一些重要項目的有意義濃度是臨床所需要的。若是由試劑廠商提供質控品，最好有不同于校準品濃度的質控，可以更好監測項目在定標時出現問題。

C: 替代质量控制程序方法

新增了沒有合適 IQC 質控品時可采用方法，在之前通常爲一些特殊項目沒有合適的商品化質控品，自製質控品又要評價均一性和穩定性，這裏可以作爲一些參考。

7.3.7.2 c) 當無法獲得合適的室內質控品時，實驗室應考慮使用其他方法進行室內質量控制。

IFCC 在 2020 年提出基於患者數據的實時質量控制（PBRTQC），它包括多種運算程序，如正態均值法（AON）、BULL 法、移動中位數法、移動均值法和指數加權移動均值法等。但其實該方法早在 1965 年就已提出，BULL 法被廣泛應用於血細胞分析質量控制。在 2016 年 CLSI 更新了室內質控標準，提出 PBRTQC 可在不額外增加人力和物力成本的情況下即時檢測檢測系統的穩定性和判斷有誤“失控”情況。

7.3.7.2 c)

1) 患者結果的趨勢分析，例如：患者結果的浮動均值，或結果低于或高于特定值的樣品的百分比，或結果與診斷相關的樣品的百分比。

《WS/T 641-2018 臨床檢驗定量測定室內質量控制》提出應用患者數據的質量控制方法包括正態均值法和移動均值法。PBRTQC 可以在一定程度上彌補 IQC 的

不足。PBRTQC 特點是實時監測失控情況，一旦發現失控可及時處理。傳統的質量控制方式不足包括無法監測到長期的系統偏差、低濃度質控水平中不精密度的臨床意義、不能在分析靈敏度下限檢測到小的正偏倚以及不能及時發現檢測系統分析性能的重大變化等、質控失控時處理較難。PBRTQC 可以在每個病人樣本結果生成後進行計算，可即實時監測檢測系統。由於 PBRTQC 需要强大的病人結果數量支持，因此國外對其的應用較少。近期有研究引入一種擴展方法，即回歸調整質量控制（RARTQC），以提高即時質量控制協定的性能，回歸調整後可以提高敏感度。在 2023 年 9 月 Clinica Chimica Acta 發表一篇文章關於 PCRTQC，其重點在於 Pre-classified（預分組）。它擺脫了過去 PBRTQC 的做法，引入臨床視角，將有臨床內在聯繫的不同檢驗項目聯合起來，從而大大提升 PBRTQC 的效能。實驗室在 PBRTQC 系統投入使用前務必進行驗證。

參考附錄 Appendix D 基於患者的實時質量控制 （PBRTQC）

7.3.7.2 c)

2) 按照規定方案，將患者樣品結果與另一替代程序檢測結果比較，該程序經確認可計量溯源至 ISO 17511 規定的同級或者更高級別的參考標準。

7.3.7.2 c)

3) 患者樣品留樣再測。

對於患者樣品留樣再測的方法存在一個較大的限制是樣本中該物質本身的儲存條件及穩定性是否可以接受。在樣本留樣時還需考慮醫學決定水平附近濃度，評價其關鍵性變化。

7.3.7.2 室內質量控制（d-g）主要講述質控頻率與質控數據管理，基本上與上一版要求一致

7.3.7.2 d) 室內質量控制的檢測頻率應基於檢驗方法的穩定性和穩健性，以及錯誤結果對患者危害的風險而確定。

CLSI C24-A4 建議的質控頻率有分批運行模式、連續運行模式和關鍵控制點質控。質控頻率與校準頻率是密切相關的。筆者認爲如果實驗室校準頻率越高，那麼相對的失控幾率可能就越少。目前對於多久做一次質控沒有直接的答案，取决于出現失控時項目發生高風險的概率、處理失控的能力等。Alan Wu 提出項目的失控率越高，則需要使用更多的質控規則來控制。

7.3.7.2 e) 記錄結果數據的方式應能檢查出趨勢和漂移，適用時，應采用統計學技術審核結果。

《醫學實驗室質量控制實踐基礎》中建議每個質控數據應有日期和時間，可使用 LJ 圖或 Z 分數圖以及柱狀圖等數據分析工具進行分析；記錄所有可能引起檢測系統穩定性的重要變量，如試劑批號更換、儀器維修、項目定標、更換操作者、更換檢測程序等。

7.3.7.2 f) 應按照規定的可接受標準定期評審室內質量控制數據，在某一時段內能够有效提示當前性能。

《WS/T 641-2018 臨床檢驗定量測定室內質量控制》建議每個月或者規定時間內進行統計分析；GB/T 22576 建議繪製室內質控圖，可使用 LJ 質控圖或 Z 分數圖，質控圖應標注質控品名稱、濃度、批號、效期、檢測結果、中心綫和控制界綫、分析儀器名稱和唯一標識、檢驗方法名稱、檢驗項目名稱、試劑和校準物批號、每個數據點的日期和時間、干預行爲的記錄、檢測人員及審核人員的簽字。

7.3.7.2 g) 室內質量控制不符合可接受標準時，實驗室應避免發布患者結果。

1) 當室內質量控制不符合可接受標準，幷提示檢驗結果可能有明顯臨床意義的錯誤時，應拒絕結果，幷在糾正錯誤後重新檢驗相關患者樣品。

2) 實驗室應評估最後一次在控的室內質控之後的患者樣品結果。

有很多網站、文獻及標準文件中都有相應的標準，那哪個才是最好符合規定的可接受標準？其實最好的標準是根據臨床要求來制定或選擇 TEa。

CLSI C24-A4 的主編 Curtis Parvin，PhD 還提出一些不需要複雜計算的質控策略，可供大家參考使用。

1) 在一批病人樣本檢測完成時進行一次質控。
2) 縮短兩次 QC 時間短於糾正結果所需的時間。
3) 對等組中本實驗室 CV 表現，讓自己處於前 20%。
4) 設置 QC 靶值在不同的儀器間。
5) 瞭解 QC 之間患者樣本檢測數量。
6) 在糾正前評估此次失控的程度。
7) 選擇一個合理的 TEa。
8) 當出現失控後，可以複測，但僅複測一次。

9) 高 Sigma 規則目標：降低誤拒絕率；低 Sigma 規則目標：增加 QC 頻率。

參考附錄 Appendix E 即時檢測 (POCT)中的內部質量控制

CNAS CL02-A001:2023 補充內容應符合 ISO 15189，7.3.7.2 條款及下列要求：

1) 宜參考相關國家/行業標準建立質量控制程序，如 WS/T 641，內容包括：質控規則（質控規則應確保試驗的穩定性和檢驗結果的可靠性）；質控物的類型、濃度和檢測頻度；質控物位置（如酶聯免疫試驗，適用時，用質控物應隨機放置且應覆蓋檢測孔位）；質控記錄。

2) 質控物可爲商品化質控物或自製質控物。

3) 定量檢測項目：應至少使用兩個濃度水平（正常和異常水平）的質控物。可利用質控圖對質控數據進行統計分析，包括失控時的分析處理 程序和糾正措施等。

4) 定性檢測項目：每次實驗應設置陰性、弱陽性和/或陽性質控物，幷對質控數據進行分析，包括陰、弱陽性和/或陽性結果是否符合預期。

5) 病理實驗室：

a) 應制定科內疑難病例討論制度，每月至少 1 次；

b) 應監測檢查結果與既往病理診斷的符合率、術中冰凍和石蠟切片診斷的符合率；

c) 應定期隨機抽取病理報告進行內部同行複閱；

d) 應建立細胞和組織學病理報告結果對照的統計分析制度。

e) 應建立婦科細胞學結果統計分析制度，如不滿意、陰性、非典型、 低級別及高級別病變的比例等各種病變的比例。

6) 分子診斷實驗室：

a) 若開展核酸提取，適當時，應評價核酸的含量和質量（如純度和完 整性）并保留評價記錄。

b) 若開展基因變異、基因多態性或基因型檢測，質控物應宜包括臨床常見的或者是最具臨床價值的變異類型或者基因型。

c) 若開展腫瘤組織分子病理檢測應評估樣品中腫瘤細胞的含量并記錄。

7) 微生物實驗室：應至少對使用中的染色劑、凝固酶、過氧化氫酶、氧化酶及抗菌藥物敏感性試驗等進行質量控制。應貯存與診斷相配套的質控物，以便在染色、試劑、試驗、鑒定系統和抗菌藥物敏感性試驗中使用。藥敏用標準菌株種類和數量應滿足工作要求，保存其來源、 傳代等記錄，并有證據表明標準菌株性能滿足要求。

2024 年國家衛生健康委臨床檢驗中心室間質量評價標準及 2024 年新增 EQA 計劃匯總

國家衛生健康委臨床檢驗中心自 1982 年開始開展全國臨床檢驗室間質量評價活動。40 多年來，室間質量評價計劃檢驗項目範圍不斷擴大，目前涵蓋臨床生物化學、免疫學、血液體液學、微生物學、分子生物學、臨床輸血等主要檢驗專業的 399 項重要常規檢驗項目(見參考文獻 9)。

參考附錄 Appendix F 定義的可接受性標準

大家也可以參考大中華區其他地區發布的關於質量控制設計、質量控制材料選擇和替代質量控制程序的指南。

"...定量檢驗報告已從提供臨床診斷、篩檢、治療與預後的參考，逐漸變轉換成醫療處置的依據。報告是否值得信賴有兩項極為關鍵的核心工作，其一是採用優良的分析系統，其二就是執行有效的品管程序。品管程序的寬鬆或嚴緊，取決於其所服務的醫院病人屬性。簡言之即是臨床的需求，才是品管程序訂定的最終目的。品管最重要的功能就是確保量測結果的一致性。以科學的途徑選擇最適宜的品管策略，並且能預測所選擇品管策略的執行目標達成率。實驗室如何應用已建構完整的品管統計學，訂定定量檢驗品管程序。期望實驗室重視分析批次長短 (時間) 或大小 (檢體數) 及品管物上機順序等作法，因為它們都可能影響到錯誤偵測的能力。對品管規則有更清楚的認知，才能了解錯誤的類型大小，能更適切的處理品管失效事件"。

摘自

定量檢驗品管指引 TSLM-MG-AA-08(3), 2019 社團法人臺灣醫事檢驗學會 Taiwan Society of Laboratory Medicine (TSLM)

https://www.labmed.org.tw (Accessed 288 February 2024)

重要提示

新版 ISO 15189 依然只是解決“要去做”的問題，沒有給出“怎麼做”的答案。

正如其標題，ISO 15189 只是規定了醫學實驗室質量能力的 “requirements”，也就是該文件只關心實驗室“要去做”哪些工作，至於“怎麼做”，ISO 15189 是沒有答案的，新版的也是如此。尤其是廠商和實驗室如何準備相應的文件，這在 ISO 15189 是沒有任何具體信息的。

之前 ISO 有關醫學實驗室的各種標準嚴重缺乏，無法閉環，形成一套完整的文件體系。但是自從 2015 年之後，ISO 開始明顯發力，頒布了一系列新標準，諸如：風險管理（ISO 22367:2020）、量值溯源（ISO 17511:2020）等，開始逐步閉環，漸漸獨立成一套體系文件。新版 ISO15189 放棄了許多 CLSI 指南的使用,幷將他們重新定向到自己的 ISO 文檔。隨著新版 CNAS-CL02:2023 的啓用，那 CNAS-CL02:2023 涉及的 ISO 文件到底有多少？

這也提醒大家，如果想真正理解 ISO 15189，不能只看 ISO 15189 文件，其它相關的 ISO 文件也要一幷閱讀，才有助于理解其中真意。

https://mp.weixin.qq.com/s/4CmG8aAn1cLIDHCZmmWjfA

(Accessed 25 January 2024)

總結

最後簡單總結新版 15189 對室內質控的要求，新版 ISO 15189：2022 版在結構和內容上有所調整，IQC 部分也由原來三個小節調整爲 a-g 七個小節。實驗室應制定 IQC 程序，根據規定的標準檢測結果的持續有效性，以驗證達到預期質量，幷確保與臨床決策相關的有效性。

- 結合 ISO 15189:2022 和 CNAS CL02-A001:2023 的要求
- 考慮不同的臨床應用場景，也是對質控的進一步細化要求
- 考慮試劑批間差，校準品批間差的檢出，增加綫性範圍的建議
- 無合適質控品時，比對方法的可以參考，類似于簡化版的 PBRTQC
- 遵守幷參考我國現有法規行業標準，在 CNAS CL02-A001:2023 中，對分子，病理，微生物的質量要求
- 理解幷結合于基礎篇室內質量控制體系的基本建立，可以進一步細化即可

參考文獻

1. International Organization for Standardization. ISO/IEC 15189:2022 Medical laboratories requirements for quality and competence. Geneva (Switzerland): International Organization for Standardization. 12/2022.
2. WS/T 641-2018 《臨床檢驗定量測定室內質量控制》 http://www.nhc.gov.cn/old_file/uploadfile/201901.....pdf (Accessed 25 January 2024)
3. The Clinical and Laboratory Standards Institute (CLSI) C24-A4 Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions, 4th Edition. September 2016. Clinical and Laboratory Standards Institute, Wayne, PA

19087 USA.

4. CNAS CL02-A001：2023《醫學實驗室質量和能力認可準則的應用要求》
https://lab.cti-cert.com/static/upload/file/20230830/1693378303792764.pdf

https://www.cnas.org.cn/zxtz/images/2023/08/01/1690872875466098898.pdf

5. The Clinical and Laboratory Standards Institute (CLSI) EP26-A User Evaluation of Between-Reagent Lot Variation; Approved Guideline. September 2013. Clinical and Laboratory Standards Institute, Wayne, PA 19087 USA.
6. GB/T 22576.4-2021 《醫學實驗室質量和能力的要求》
https://img.antpedia.com/standard/files/.....2021.pdf
7. CNAS GL0-XX1: 202x《醫學實驗室基於患者數據實時質量控制方法建立及評估指南》(徵求意見稿)
https://www.cnas.org.cn/zxtz/images/2023/05/29.....pdf
8. 質控編年史 CNAS- CL02:2023 涉及的 ISO 文件到底有多少? ISO15189 認可納入的這些 ISO 文件你真的都讀了麼？
https://mp.weixin.qq.com/s/4CmG8aAn1cLIDHCZmmWjfA
(Accessed 25 January 2024)
9. 《國家衛生健康委臨床檢驗中心室間質量評價標準》
https://mp.weixin.qq.com/s/oWKsx9KdJIJGUr7hGt0DrA
(Assessed 5 February 2024)
10. 定量檢驗品管指引 TSLM-MG-AA-08(3) ,2019 社團法人台灣醫事檢驗學會 Taiwan Society of Laboratory Medicine (TSLM)
https://www.labmed.org.tw (Accessed 28 February 2024)

(This page is intentionally left blank)


HONG KONG ASSOCIATION OF MEDICAL LABORATORIES LIMITED
HKAML
香港醫務化驗所總會