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# EP23™

## Laboratory Quality Control Based on Risk Management

This guideline provides recommendations based on risk management for laboratories to develop quality control plans tailored to the combination of measuring system, laboratory setting, and clinical application of the test.

A guideline for global application developed through the Clinical and Laboratory Standards Institute consensus process.

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## Abstract

Clinical and Laboratory Standards Institute guideline EP23—*Laboratory Quality Control Based on Risk Management* provides recommendations based on risk management for laboratories to develop quality control plans (QCPs) tailored to the combination of measuring system, laboratory setting, and clinical application of the test. Regulatory requirements, information provided by the developer, information pertaining to the laboratory environment, and medical requirements for the test results are evaluated, using risk-management principles, to develop a QCP tailored to the combination of measuring system, laboratory environment, and clinical application. The effectiveness of the laboratory QCP is monitored to detect trends, identify corrective actions, and provide continual quality improvement opportunities. The advantages and limitations of various QC processes are discussed.

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# Foreword

This guideline presumes that the type of measuring system, testing personnel, and location where the test will be performed were all considered before the measuring system was selected. Although the developer is responsible for design quality of its measuring system and reagents, the laboratory and, ultimately, the laboratory director are accountable for the quality of test results. To establish effective QC, laboratories should gather and analyze an array of information (regulatory and accreditation requirements, developer-provided information, the laboratory's environment, and the medical applications of tests performed) through a risk-assessment (RA) process. This process identifies potential weaknesses in the measuring system and test environment that are weighed against the probability for error, the effectiveness of control processes built into the measuring system, and the laboratory's assessment of risk when the clinical use of a laboratory result is considered. This guideline provides recommendations to laboratories for establishing a quality control plan (QCP). Once developed, the QCP is monitored for effectiveness. It is modified when a laboratory process or procedure is revised per regulatory or accreditation requirements and when unanticipated failure modes or underestimated risks of error are discovered. When sufficient objective data demonstrate reliable performance, some control procedures might no longer be needed. The advantages and limitations of a variety of QC measures are discussed to help the laboratory develop a QCP that is appropriate for its measuring system and clinical environment.

This guideline supports the development of an individualized quality control plan (IQCP) under Clinical Laboratory Improvement Amendments requirements[1] and provides guidance for implementing risk management. Compliance with EP23 might not satisfy the requirements of all regulatory, accreditation, or certification organizations. Laboratories need to comply with all applicable regulatory and accreditation requirements when developing QCPs.

## Overview of Changes

This guideline replaces the previous edition of the approved guideline, EP23-A, published in 2011. Several changes were made in this edition, including:

- Aligning EP23 with international standards[2,3] and an IQCP
- Incorporating detectability in the RA
- Replacing the hypothetical "glucose concentration measurement on an automated measuring system" example with a real-world example of a QCP for a noninstrumented single-use device, instrumented single-use device, and exempt microbiological media

**NOTE:** The content of this guideline is supported by the CLSI consensus process and does not necessarily reflect the views of any single individual or organization.


**KEY WORDS**

**analyte**

**individualized quality control plan**

**measurand**

**quality assessment**

**quality control**

**quality control plan**

**risk assessment**

**risk management**

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# Chapter 1

# Introduction

# Laboratory Quality Control Based on Risk Management

## 1 Introduction

### 1.1 Scope

This guideline is intended for global use in laboratories to help determine QC procedures that are appropriate and effective for the test being performed. Developers will also find it useful for understanding laboratory QC requirements and how they will be assessed. The use of risk management is broadly applicable to all processes in the laboratory and can be used beyond the focus of QC. This guideline describes good laboratory practice for developing and maintaining a quality control plan (QCP) for medical laboratory testing using internationally recognized risk-management principles. An individual QCP should be established, maintained, and modified as needed for each measuring system. The QCP is based on the performance required for the intended medical application of the test results. Risk mitigation information obtained from the developer and identified by the laboratory, applicable regulatory and accreditation requirements, and the individual health care and laboratory setting are considered in the development of a QCP.

This guideline supports the development of an individualized quality control plan (IQCP) under Clinical Laboratory Improvement Amendments requirements[1] and provides guidance for implementing risk management. This guideline might not satisfy the requirements of all regulatory, accreditation, or certification organizations. Laboratories need to comply with all applicable requirements when developing QCPs.

### 1.2 Background

Regular performance of intralaboratory QC has been invaluable in ensuring that measuring systems are performing as expected. Existing highly reliable measuring systems, however, demonstrated that conventional intralaboratory QC practices were seemingly excessive (eg, exempt microbiology media, automated systems for microbiology organism identification, or antimicrobial susceptibility testing). The evolution and availability of unit-use test devices (eg, single-use device and/or cassette that contains reagent necessary for performing one test), some with an accompanying measuring system containing integrated controls, measuring system function checks, and/or electronic system and calibration checks additionally identified the need for a different QC process; by design, these unit-use devices did not permit simultaneous testing of intralaboratory control(s) and a patient sample. A risk-assessment (RA) approach incorporates the unique features and performance of each of these measuring systems in individual laboratories, formulated into IQCPs, with the original goal of conventional QC (ie, ensuring reliable and accurate results).

### 1.3 Standard Precautions

Because it is often impossible to know what isolates or specimens might be infectious, all patient and laboratory specimens are treated as infectious and handled according to "standard precautions." Standard precautions are guidelines that combine the major features of "universal precautions and body substance isolation" practices. Standard precautions cover the transmission of all known infectious agents and thus are more comprehensive than universal precautions, which are intended to apply only to transmission of bloodborne pathogens. Published guidelines are available that discuss the daily operations of diagnostic medicine in humans and animals while encouraging a culture of safety in the laboratory.[4] For specific precautions for preventing the laboratory transmission of all known infectious agents from laboratory instruments and materials and for recommendations for the management of exposure to all known infectious diseases, refer to CLSI document M29.[5]

## 1.4 Terminology

CLSI, as a global leader in standardization, is firmly committed to achieving global harmonization whenever possible. Harmonization is a process of recognizing, understanding, and explaining differences while taking steps to achieve worldwide uniformity. CLSI recognizes that medical conventions in the global metrological community have evolved differently in different countries and regions and that legally required use of terms, regional usage, and different consensus timelines are all important considerations in the harmonization process. CLSI recognizes its important role in these efforts, and its consensus process focuses on harmonization of terms to facilitate the global application of standards and guidelines. Table 1 is provided to clarify the intended interpretations of common terms.

**NOTE:** Laboratories and commercial manufacturers are collectively referred to as "developers" in this guideline.

**Table 1. Common Terms or Phrases With Intended Interpretations**

| Term or Phrase | Intended Interpretation |
|---|---|
| "Needs to" or "must" | Explains an action directly related to fulfilling a regulatory and/or accreditation requirement or is indicative of a necessary step to ensure patient safety or proper fulfillment of a procedure |
| "Require" | Represents a statement that directly reflects a regulatory, accreditation, performance, product, or organizational requirement or a requirement or specification identified in an approved documentary standard |
| "Should" | Describes a recommendation provided in laboratory literature, a statement of good laboratory practice, or a suggestion for how to meet a requirement |
| "May" | Indicates permission |

### 1.4.1 Definitions

For purposes of this guideline, the terms and definitions listed below apply. Consult CLSI's Harmonized Terminology Database at https://htd.clsi.org for related terms and definitions.

**acceptable risk** – a state achieved in a measuring system in which all known potential events have a degree of likelihood for or a level of severity of an adverse outcome small enough such that, when balanced against all known benefits (whether perceived or real), patients, physicians, institutions, and society are willing to risk the consequences.

**accuracy (of measurement)** – closeness of agreement between a measured quantity value and a true quantity value of a measurand.[6]

**allowable error limits** – symmetrical tolerance, plus and minus, around the target value for an analyte.

**analyte** – component represented in the name of a measurable quantity[7]; **NOTE:** In the type of quantity "mass of protein in 24-hour urine," protein is the analyte. In "amount of substance of glucose in plasma," glucose is the analyte. In both cases, the long phrase represents the measurand.[7]

**assayed quality control material** – control materials with assigned analyte values provided by the manufacturer.

**bias (of measurement)** – estimate of a systematic measurement error.[6]

**built-in** – anything incorporated into the measuring system by the manufacturer.

**commutability (of a reference material)** – property of a reference material, demonstrated by the closeness of agreement between the relation among the measurement results for a stated quantity in this material, obtained according to two given measurement procedures, and the relation obtained among the measurement results for other specified materials[6]; **NOTE 1:** Commutability is a property of a reference material, demonstrated by the equivalence of the mathematical relationships among the results of different measurement procedures for a reference material and for representative samples of the type intended to be measured; **NOTE 2:** A property of a reference material that relates to the closeness of agreement for a reference material and results for clinical samples when measured by two or more measurement procedures.[8]

**continual improvement** – recurring activity to enhance performance[9]; **NOTE 1:** Also known as continuous improvement; **NOTE 2:** Includes the actions taken throughout an organization to increase the effectiveness and efficiency of activities and processes to provide added benefits to the customer and organization[10]; **NOTE 3:** The process of establishing objectives and finding opportunities for improvement is a continual process through the use of audit findings and audit conclusions, analysis of data, management reviews, or other means and generally leads to corrective (or preventive) action.[9]

**control point** – a point, step, or procedure in a process at which a control can be applied, and as a result, a hazard can be prevented, eliminated, or reduced.

**corrective and preventive action (CAPA):**

- **corrective action** – action taken to eliminate the cause of the existing nonconformity to prevent its recurrence[11]; **NOTE 1:** There may be more than one cause for a nonconformity; **NOTE 2:** Corrective action is taken to prevent recurrence, whereas preventive action is taken to prevent occurrence.[9]
- **preventive action** – action taken to eliminate the cause of potential nonconformity[11]; **NOTE:** There can be more than one cause for a potential nonconformity.

**critical-risk results** – a category of quantitative, semiquantitative, or qualitative results of laboratory or anatomic pathology examinations that signify immediate risk of major adverse outcomes. These results need to be actively communicated to responsible health care providers without delay to ensure urgent clinical evaluation and medical intervention.

**detectability** – the ability to discover or determine the existence, presence, or fact of a hazard.[12]

**electronic control** – control procedure or algorithm that checks the electronics, software, or other components or procedures of a diagnostic measuring system via electronic circuits or software logic.

**environmental factors** – conditions that may affect the analysis that include but are not limited to temperature, airflow, humidity, barometric pressure, light, power supply, vibration, electromagnetic radiation, and water.

**error (measurement)** – measured quantity value minus a reference quantity value[6]; deviation from truth, accuracy, or correctness; includes mistakes; **NOTE:** In EP23, the term "error" includes but is used in a much broader sense than the International Vocabulary of Metrology term "error of measurement."

**examination** – set of operations having the object of determining the value or characteristics of a property[13]; **EXAMPLE:** A test procedure or measurement procedure.

**failure** – in the broadest sense, a case when the system does not meet the user's expectation; **NOTE 1:** This includes the inability to perform its intended functions satisfactorily or within specified performance limits; **NOTE 2:** Errors of measurement and errors of use are subsets of failures.

**failure mode** – manner by which a failure occurs.

**fault** – state of an item, characterized by the inability to perform a required function, excluding inabilities due to preventive maintenance, other planned actions, or lack of external resources.

**fishbone diagram** – diagram that shows the causes of a certain event; **NOTE:** Common uses of the diagram are product design and quality defect prevention to identify potential factors causing an overall effect.

**harm** – injury or damage to the health of people, or damage to property or the environment[14]; **NOTE:** In EP23, damage to property or the environment is considered harmful only if that damage directly harms people.

**hazard** – potential source of harm.[14]

**imprecision** – the random dispersion of a set of replicate measurements, values, or both expressed quantitatively by a statistic, such as standard deviation or coefficient of variation; **NOTE:** It is defined in terms of repeatability and reproducibility. See also **precision.**

***in vitro* diagnostic medical device** – a device, whether used alone or in combination, intended by the manufacturer for the *in vitro* examination of specimens derived from the human body solely to provide information for diagnostic, monitoring, or compatibility purposes. This includes reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles.[15]

**incorrect result** – result that does not meet the requirements for its intended medical use; **NOTE 1:** In the case of quantitative test procedures, a result with a failure of measurement that exceeds a limit based on medical utility; **NOTE 2:** In the case of qualitative test procedures, a result that is contrary to a true value of the measurand.

**instructions for use (IFU)** – information supplied by the manufacturer with an *in vitro* diagnostic medical device concerning the safe and proper use of the reagent(s), calibrator(s), and control(s) or the safe and correct operation, maintenance, and basic troubleshooting of the instrument.[16]

**laboratory director** – competent person(s) with responsibility for and authority over a laboratory[13]; **NOTE 1:** The person or persons referred to are designated collectively as laboratory director[13]; **NOTE 2:** National, regional, and local regulations may apply with regard to qualifications and training.[13]

**matrix (of a material system)** – totality of components of a material system except the analyte.[7]

**matrix effect** – influence of a property of the sample, other than the measurand, on the measurement of the measurand according to a specified measurement procedure and thereby on its measured value.[7]

**measurand** – quantity intended to be measured[6]; **NOTE 1:** The specification of a measurand requires knowledge of the kind of quantity, description of the state of the phenomenon, body, or substance carrying the quantity, including any relevant component, and the chemical entities involved[6]; **NOTE 2:** A measurand can refer to an analyte concentration, a clotting time, an enzyme activity, an epitope, etc., in a particular sample type.

**measurement** – process of experimentally obtaining one or more quantity values that can reasonably be attributed to a quantity.[6]

**measuring system** – set of one or more measuring instruments and often other devices, including any reagent and supply, assembled and adapted to provide information used to generate measured quantity values within specified intervals for quantities of specified kinds[6]; **NOTE:** May also be referred to as a measurement system.

**middleware** – software and hardware inserted between instrument(s) and/or automation line(s) and the laboratory information system to facilitate the management of the instrument, test requests, validation of results, and reporting.[17]

**mitigation** – an action to lower or eliminate the risk associated with an adverse situation or to prevent the occurrence of future errors.

**postexamination (postanalytical phase)** – processes following the examination, including review of results, retention and storage of clinical material, sample (and waste) disposal, and formatting, releasing, reporting, and retention of examination results.[13]

**precision (of measurement)** – closeness of agreement between indications or measured quantity values obtained by replicate measurements on the same or similar objects under specified conditions[6]; **NOTE 1:** Measurement precision is usually expressed numerically by measures of imprecision, such as standard deviation, variance, or coefficient of variation under the specified conditions of measurement[6]; **NOTE 2:** The "specified conditions" can be, for example, repeatability conditions of measurement, intermediate precision conditions of measurement, or reproducibility conditions of measurement[6]; **NOTE 3:** Measurement precision is used to define measurement repeatability, intermediate measurement precision, and measurement reproducibility.[6]

**preexamination (preanalytical phase)** – processes that start, in chronological order, from the clinician's request and include the examination request, preparation and identification of the patient, collection of the primary specimen(s), and transportation to and within the laboratory and that end when the examination begins.[13]

**process mapping** – graphical descriptions of processes that include detailed flow charts, workflow diagrams, and value stream maps; **NOTE:** A lean manufacturing technique used to analyze the flow of materials and information currently required to bring a product or service to a consumer.

**quality** – degree to which a set of inherent characteristics of an object fulfills requirements.[9]

**quality assessment** – an ongoing mechanism to monitor, assess, and when indicated, correct identified problems.

**quality assurance** – part of a quality management system focused on providing confidence that quality requirements will be fulfilled.[9]

**quality control (QC)** – part of a quality management system focused on fulfilling quality requirements[9]; **NOTE 1:** The set of mechanisms, processes, and procedures designed to monitor the measuring system to ensure the results are reliable for the intended clinical use; **NOTE 2:** Includes the operational techniques and activities used to fulfill requirements for quality; **NOTE 3:** In medical laboratory testing, QC includes the procedures intended to monitor the performance of a test procedure to ensure reliable results; **NOTE 4:** A system for ensuring maintenance of proper standards by periodic inspection of the results and the operational techniques that are used to ensure accuracy and reproducibility.

**quality control plan (QCP)** – a document that describes the practices, resources, and sequences of specified activities to control the quality of a particular measuring system or test process to ensure requirements for its intended purpose are met; **NOTE:** An individualized quality control plan (IQCP) is the Clinical Laboratory Improvement Amendments procedure for an alternate QC option allowed by 42 CFR §493.1250.[1] The Centers for Medicare & Medicaid Services guidance and concepts for IQCP are a formal representation and compilation of many current laboratory practices to ensure quality test results. IQCP permits the laboratory to customize its QCP according to test method and use, environment (laboratory setting), and testing personnel while providing for equivalent quality testing.

**quality control sample** – a stable sample designed to monitor performance of a test system that is intended to measure patient sample measurands and hence simulate the response of the test system to a patient specimen matrix.

**quality management system (QMS)** – part of the management system with regard to quality; **NOTE 1:** Systematic and process-oriented efforts are essential to meet quality objectives; **NOTE 2:** The "quality" referred to in this definition relates to both management and technical competence[13]; **NOTE 3:** A QMS typically includes the organizational structure, resources, processes, and procedures needed to implement quality management; **NOTE 4:** These principles include the following categories: Organization and Leadership, Customer Focus, Facilities and Safety Management, Personnel Management, Supplier and Inventory Management, Equipment Management, Process Management, Documents and Records Management, Information Management, Nonconforming Event Management, Assessments, and Continual Improvement.

**reliability** – probability that an item will perform its required function under given conditions for a stated time interval.

**repeatability (of measurement)** – measurement precision (closeness of agreement between indications or measured quantity values obtained by replicate measurements on the same or similar objects under specified conditions) is a set of repeated measurements that includes the same measurement procedure, same operators, same measuring system, same operating conditions, and same location, and replicate measurements on the same or similar objects over a short period of time.[6]

**residual risk** – risk remaining after risk control measures have been taken.[3]

**risk** – combination of the probability of occurrence of harm and the severity of that harm.[14]

**risk analysis** – systematic use of available information to identify hazards and to estimate the risk[14]; **NOTE:** Risk analysis includes examination of different sequences of events that can produce hazardous situations and harm.[13]

**risk assessment (RA)** – overall process composed of a risk analysis and a risk evaluation.[14]

**risk estimation** – process used to assign values to the probability of occurrence of harm and the severity of that harm.[3]

**risk evaluation** – process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk.[3]

**risk management** – systematic application of management policies, procedures, and practices to the tasks of analyzing, evaluating, controlling, and monitoring risk.[3]

**root cause analysis** – systematic process for identifying "root causes" of problems or events and an approach for responding to them[18]; **NOTE:** Root cause analysis is based on the idea that effective management is not merely "managing unexpected emergencies" for problems that develop but finding a way to prevent them.[18]

**sample** – one or more parts taken from a system, and intended to provide information on the system, often to serve as a basis for decision on the system or its production[13]; **EXAMPLE:** A portion of serum taken from a specimen of coagulated blood.

**severity** – measure of the possible consequences of a hazard.[3]

**specimen (patient)** – discrete portion of a body fluid or tissue taken for examination, study, or analysis of one or more quantities or characteristics, to determine the character of the whole[19]; **NOTE:** In some countries, the term "specimen" may be used to mean a sample of biological origin intended for examination by a medical laboratory.[19]

**stability** – the ability of an *in vitro* diagnostic (IVD) reagent to maintain its performance characteristics consistently over time; **NOTE:** Stability applies to IVD reagents, calibrators, and controls when stored, transported, and used in the conditions specified by the manufacturer; reconstituted lyophilized materials, working solutions, and materials removed from sealed containers when prepared, used, and stored according to the manufacturer's instructions for use; and measuring instrument or measuring systems after calibration.

**system** – set of interrelated or interacting elements.[9]

**systematic error (of measurement)** – component of measurement error that in replicate measurements remains constant or varies in a predictable manner[6]; **NOTE 1:** A reference quantity value for a systematic measurement error is a true quantity value, or a measured quantity value of a measurement standard of negligible measurement uncertainty, or a conventional quantity value[6]; **NOTE 2:** Systematic measurement error and its causes can be known or unknown. A correction can be applied to compensate for a known systematic measurement error[6]; **NOTE 3:** Systematic measurement error equals measurement error minus random measurement error.[6]

**test** – determination according to requirements for a specific intended use or application.[9]

**trueness (of measurement)** – closeness of agreement between the average of an infinite number of replicate measured quantity values and a reference quantity value[6]; **NOTE:** Trueness is usually expressed numerically by the statistical measure "bias," which is inversely related to trueness.

**trueness control material** – a reference material with measurand value assigned by a procedure traceable to a higher-order reference system and with commutability properties suitable for use to assess the bias of measurement of a specified measurement procedure.[7]

**unassayed quality control material** – control material that has no assigned analyte values provided by the manufacturer.

**unit-use test system** – *in vitro* diagnostic medical device in which reagents, calibrators, sample conduits, vessels, and other reaction components supplied in a disposal carrier require no user preparation before the analysis and are used in the examination of a single sample.

**use error** – act or omission of an act that has a different medical device response than that intended by the manufacturer or expected by the operator[19]; **NOTE:** User action or lack of user action using the medical device that leads to a different response intended by the manufacturer or expected by the user.

**user** – the laboratory or person using the measuring system; **NOTE:** Person interacting with (operating or handling) the medical device.

### 1.4.2 Abbreviations and Acronyms

| | |
|---|---|
| **CV** | coefficient of variation |
| **EQA** | external quality assessment |
| **IFU** | instructions for use |
| **IQCP** | individualized quality control plan |
| **IVD** | *in vitro* diagnostic |
| **LIS** | laboratory information system |
| **PT** | proficiency testing |
| **QC** | quality control |
| **QCP** | quality control plan |
| **QMS** | quality management system |
| **RA** | risk assessment |
| **RMI** | risk management index |
| **RPN** | risk priority number |
| **SD** | standard deviation |

### 1.4.3 Symbols

| | |
|---|---|
| $P_H$ | probability of patient harm |
| $P_E$ | probability of producing erroneous results |
| $P_{E\|H}$ | probability of an erroneous result harming a patient |

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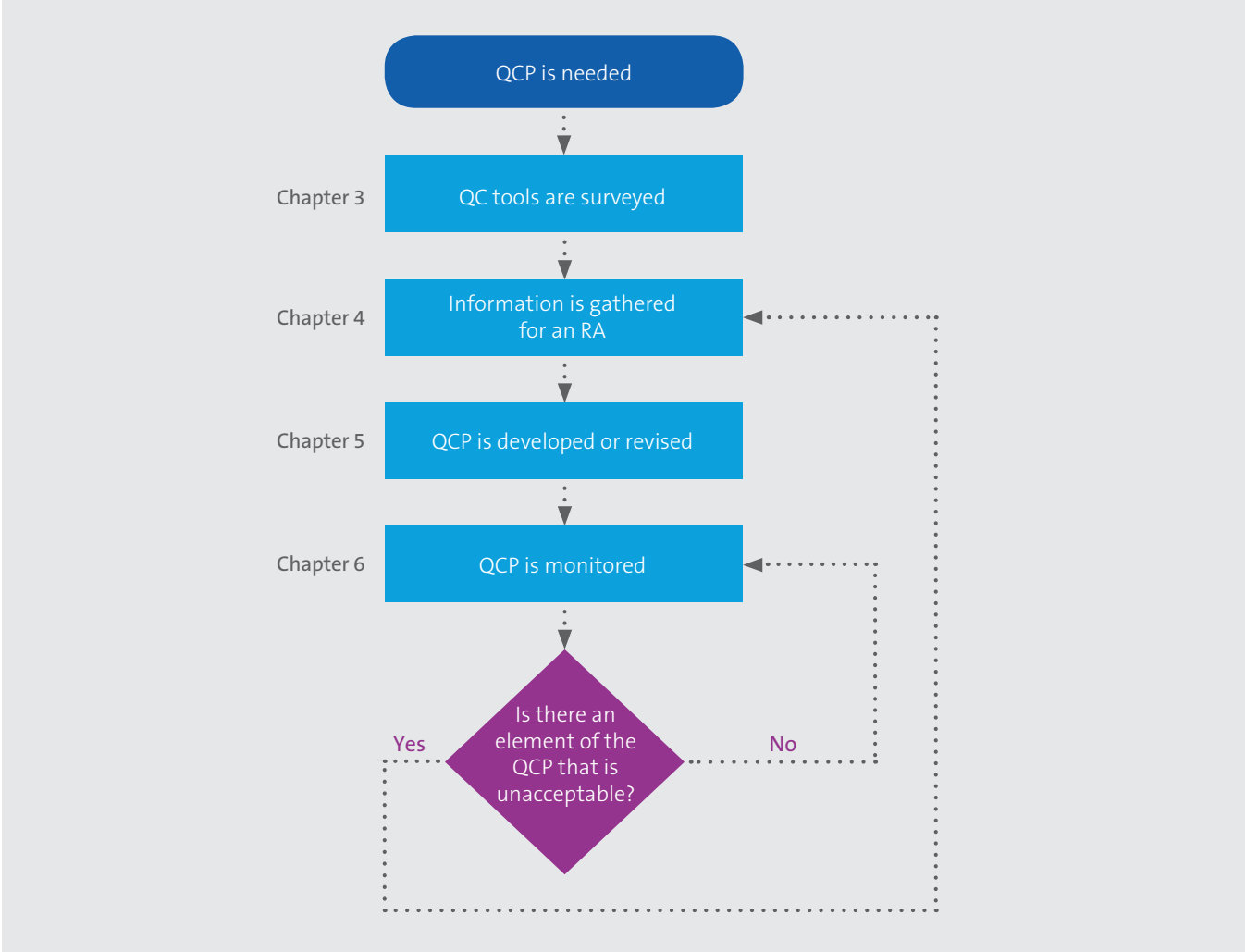
# Chapter 2

# Path of Workflow

# 2 Path of Workflow

## 2.1 Process Flow Chart

A basic overview of the processes involved in developing a QCP is shown in Figure 1.




Abbreviations: QC, quality control; QCP, quality control plan; RA, risk assessment.
[a] Four basic symbols are used in this process flow chart: oval (signifies the beginning or end of a process), arrow (connects process activities), box (designates process activities), diamond (includes a question with alternative "Yes" and "No" responses).

**Figure 1. Process Flow Chart for QCPs[a]**

## 2.2 Overview of the Quality Control Plan

Health care providers need test results that are relevant, accurate, timely, and reliable for patient care. Several factors can adversely affect the quality of test results and present risk to the patient, from failures of the measuring system, to operator errors, to environmental conditions. Failure is used in this guideline in the context of risk management and means, in the broadest sense, a case when the system does not meet the user's expectation. Errors should be considered, specifically operation of a device within the intended use as well as reasonably foreseeable misuse of a device. Failure includes the inability of a measurement process to perform its intended functions satisfactorily or within specified performance limits, errors of a measuring system that can produce an incorrect result (or a misidentified, delayed, or corrected result), and incorrect use of a measuring system that can cause an incorrect result. Risk management is the systematic application of management policies, procedures, and practices to the tasks of analyzing, evaluating, controlling, and monitoring risk. QC in this guideline is defined as the set of operations, processes, and procedures designed to monitor the measuring system to ensure the results are reliable for the intended clinical use. In this context, QC is broader than, although not necessarily exclusive of, the measurement of QC samples intended to simulate clinical patient samples.

A QCP is a documented strategy that describes the practices, resources, and sequences of specified activities to control the quality of a measuring system or measurement process to ensure intended purposes are met. The laboratory establishes QCPs to minimize failures, detect nonconformities, and implement corrective actions to handle failures that can occur before incorrect results are reported to health care providers and clinical action is taken.

Developing a QCP necessitates an understanding of the preexamination (preanalytical), examination (analytical), and postexamination (postanalytical) processes, as well as identification of the weaknesses (potential failure modes) in these processes when failures can affect a measuring system and potentially cause patient harm. Appendix A lists potential sources of error in the workflow. Risk should be considered throughout the test life phases of a device or test in the laboratory. The Test Life Phases Model presented in CLSI document EP19[20] takes a measuring system through different phases. It starts with the Feasibility and Design Phase, when methodology is selected, through the Retirement Phase, when testing is stopped or a measuring system is replaced. If a laboratory needs additional information to create a QCP, it should contact the developer and request that information.

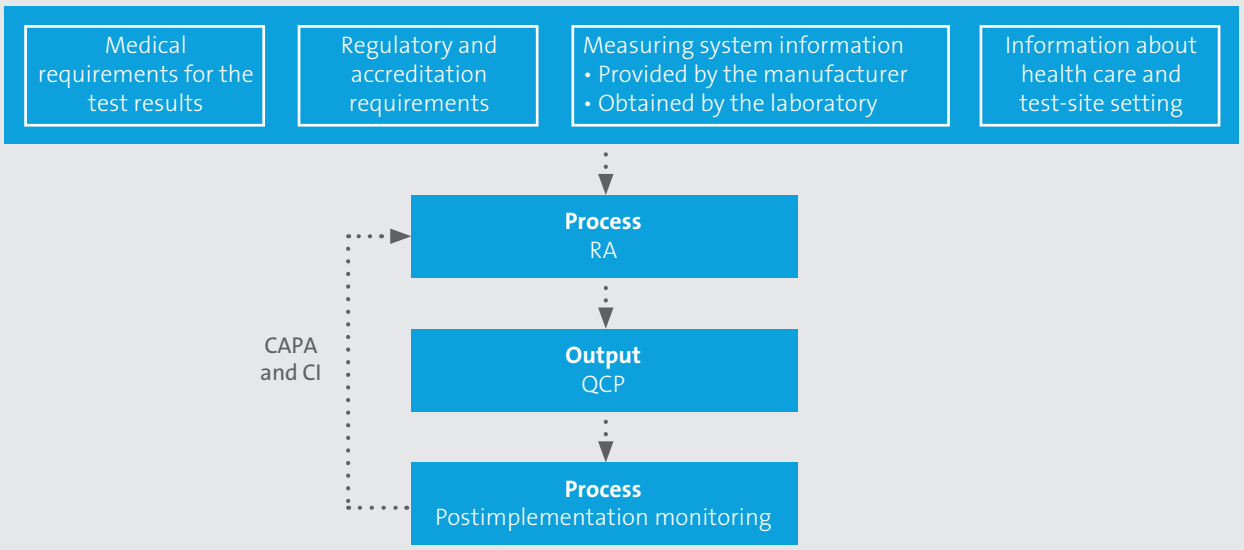
The laboratory should manage risk by implementing QCPs that provide for immediate detection of errors caused by measuring system failure, adverse environmental conditions, and operator performance. QCPs should serve to mitigate the occurrence of errors and to ensure test result quality is appropriate for clinical use of the information by:

- Monitoring the testing process for the occurrence of errors related to the accuracy and precision of test performance that can be influenced by changes in the sample, measuring system, testing materials, environment, or variance in operator performance
- Introducing QC procedures that specify the amount, type, and frequency of QC necessary based on the frequency and volume of patient testing
- Taking corrective actions to include investigation of the root cause and identification of steps to mitigate failures

Given the variety of testing and settings in a typical health care facility, with measuring systems, examination procedures, laboratory environments, and clinical applications, laboratories need guidance to determine effective combinations of QC strategies to achieve reliable test results. This guideline discusses some of the QC tools available to the laboratory and summarizes their advantages and limitations. It describes an approach to develop a QCP that involves the following procedures:

- Collecting the necessary information from developers, the literature, regulatory and accreditation agencies, the laboratory's particular environment, and the clinical application of test results
- Conducting an RA
- Identifying effective QC measures to reduce risk
- Monitoring the QCP for elements that are unacceptable

In the risk management process, attempts are first made to identify and eliminate the causes of potential process and system failures before measures to detect failures and/or their effects (eg, incorrect test results) are implemented. Activities to monitor ongoing performance are directed toward the identification of unpredicted events that cause risks, modification of the QCP, and continual improvement. Figure 2 shows the inputs needed to develop and continually improve a QCP.




Abbreviations: CAPA, corrective and preventive action; CI, continual improvement; QCP, quality control plan; RA, risk assessment.

**Figure 2. Process to Develop and Continually Improve a QCP**

## 2.3 Risk Management

Applying risk management to the entire life of a laboratory measuring system (ie, *in vitro* diagnostic [IVD] medical device) is described for developers in international standards.[3] The principles described are adapted in this guideline for use by laboratories to develop a QCP for measuring systems currently in use or introduced in a health care setting.

The central component of the overall risk management process is RA. It is based on analysis (identifying hazards and estimating the probability and severity of harm) and evaluation of risks that can result from a measuring system failure, as shown in Figure 3.

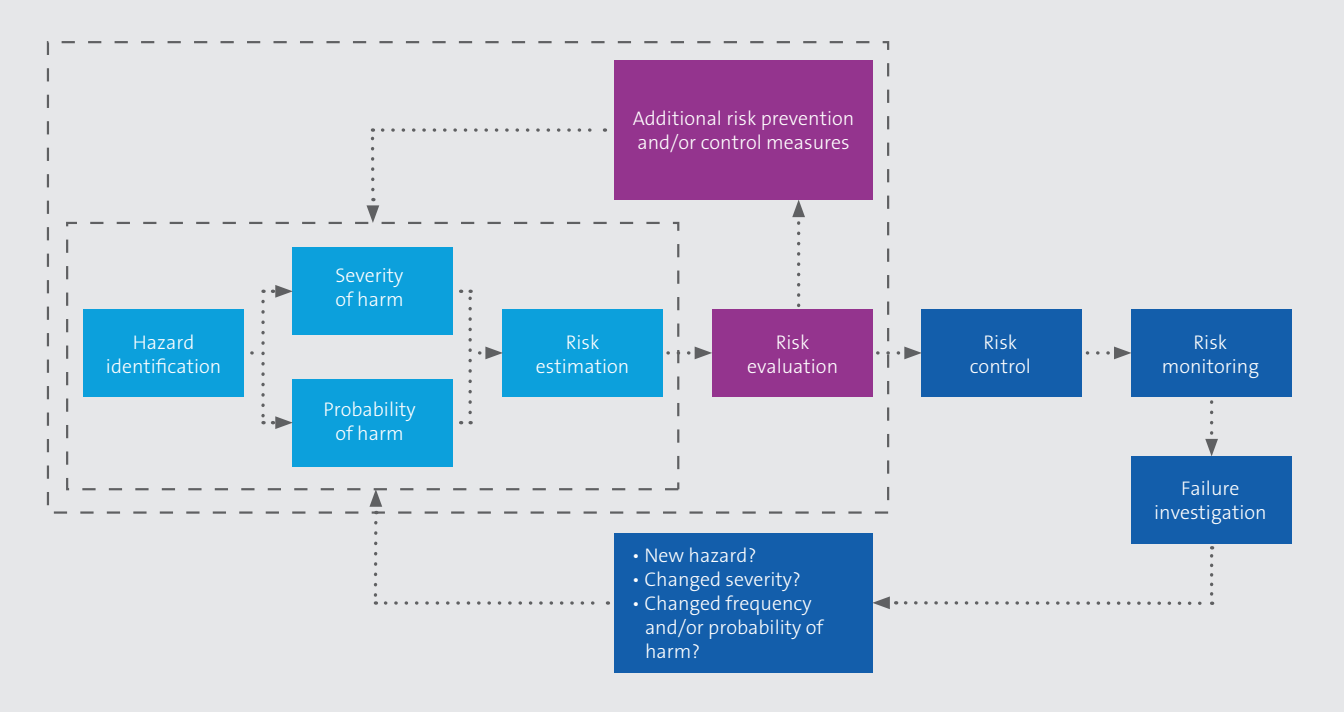



**Figure 3. Risk Management Process**

During the RA process, each laboratory should consider how built-in and laboratory-applied QC procedures for a measuring system can detect and reduce the risk from an erroneous result, a delayed result, or nondelivery of a result. When RA is performed, information on the performance required for the medical applications of the test results (see Subchapter 4.1), the measuring system (see Subchapter 4.3), and the laboratory (see Subchapter 4.4) should be considered. Risk estimation is the combination of the probability of occurrence of harm and the severity of that harm. Risk estimation should account for the hazardous situations that can occur from incorrect test results or delays in treatment.

Residual risk remains after all control measures have been implemented to detect, prevent, and/or mitigate adverse events that cannot be avoided by improving the measuring system or its components, processes, or testing personnel. A determination of the acceptability of this residual risk to the patient is made for the specific clinical application for which a test result is to be used. This determination is based on an evaluation of the potential costs both in terms of the patient's well-being and financial liability of the treating parties vs known benefits to the patient. All laboratory tests have some associated residual risk. Therefore, if the known residual risk is found to be unacceptable, a determination should be made regarding the feasibility of adding more risk control measures vs avoiding the risk by not implementing the test or the measuring system being considered.

A QCP is developed to reduce residual risk (see Subchapter 5.5), initially through measures that prevent failures from occurring, followed by methods that detect failures in time to prevent harm. The final QCP is the aggregate of all laboratory-applied QC procedures required to achieve clinically acceptable patient risk. The final QCP should also comply with all regulatory and accreditation requirements.

Once the QCP is implemented, any future incidents of measuring system failure are investigated to determine the sources of failure and whether modification of the QCP is necessary (see Chapter 6). If a new hazard is identified, or if the severity or probability of harm is greater than anticipated, or the ability to detect and prevent the hazard is impaired, the output of risk monitoring feeds back to the appropriate step in the RA process, and risk control procedures are revised to reduce the risk to an acceptable level. The laboratory should ensure that there are no unintended consequences before implementing the new risk control. The laboratory is ultimately responsible for ensuring that the testing processes and the QCPs can provide the analytical quality of results required for patient care.

## 2.4 Process Mapping

It is useful to break down the total testing process into steps to facilitate identification of steps with significant potential for failure and enable the laboratory to recognize potential failure modes that can present significant risks to patients and to identify opportunities in the process to control these risks. For effectiveness, process mapping should provide a useful level of detail.

To create a process map, the steps of the preexamination, examination, and postexamination phases are outlined to facilitate identification of the potential failure modes and possible control points (see Table 2).

**Table 2. Key Processes in the Laboratory Path of Workflow[a]**

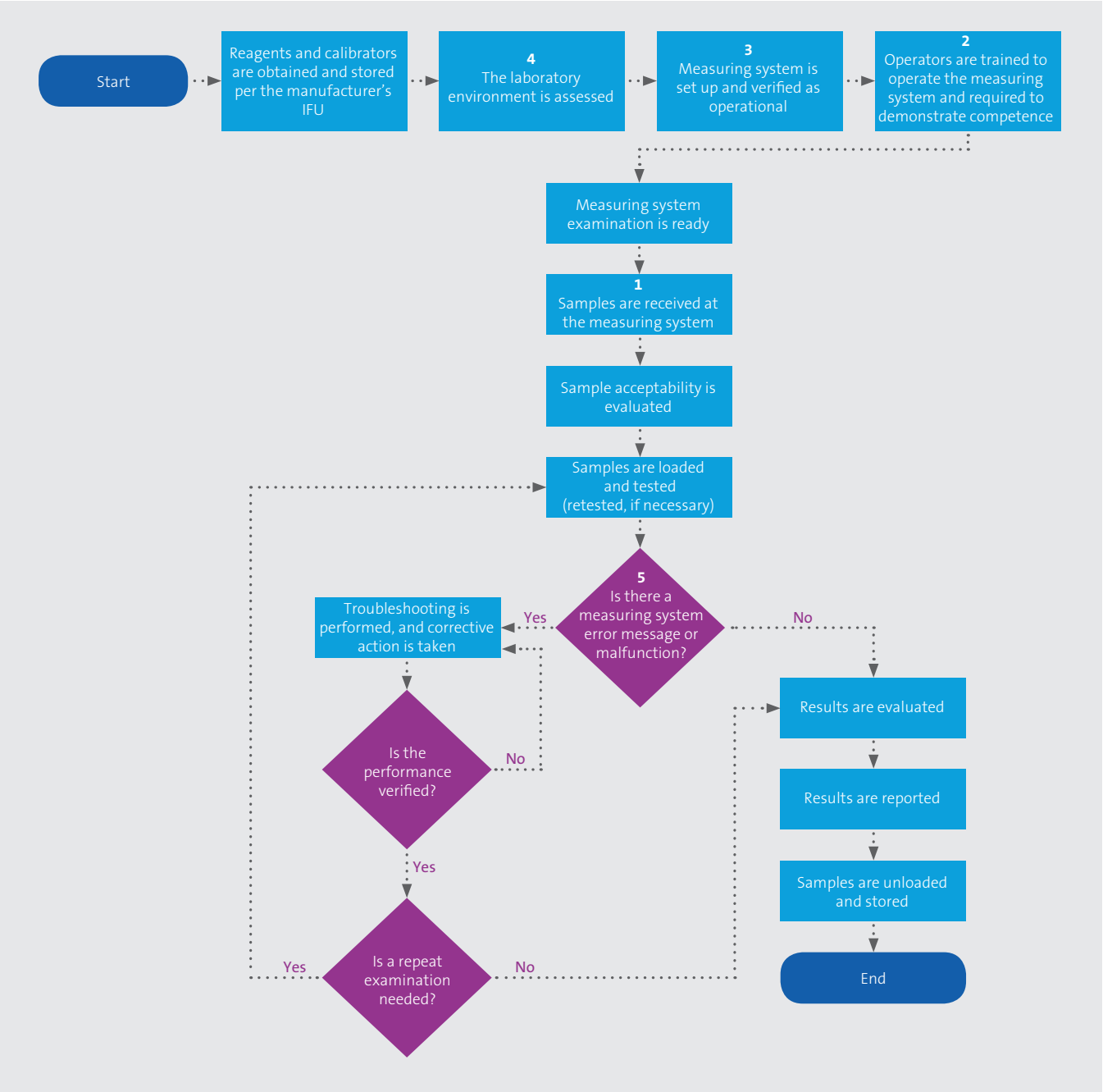
| Preexamination Processes | Examination Processes | Postexamination Processes |
|---|---|---|
| • Examination ordering<br>• Specimen collection<br>• Specimen transport<br>• Specimen receipt, accessioning, and processing<br>• Specimen storage | • Examination method selection<br>• Examination performance<br>• Results review and follow-up<br>• Laboratory results interpretation | • Communication of critical values and issuance of preliminary reports<br>• Release of final reports<br>• Specimen management<br>• Data and report storage |

[a] See CLSI documents QMS01[21] and QMS02[22] for more information.

The following list provides some topics to consider for developing a process map when an automated measuring system is used. In many cases, the same logic can apply to a group of measurands and/or analytes performed on a single measuring system or to a group of identical measuring systems used within a health care environment. A single QCP can apply to a measuring system or multiple measuring systems, or to individual measurands and/or analytes.

- **Operator training and competence:** An operator is trained to operate the measuring system and required to demonstrate competence to follow the developer's instructions for use (IFU).
- **Start-up:** The measuring system is set up and verified as operational before patient samples can be tested.
- **Reagent, calibrator, and/or parts procurement and storage:** Reagents and calibrators are obtained from the developer and distributors and handled and stored in the laboratory according to the manufacturer's IFU.
- **Calibration:** The measuring system is calibrated, and its performance is evaluated to verify that the measuring system is functioning within specification.
- **Proper device function:** For automated measuring systems, the measuring system conducts the test by pipetting the required volume of sample, mixing it with the appropriate amount of reagent, incubating it for the appropriate time at the appropriate temperature, and measuring the measurand and/or analyte concentration by comparing the response with the calibration function.
- **Patient sample acceptability evaluation:** A sample should be available in the appropriate collection tube, evaluated for integrity, and processed as intended.
- **Loading and testing of patient samples:** For analysis, the operator places a prepared sample tube on the measuring system intake component where the bar-coded label can be read to identify the specific patient sample, or a load list can be prepared to identify the sequence of samples.
- **Test result review:** A test result is generated unless the measuring system detects a problem, in which case, the result is suppressed and an error code is displayed.

After the measuring system is set up, performance is verified and characterized before patient samples are measured. During the process performance characterization, the process error may be evaluated with either uncertainty analysis (top-down modeling) or with error propagation (bottom-up modeling) approaches. Additional information can be found in CLSI documents EP29[23] (measurement uncertainty) and EP21[24] (total analytical error). A high-level measurement process map is shown in Figure 4. Many of these processes are common to other measuring systems.

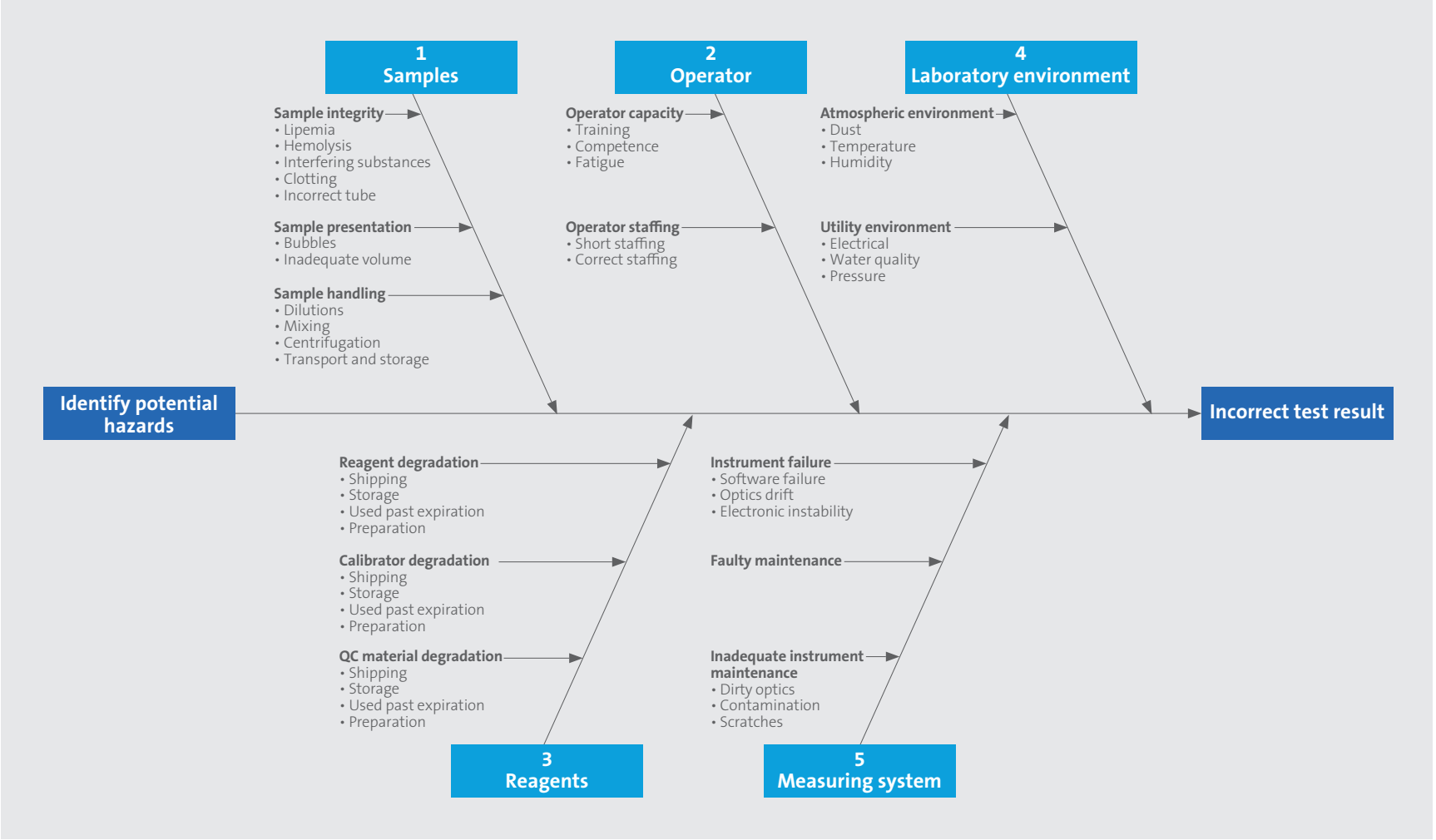



Abbreviation: IFU, instructions for use.

[a] Four basic symbols are used in this process flow chart: oval (signifies the beginning or end of a process), arrow (connects process activities), box (designates process activities), diamond (includes a question with alternative "Yes" and "No" responses).

**Figure 4. Example of Process Map.**[a] The intent of this process map is to help identify potential steps in the process that might require subsequent failure modes and effect analysis. The steps can be used to identify control points for which procedures can be included in the measuring system QCP. The numbers in the process map boxes above are examples linking to specific branches in the fishbone diagram shown in Figure 5 to identify potential failure modes.

A fishbone diagram identifies the possible causes of failure modes and their effects. In this example, failures that could lead to incorrect results, misidentified results, delayed results, or corrected test results are identified. The components of the measuring system (and their potential sources of failure) include the sample (integrity and presentation), the operator (inadequate training, human error, incompetence, and staffing), the reagent and/or calibrator (improper shipping or storage conditions), the laboratory environment (atmospheric dust, temperature, humidity, electrical or water quality), and the measuring system (instrument failure). This diagram does not include QC or maintenance branches, which are control processes. This diagram is an example and is not all-inclusive. Appendix A provides a detailed list of potential sources of error (potential failure modes).




Abbreviation: QC, quality control.

**Figure 5. Example of Fishbone Diagram for the Identification of Potential Failure Modes**

# Chapter 3

# Quality Control Toolbox

# 3 Quality Control

Using the appropriate combination of QC "tools" enables a laboratory to develop a comprehensive QCP that can effectively monitor and evaluate the performance of a measuring system. Each QC tool has strengths and weaknesses. Although there is no perfect QC tool that consistently prevents or detects all failures, understanding their strengths and weaknesses helps to effectively reduce risk. This chapter describes some of the established QC tools that are part of a well-designed QCP and outlines their strengths and weaknesses.

## 3.1 Analysis of Quality Control Samples

### 3.1.1 Intralaboratory Quality Control

Historically, statistical process control of measuring systems has involved the periodic measurement of stable QC materials designed to mimic as much as possible the analytical behavior of patient samples. Depending on the number and frequency of measuring such QC samples and the statistical limits set for allowable result variability, the use of appropriate QC materials can provide an effective strategy for detecting clinically significant changes in the quality of results produced, particularly in relation to bias and imprecision.

The QC samples included during routine testing are subjected to as much of the total measuring system as possible. The principle behind testing QC samples is that measuring system failures or errors and use errors that will negatively influence the testing of patient samples also affects the results obtained with the QC samples for many (but not all) failure modes.

Using QC samples to monitor a measuring system involves establishing the mean and SD for the specific QC sample lot and determining statistical limits that will identify unacceptable changes in performance of the measuring system. The QC strategy using QC samples should include the following information for each measuring system:

- Frequency of QC sample test events
- Type and number of QC samples tested per test event
- Statistical QC limits used to evaluate the results
- Frequency of periodic review for detecting shifts and trends
- Actions taken when results exceed acceptable limits

When selecting an appropriate QC sample testing frequency, laboratories should consider that any systematic (ie, persistent, nontransient) errors that occur after a QC sample is tested can remain undetected until the next control event. Additionally, when an error is detected, it might not be known when the error occurred in the time interval since the last QC samples were tested. The clinical use of the test results (eg, the effect of errors on patient care), stability of the measurand and/or analyte, stability of the examination process, number of patient samples processed between QC events, and frequency of calibration will influence the maximum interval between QC events. When the effectiveness of QC samples is evaluated, the following items should be considered:

- Suitable QC samples are capable of monitoring only the part of the measuring system in which the samples are used. Other steps in the total measuring system might not be challenged by the QC procedure (eg, phlebotomy and specimen collection).
- QC might detect only systematic persistent errors and might not be sensitive to random or human errors that occur between QC events.

- The end user should confirm the performance of QC with the measuring system and assign expected results to QC material.
- QC samples cannot mimic patient samples in all properties. Matrix effects can exist because of noncommutability of a QC sample with patient samples, which can cause incorrect inferences regarding the measuring system results for patient samples to be made (eg, QC results after a reagent lot change might not mirror the performance with patient samples).[25] Also, QC samples might not mimic patient samples in other respects, such as ability to form clots, create sample bubbles, or challenge measurement selectivity by containing interfering substances.
- Sufficient QC samples with an extended shelf life are needed to avoid frequent crossover evaluations between lots. Maintaining adequate stability after the container is opened should also be considered. Measurand and/or analyte instability is a potential source of variability that can confound interpretation of a QC sample result.
- If the QC samples are sensitive to contamination or degradation (eg, molecular testing), it may be appropriate to consider one-time–use vials of QC material.
- If a laboratory has identical measuring systems for the same measurand and/or analyte, the QC material may be used to compare instruments, provided the same reagent lot is used in the comparison.

To establish and maintain an effective QC strategy for quantitative tests using QC samples, see CLSI document C24.[26]

Qualitative and semiquantitative measuring systems that produce numerical values can also be monitored by statistical process control. For qualitative and semiquantitative measuring systems that do not produce numerical results, QC samples with known measurand and/or analyte values can be used to verify method performance. For information on qualitative assays, see CLSI document EP12.[27] **NOTE:** Semiquantitative assays are considered quantitative for establishing and verifying performance specifications.

### 3.1.2 Interlaboratory Quality Control

Additional information about the consistency and reliability of QC test results is obtained when the same lot of QC sample is tested by the same measuring system in multiple laboratories. Statistical analysis of the QC test results is used to determine target values and QC limits. Examples include commercial QC samples with values assigned from "peer group" data from participating laboratories. However, peer data can be influenced by matrix effects such that reagent lot differences within a peer group might affect peer statistics and limit the usefulness of peer-based targets for a laboratory. Pooled patient samples can also be used as a QC sample and shared among laboratories to establish consensus target values.

An effective QC sample strategy generally combines intralaboratory QC to monitor for day-to-day changes with interlaboratory QC to verify that the test results remain consistent. The same limitations associated with using QC samples (eg, stability, matrix effects, measurand and/or analyte availability) apply.

### 3.1.3 Trueness Control Material

Target values may also be assigned to reference or QC sample materials by reference measurement laboratories using certified primary reference measurement procedures. These QC samples may be used to verify the trueness of a laboratory's measuring system, if their commutability with patient samples has been validated for a given measurement procedure. Trueness controls should also have product labeling that states the materials are intended for trueness of measurement and identifies the measuring systems for which the commutability was validated.

Trueness controls are generally too expensive for routine use in QC, but they are invaluable for verifying that a measuring system is properly calibrated when it is first implemented or periodically thereafter. Trueness controls are also useful for routine verification of calibration or troubleshooting when the accuracy of patient results is suspect.

### 3.1.4 Quality Control Materials With Assigned Values (Assayed Quality Control Samples)

Measuring system–specific values can also be assigned to QC samples as target values. Such materials are often called "assayed controls," and the values are assigned by the QC material manufacturer or by laboratories in a value assignment program using a given measuring system. These materials are intended to provide individual laboratories a means to determine whether their performance is as expected for a given measuring system. The usefulness of these system-specific values depends on the traceability and uncertainty of the assigned values. Also, assigned values might be valid only for the individual reagent lot used during value assignment due to QC matrix effects with the measurement procedure.

### 3.1.5 Quality Control Materials Without Assigned Values (Unassayed Quality Control Samples)

Unassayed QC material is widely used in medical laboratories. It is generally less expensive than assayed QC material and is used to evaluate accuracy and precision. Unassayed QC material has no assigned measurand and/or analyte values provided by the manufacturer and is not linked to specific measurement procedures and/or measuring systems. The medical laboratory assigns expected results to unassayed QC material while ensuring that the measuring system and/or measurement procedure is operating within specifications. The manufacturer can indicate whether a specific measurand and/or analyte is present or absent in the QC material preparation without indicating an expected test result.

### 3.1.6 Frequency of Quality Control Sample Testing

The optimal frequency of QC sample procedures depends on built-in controls and other QCs for a given measuring system, the stability of that measuring system, and conditions in the laboratory identified through RA that can affect the reliability of testing, such as staff turnover and the clinical risk to a patient if an erroneous result is reported and acted on. The frequency of QC procedures should also conform to applicable regulatory and accreditation requirements.

Monitoring the measuring system at shorter intervals increases the likelihood that systematic errors are detected before incorrect results are reported or decreases the time before alerting the health care provider who might have received incorrect results. For example, a laboratory that evaluates the examination process every eight hours can identify a systematic error condition much earlier than a laboratory that monitors the examination process every 24 hours. However, the total number of samples tested in a time interval can also influence the frequency of monitoring. For example, a laboratory that tests 2000 samples in one 24-hour period might perform QC procedures several times a day, whereas a laboratory that tests 50 samples in an eight-hour shift might perform QC procedures at the beginning and end of a shift. The complex relationship between the frequency of QC sample testing, frequency of false rejection, and quality of patient results has been explored in the literature.[28-30]

## 3.2 Quality Control Built Into the Measuring System

### 3.2.1 Integrated Quality Control Samples

QC samples are sometimes built into reagent packs or unit-use reagent systems by the developer and are measured automatically by the measuring system. In general, integrated QC samples produce results that are evaluated against predetermined limits with the same approach used for traditional QC samples described in Subchapter 5.1.

Information concerning these integrated QC samples and their effectiveness in risk mitigation should be included in the information obtained from the developer. Not all parts of the measuring system are controlled by a QC sample integrated into the measuring system (eg, introduction of the sample is frequently excluded). The laboratory should evaluate the information provided by the developer and determine whether:

- The integrated QC sample is introduced into the measuring system in the same manner as a patient sample and therefore adequately controls the entire sampling step.
- Any other parts of the measuring system are excluded because of the way the QC sample is integrated into the system.

Laboratories should also consider the possibility that the formulation of the QC sample can be optimized for a specific measuring system. For example, a QC sample might be too closely related to the calibrators; therefore, it does not simulate routine patient samples and cannot serve as an effective QC.

### 3.2.2 Measuring System Function Checks

Measuring systems often incorporate sensors or detectors to monitor measuring system functions, sometimes continuously, and provide feedback to the user if a fault occurs. Feedback is generally provided by error messages, and results might not be reported when a component fails to operate within acceptable limits. Parameters such as temperature, incubation time, correct transfer of volume of reagent or sample, and response or signal for each sample tested can be monitored.

Modern measuring systems can also incorporate procedures for detecting use errors. These errors include sample underfills, overfills, bubbles, and clots; sample hemolysis; use of the wrong anticoagulant; and out-of-specification room temperature, pressure, or humidity. Measuring systems can also incorporate checks on computer and software function, such as valid software installation, available disk space, and system resources. Information concerning these function checks and their effectiveness in risk mitigation can be included in the information obtained from the developer. Measuring system function checks might not monitor the entire examination process but can prevent some failures from affecting a single sample or a group of samples. The information provided by the developer should indicate which functions are critical to producing accurate results, as well as which are monitored.

### 3.2.3 Electronic System Checks

Some measuring systems include software algorithms that check electronic components of the measuring system. Information concerning electronic system checks and their effectiveness in risk mitigation should be included in the information obtained from the developer. Such information should indicate which components and functions are monitored electronically and how reliably the system checks can prevent incorrect results.

### 3.2.4 Calibration Checks

Automated calibration checks are intended to detect certain calibration problems before running QC and patient samples. They typically involve comparing the current calibration responses or curve shapes against expected calibration data to verify that the responses or curve shapes are within expected limits. The limits are typically provided by the developer or derived from previous valid calibrations.

Calibration checks are normally performed automatically by the measuring system after each calibration, but they can also be performed manually for some measuring systems following instructions provided by the developer or developed by a laboratory. Information concerning calibration checks and their effectiveness in risk mitigation should be included in the information obtained from the developer.

**NOTE:** Calibration verification is performed routinely on hematology measuring systems. Calibration is performed only when the system identifies a deviation from the assigned SD and CV. The validity of calibration checks should be verified by QC and patient samples.

## 3.3 Quality Control Processes Using Patient Test Results

### 3.3.1 Repeat Testing of Patient Samples

When patient samples are sufficiently stable and when suitable QC samples are not available for routine monitoring, or when an additional check of repeatability is desirable, retesting of selected patient samples on the same measuring system and/or on multiple measuring systems can verify precision or agreement among results from different measuring systems. Results are evaluated based on the expected agreement among the results. If the difference between results exceeds limits based on the measurement imprecision, an investigation is initiated to determine the cause. Repeat testing of a single patient sample on the same measuring system is a supplementary risk mitigation tool. See CLSI document EP31[31] for recommended protocols for comparability of results.

In most cases, patient sample testing eliminates matrix effects. Principal limitations are that some measurands and/or analytes might not be stable under storage to allow for replicate testing over various time intervals, and routine handling of patient samples might prevent the ability to repeat the test.

### 3.3.2 Monitoring Aggregated Patient Results

Trends in the distribution of patient test results can be monitored over time to detect changes in performance, provided the patient population and test results distribution are relatively stable. This technique reduces significant matrix effects on bias and can detect systematic errors.[32,33]

The effectiveness of using aggregated patient results depends on using an adequate number of results to calculate the aggregated value. The necessary number of results for effective performance varies between measurands and/or analytes and might not be practical, especially in low-volume situations. The ability to detect trends in patient results depends on the measurement imprecision and the biological variability of the measurands and/or analytes but can be difficult to implement in real time. Robust estimation and/or outlier rejection techniques might be required for successful monitoring.[34] Changing patient populations and their effect on the overall distribution of results can limit the effectiveness of this technique or could detect that patient reference intervals might need to be adjusted. For example, the addition of an oncology population to the patient mix will alter the distribution of hematology results.[35-37]

### 3.3.3 Identifying Implausible Values

Implausible values are results that are considered physiologically impossible or so improbable they are simply not believable. They can indicate a failure of the measuring system or a problem with the patient sample (eg, presence of an interfering substance, contamination with intravenous fluid, or an insufficient sample volume). Patient results exceeding a predefined limit are flagged for review and possible investigation. Identification of implausible values mitigates risks stemming from unpredictable, sporadic events or occurrences that cause large deviations from the expected values. Although many health care providers could question such results based on their experience or training, preventing such results from being reported adds an additional safeguard.

Implausible value limits are not practical for all measurands and/or analytes. For many, it is difficult to select a limit that will not suppress valid results or trigger too many false alerts. The time necessary to investigate false alerts can be extensive, generally requiring the laboratory to obtain additional clinical information to differentiate true from false alerts. Manual implementation is generally not practical for most laboratories. To be used effectively as a QC tool, implementation through an LIS, middleware, or other computer system is needed.

### 3.3.4 Delta Checks

A delta check detects the difference between a current test result and a previous test result for the same patient. If the difference between results exceeds a predefined limit, the current result is flagged for review as a possible error. The limits are established based on the magnitude of change expected from the physiological factors and measurement uncertainty that can influence a result (see CLSI document EP33[38] for more information on delta checks).

Delta checks can be useful for detecting sample mislabeling or improperly collected samples. Delta checks detect measurement errors only when they are clinically relevant.[39,40] They provide an additional safeguard in case a health care provider does not question an unexpected result. Establishing and verifying optimal delta check limits can be difficult. The delta or degree of difference that is significant can vary over the entire interval of concentrations for a given measurand and/or analyte. The variation also depends on the time interval between samples. The same delta values might not apply to all patient populations. The time required to investigate false-positive delta checks can be extensive and can require laboratories to obtain additional clinical information to differentiate true errors from false-positive errors. Manual implementation is not practical. To be used effectively as a QC tool, implementation through an LIS, middleware, or other computer system is needed.

### 3.3.5 Correlation of Multiple Measurand and/or Analytes in the Same Sample

The concentrations of several measurands and/or analytes are often measured in the same patient sample. In some cases, the relationship between these test results is an effective tool for identifying significant errors. Examples of such relationships include hemoglobin and hematocrit, anion gap, alanine aminotransferase and aspartate aminotransferase in patients with liver disease, and thyroid-stimulating hormone and free T4 in patients with thyroid disease.

Algorithms to identify inconsistent test results can be automated in the measuring system software, middleware, or LIS. However, acceptable limits for the differences between test results can be difficult to establish. This approach applies only to measurands and/or analytes with consistent relationships in pathological conditions. The time required to investigate false-positive alerts can be extensive and might require obtaining clinical information to differentiate true errors from false-positive errors.

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# Chapter 4

# Information Gathering for Risk Assessment

# 4 Information Gathering for Risk Assessment

To prepare for an RA, the laboratory should systematically identify potential failure modes, determine possible failure causes, and estimate the probability that the failures will occur. The laboratory also needs to estimate the probability of detecting the failure before the result reaches the patient, health care provider, or laboratory and the probability that each failure could lead to a hazardous situation (eg, a clinically incorrect result reported to a health care provider). The likelihood and/or severity of harm that could arise from the hazardous situation also needs to be determined.

The laboratory should collect information, when available, from the sources listed in Table 3. Many IVD device developers provide additional information on potential failure modes for their devices and how they are or are not covered in product design or labeling. If a laboratory needs additional information to create a QCP, it should contact the developer to request it. Appendix B provides a checklist for establishing a QCP based on information collected for RA, which is outlined in Table 3.

**Table 3. Sources for Collecting Information for RA**

| Information | Source |
|---|---|
| Regulatory and accreditation requirements:<br>• Mandated QC procedures<br>• Required QA activities<br>• Recall and device failure notifications | Regulatory and accreditation organizations |
| Measuring system information:<br>• Intended use (including limitations, warnings, and precautions)<br>• Environmental requirements<br>• Instructions for calibration, maintenance, use, and reagent handling and storage<br>• Calibrator traceability information<br>• QC features<br>• Risk mitigation recommendations | IVD device manufacturer |
| Laboratory information: environmental conditions, including facilities and utilities, as well as existing QCs:<br>• Installation and/or operational qualification reports<br>• Operator training and competence<br>• Internal performance evaluation and/or verification data<br>• External performance data (eg, PT results)<br>• Process map covering the steps analyzed | Laboratory |
| Publications and reports from laboratory peers:<br>• Published performance evaluations<br>• Published clinical studies<br>• Other users (eg, user groups, listservs, forums) | Laboratory |
| Clinical information:<br>• Specimen collection and handling<br>• Clinical applications for use of a test result<br>• Biological reference intervals and clinical decision levels<br>• Foreseeable medical errors resulting from incorrect, delayed, or no results<br>• Severity of patient harm resulting from different hazards | Laboratory |

Abbreviations: IVD, *in vitro* diagnostic; PT, proficiency testing; QA, quality assurance; QC, quality control; RA, risk assessment.

## 4.1 Clinical Application Information

The laboratory should consider the intended medical uses and potential effects of a patient's test result when the QCP is created. Developing the QCP can require consultation with the health care providers using the test results. Factors to consider include influence of the test result on screening, diagnosis, and/or patient management decisions, whether the test results are usually acted on immediately, whether patient assessment (eg, signs and symptoms) influences the interpretation of the test results, and whether any medical actions in response to an erroneous test result are likely to lead to serious patient harm. The potential for results misinterpretation by the health care provider or failure to act on test results should also be considered.

The amount of time that typically lapses between reporting a test result and a health care provider acting based on that result should be considered when the QCP is developed. When a result is likely to be acted on immediately, such as in the emergency department, intensive care unit, or operating room, it is advisable to focus the QCP on preventing incorrect results, because there is no time to issue a corrected report for an erroneous result. For example, a blood gas or electrolyte result can be acted on immediately with serious patient consequences before an erroneous result can be corrected. When there is sufficient time to allow for retraction and correction of incorrect test results, such as for cholesterol screening, the QCP can be less stringent. Specific identified risks for different laboratory specialities are listed in international standards.[2]

## 4.2 Regulatory and Accreditation Requirements

Laboratory personnel should be aware of the regulatory and accreditation requirements applicable to tests performed by their laboratory. The laboratory should ensure that the QCP conforms with regulatory and accreditation requirements.

## 4.3 Measuring System Information

### 4.3.1 Information Obtained From the Developer

Awareness of key risk mitigation features for the measuring system is another important piece of information necessary for developing an appropriate and effective QCP. Developers should provide adequate IFU. These instructions typically include specimen collection and storage requirements, intended use, test procedure, technical performance, maintenance, storage recommendations (temperature, humidity, and light), environmental conditions of operation, limitations, requirements for testing personnel and training, and other information needed to properly install, verify, and use the measuring system. Requirements for transporting and handling reagents from the supplier to the laboratory should be considered.

For laboratory-developed tests or laboratory-modified tests (eg, measuring systems that have not been cleared, approved, or authorized by a recognized authority), the laboratory is responsible for determining and documenting information analogous to that listed for IVD device developers in Table 3.

### 4.3.2 Information Obtained by the Laboratory

Measuring system performance data, generated by sources independent of the developer, can be obtained from:

- In-house–generated evaluation data
- Interlaboratory comparison programs provided by suppliers of QC samples
- External quality assessment (EQA) or PT programs
- Evaluations published in peer-reviewed literature

## 4.4 Laboratory Information

### 4.4.1 Laboratory Environment

When the laboratory is following the developer's IFU, it needs to assess how conditions specific to the laboratory can affect the measuring system. Examples of potential environmental hazards are dust, temperature, humidity, electrical or water quality, sunlight, vibration, radio frequency interference, magnetic interference, and atmospheric pressure. The QCP should reflect these conditions and their potential influence on test results.

### 4.4.2 Personnel Training and Competence

Personnel training and competence (see CLSI document QMS03[41]) can affect the quality of patient test results, and the following factors should be assessed:

- Staff turnover and loss of trained testing personnel
- Literacy and language skills
- Ability to assimilate and retain new information
- Problem-solving skills
- Ability to communicate clearly
- Job experience
- Orientation to organizational policies
- Technical and interpretive laboratory skills
- Continuing education
- Education, licensure, and/or certification
- Visual acuity, color perception, and hearing impairment
- Operator fatigue

The effectiveness of the laboratory's QMS in managing personnel knowledge and skills should be considered when the laboratory is developing the QCP (see CLSI document QMS01[21] for more information on the personnel component of the quality system essentials). If the main laboratory is responsible for maintaining the quality of testing at remote sites, each satellite laboratory should evaluate its personnel. Laboratory managers should be sensitive to the fact that personnel who perform testing remotely might have limited laboratory training and/or less competence in performing testing. The QCP might need to reflect such conditions, depending on the susceptibility of the measuring system to user influence.

### 4.4.3 Frequency of Patient Testing

The QCP should include the frequency of patient testing. Operators might be less familiar with the details of a procedure performed infrequently, thereby increasing the probability of use errors and erroneous results. Frequent repetition of the steps in a measuring system leads to operator competence. Consequently, when a test is not performed frequently in a laboratory, refresher training or more frequent QC sample testing might be needed. The simplicity and/or complexity of the procedure and whether the procedure is fully automated, semiautomated, or manual should also be considered. Performing dilutions, extractions, and calculations and maintaining measuring systems and support equipment (eg, refrigerators, centrifuges, balances) can be challenging for operators. Performing steps manually typically poses more risks than the use of automated processes owing to the greater likelihood of use errors.

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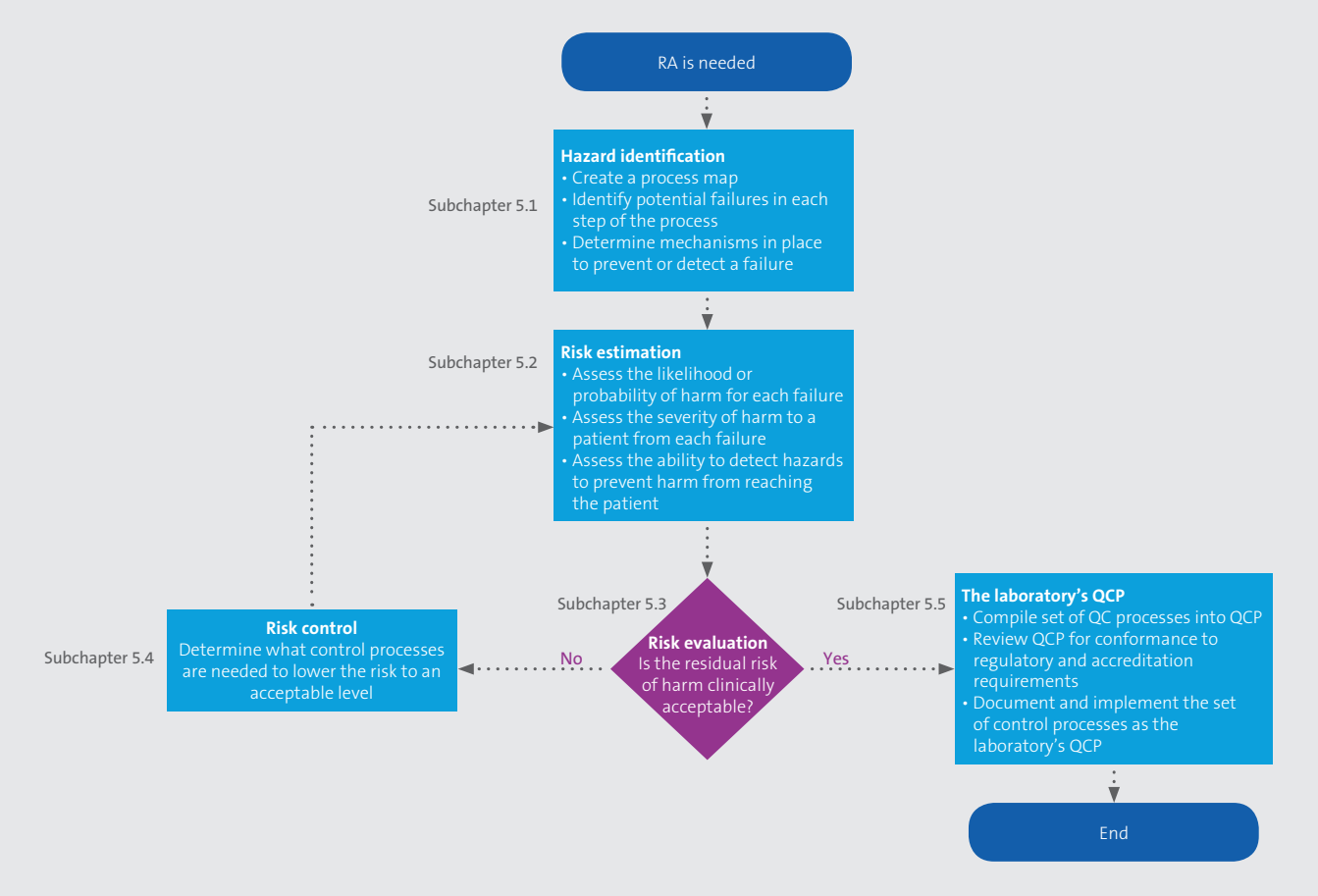
# Chapter 5

# Developing the Quality Control Plan

# 5 Developing the Quality Control Plan

The overall process for assessing risk and establishing a QCP is shown schematically in Figure 6. The subchapters noted in the flow chart correspond to upcoming subchapters in this chapter.




Abbreviations: QC, quality control; QCP, quality control plan; RA, risk assessment.
[a] Four basic symbols are used in this process flow chart: oval (signifies the beginning or end of a process), arrow (connects process activities), box (designates process activities), diamond (includes a question with alternative "Yes" and "No" responses).

**Figure 6. RA Flow Chart[a]**

## 5.1 Hazard Identification

The first step in RA is to identify potential risks and their causes. The laboratory should map the total testing process in detail (see Subchapter 2.4 for more information on process mapping) and collect the information discussed in Chapter 4. This information is used to identify potential failure modes in the testing process that can affect patient care and enable the laboratory to identify appropriate QC points to prevent and/or detect the failures.

### 5.1.1 Review of Information Obtained From the Developer

The information obtained from the developer (see Subchapter 4.3.1) should be reviewed to identify potential failure modes in the process. It might not be necessary or even practical to document all possible failure modes in a measuring system. The potential for intermittent as well as persistent systemic failures should be considered. Some failures can clearly create hazards (eg, incorrect results, no result, or delays in testing). Other failures can be prevented by designing risk mitigation features into the measuring system.

Ideally, developers identify important potential failure modes that can affect the reliability of test results, describe the features designed into the measuring system to mitigate the risks, provide information that describes the effectiveness and limitations of the mitigation to reduce the likelihood of failures, and provide recommendations for laboratories to mitigate the residual risks. Information regarding significant potential failures and information that describes limitations of the test can be provided in developers' IFU and operator manuals (see Table 3).

The QCP described in this guideline relies on information obtained from the measuring system developer. Laboratories should evaluate the information and confirm that any risk mitigation features are appropriate to meet patient care needs. Table 4 provides a template for organizing the information obtained from the developer.

**Table 4. Template for Organizing Information on Risk Mitigation Features Provided by the Developer**

| Targeted Failure Mode, hazard | Measuring System Feature or Recommended Action | Known Limitations of Feature or Recommended Action | QC Process Effective? (Yes/No) | QCP Actions Necessary to Handle Known Limitations | Residual Risk Acceptable? (Yes/No) |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

Abbreviations: QC, quality control; QCP, quality control plan.

Laboratories need to critically assess the information provided by developers irrespective of its regulatory approval status and apply their own knowledge of measuring systems to the risk analyses. As laboratories review developers' information, they should be aware that the information (eg, frequency of testing QC) might not have been reviewed or verified by a regulatory and accreditation organization.

### 5.1.2 Review of Laboratory Environment Information

The laboratory should confirm and document that the developer's specifications for the facility where the testing is performed, including all installed utilities, are met. Potential failure modes and use errors that might occur from variables within the laboratory's control are identified. The laboratory can identify these failures in a fishbone diagram, as shown in Figure 5. The information about the specific laboratory setting (see Subchapter 4.4) is included in the RA.

## 5.2 Risk Estimation

The next step in the RA is to determine the degree of risk associated with the hazards by assigning values to the probability of occurrence of harm associated with an identified hazard and the severity of that harm. The ability to detect a hazard should also be considered to prevent patient harm.

### 5.2.1 Probability of Harm

Once potential failure modes are identified, an estimate of the likelihood or probability of harm is needed. Patient harm related to laboratory test result failures is often indirect, and judging potential harm requires an understanding of how the test is used clinically. The overall probability of harm from laboratory systems can be substantially lower than the probability of the failure, because not every instance of failure leads to patient harm. Figure 7 illustrates a representative sequence of events. Although the medical action taken might not be hazardous and might be an absence of action, it is an inappropriate medical action based on the erroneous test result.

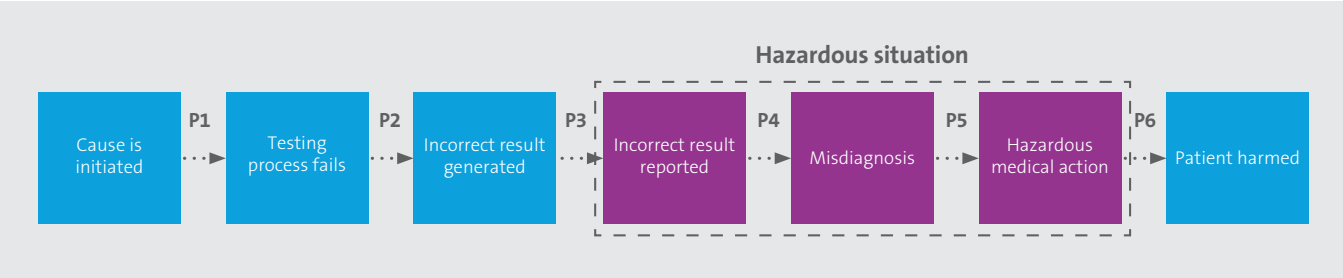



**Figure 7. Example Sequence of Events Creating Patient Risk**

A probability is associated with each of the steps in the sequence (indicated as P1 to P6 in Figure 7). A quantitative estimate of the expected failure rate (P1) is desirable when based on accurate and reliable data, but such data are often difficult to obtain. In some situations, the probability of failure is difficult to estimate, and the accuracy of any such estimation will be in doubt.[2] In this case, it is not possible to estimate risk, and evaluation might be based solely on the severity of the potential harm alone. For example, a laboratory might consistently have an average of 20 misidentified samples per month, but this average reflects only instances for which the incorrect sample can be clearly differentiated from the labeled patient's previous data. This average represents at best a lower bound on the true number of misidentified sample events per month. Furthermore, the rate estimate requires a denominator to calculate the estimate. In the case of misidentified samples, possibilities include the number of patient draws, submitted samples, accessions, or other monthly counts, depending on how the occurrence is counted. The way misidentified samples are counted might not produce an estimated failure rate that is directly applicable to the probability of harm to a patient. Similarly, the probabilities associated with the other steps in the sequence might not be easily quantifiable. In such cases, a descriptive approach is used to estimate the probabilities (ie, create descriptive categories) so there is no confusion caused by the meaning of a term. An example of semiquantitative descriptive scoring is shown in Table 5.

**Table 5. Example of Semiquantitative Estimating Probabilities**

| Descriptive Probability | Frequency of Event |
|---|---|
| Frequent | Once per week |
| Probable | Once per month |
| Occasional | Once per year |
| Remote | Once every few years |
| Improbable | Once in the life of the measuring system |

When there is insufficient information to estimate a semiquantitative expected failure rate, expert judgment can provide a qualitative estimate for P1. An example is shown in Table 6.[2]

**Table 6. Example of Qualitative Estimating Probabilities[2]**

| Descriptive Probability | Frequency of Event |
|---|---|
| Frequent | Likely to occur regularly; expected to occur continuously |
| Reasonably likely | Likely to occur multiple times; expected to occur frequently |
| Occasional | Likely to occur sometimes; expected to occur several times |
| Remote | Unlikely to occur but possible; expected to occur few times |
| Improbable | Extremely unlikely to occur; might happen once or twice |

In the rare situation in which robust data that are well defined and appropriate to the estimation of the failure rate are available, a semiquantitative approach may be used in the risk estimation. In this case, the ratio of potentially harmful events to total events is calculated and stratified by frequency. An example is shown in Table 7.

**Table 7. Example of Estimating Probabilities With a Ratio of Harmful to Total Events**

| Descriptive Probability | Frequency |
|---|---|
| Frequent | 1/100 or 0.01 |
| Probable | 1/1000 or 0.001 |
| Occasional | 1/10 000 or 0.0001 |
| Remote | 1/100 000 or 0.00001 |
| Improbable | 1/1 000 000 or 0.000001 |

In all these instances, the definitions of each category should be appropriate to the risk estimate being made. The examples in this subchapter are solely for illustration and should be adapted as necessary to the situation at hand. It is essential that each category is well defined, explicit, and reproducible.

If the probability of failure cannot be reasonably estimated, evaluation may need to be based solely on the severity of the potential harm. A situation in which minimal severity of little clinical and practical significance is present can be determined to be of extremely low risk, whereas when the potential for marked and long-lasting patient harm exists, no probability of occurrence can be so low as to be acceptable. In such instances, a reasonable worst-case scenario approach to the estimation of risk is appropriate.

The probabilities leading to the hazardous situation, which usually occurs when an incorrect result is reported to a health care provider capable of acting on the result, are usually estimated individually and then combined. The probabilities leading to harm after an incorrect result is received are more difficult to estimate, and medical judgment is used to estimate the overall probability of harm caused by receiving an incorrect result. The effects of delays in the availability of test results are analyzed in a similar way.

Estimates of the probability of events in the sequence leading to harm can be obtained from health care providers, technical bulletins, peer-reviewed literature, laboratory records, product alerts, and trade journals. The following sources of information can help the laboratory estimate the probability of reporting an incorrect result or failing to report a critical-risk result:

- Historical failure data
- Method evaluation and/or verification data
- Reliability estimates
- Site environmental assessments
- QC data
- PT performance or EQA information

The following sources of information can help the laboratory estimate the probability of harm from receiving an incorrect result or failing to receive a critical-risk result:

- Medical literature
- Medical judgment
- Consultation
- Other users (eg, user groups, listservs, forums)
- Recall and device failure notifications from regulatory and accreditation organizations

### 5.2.2 Severity of Harm

The consequences of a failure include an incorrect result, a delayed result, or no result, all of which can lead to a hazardous situation for a patient. For example, if the result contributed to a misdiagnosis, harm to the patient might occur through inappropriate treatment or lack of appropriate treatment. The significance of each failure is evaluated as the severity of harm to a patient if a hazardous situation occurs. Estimating the severity of harm requires the judgment of the laboratory in collaboration with the health care providers who use the test results. Key considerations include:

- What medical interventions should be initiated for a patient based on an erroneous, delayed, or missing result?
- What risk is caused by an inappropriate medical intervention?
- How severe might that harm be?
- What is the liability for causing this harm?
- Will this harm cause the patient mental anguish?

If the laboratory is unable to assess these key considerations, it should assume the most harmful scenarios. Severity of harm is described using a qualitative scale of severity levels, as shown in Table 8.[3] The laboratory should select the number of levels needed to represent the interval of possible severities. However, too many levels can result in debates over meaningless differences.

**Table 8. Qualitative Description of Harm Based on Scale of Severity Levels**

| Descriptive Category | Severity Level |
|---|---|
| Negligible | Inconvenience or temporary discomfort |
| Minor | Temporary injury or impairment not requiring professional medical intervention |
| Serious | Injury or impairment requiring professional medical intervention |
| Critical | Permanent impairment or life-threatening injury |
| Catastrophic | Patient death |

### 5.2.3 Detection of Hazards and Prevention of Harm

Risk evaluation should include the ability to detect an erroneous result and prevent medical action before patient harm occurs. Some hazards can be detected internally by a measuring system, leading to error messages or result flags that direct the operator to perform corrective actions. Other hazards can be identified and mitigated through the laboratory's QMS, such as operator training and competence, instrument maintenance, or analysis of QC samples with each batch of patient samples. The existing QCs built into the measuring system and the laboratory's existing QMS are considered when the risks are estimated, but it cannot be assumed that a built-in or user-applied QC is 100% effective in detecting or preventing a failure unless this assumption is supported by data. Additional considerations include but are not limited to:

- What will a health care provider do with the result?
- What other information is used to corroborate the test result?
- How likely is the health care provider to receive a confirmatory test result before acting on a result?
- How quickly will the results lead to a medical decision?
- What are the measuring system capabilities that can detect hemolysis, lipemia, icterus, and drug and other sample interferences?
- Are there electronic checks, bar-coded reagents, or instrument QC processes that can detect the use of expired reagents or use past the open-bottle stability time frame?
- Does the measuring system have lockout features that allow only trained and competent staff to operate the instrument?
- Does the measuring system have QC lockout features that require staff to perform QCs at designated time intervals and frequency?
- Does the measuring system have QC lockout features that prevent patient testing when QC is unacceptable?
- Does the LIS have rules to quarantine abnormal or spurious results before reporting them?

## 5.3 Risk Evaluation

The probability or likelihood of a failure leading to harm combined with the severity of that harm and the previously validated or verified method that can detect and prevent harm is used to evaluate risk to a patient. Typically, the ability to detect harm is considered part of the likelihood of failure, because undetected failure will lead to an underestimation of the probability of failure. Risk evaluation is the process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk. Risk can never be eliminated, just reduced below an acceptable threshold. A benefit-RA is important in determining whether residual risk is outweighed by the benefits of the test. The evaluation should account for the medical benefits of the test and what is achievable

in the current state of the art. Acceptable risk can be ascertained through an ongoing process of literature review, expert consultation, local experience, and cooperative evaluation with clinical providers and risk managers. Various stakeholders will place different values on the acceptability of risk vs the anticipated benefits. Risk acceptability criteria can be based on:

- Laboratory policy
- National and/or regional regulations and standards
- State of the art
- Laboratory director discretion

The laboratory, in consultation with health care providers, is responsible for determining whether the residual risk, after all attempts to reduce the risk have been implemented, is clinically acceptable. The criteria for acceptable risk should be decided based on clinical application of the test result. When a test result is used in different clinical settings, the risk should be assessed for the most stringent clinical situation.

Because both the probability of harm and the severity of harm are usually descriptive categories, it is difficult to provide a procedure to combine these two factors. A practical approach is to construct a matrix with the probability of occurrence of harm on one axis and the severity of harm on the other. The organization or laboratory defines risk acceptability. The appropriate cell within the table indicates whether the risk is acceptable or unacceptable based on the combination of the two factors. In this manner, a qualitative conclusion that does not consider detectability is reached regarding risk. An example risk matrix is shown in Table 9.

**Table 9. Risk Acceptability Matrix**

| | Severity of Harm[a] | | | | |
|---|---|---|---|---|---|
| **Probability of Harm** | **Negligible** | **Minor** | **Serious** | **Critical** | **Catastrophic** |
| Frequent | **Unacceptable** | **Unacceptable** | **Unacceptable** | **Unacceptable** | **Unacceptable** |
| Probable | Acceptable | **Unacceptable** | **Unacceptable** | **Unacceptable** | **Unacceptable** |
| Occasional | Acceptable | Acceptable | Acceptable | **Unacceptable** | **Unacceptable** |
| Remote | Acceptable | Acceptable | Acceptable | Acceptable | **Unacceptable** |
| Improbable | Acceptable | Acceptable | Acceptable | Acceptable | Acceptable |

[a] Shaded cells with bold type indicate unacceptable risk.

### 5.3.1 Quantitative Quality Control Planning Based on the Risk of Patient Harm From Erroneous Results

When the probability of harm descriptive categories are expressed as maximum acceptable probabilities, they can be used to find QC strategies that have acceptable risk of patient harm from erroneous results. A measurand and/or analyte can be assigned a severity of harm category according to how the clinical system uses measurand and/or analyte results with respect to the patient. Will an erroneous result simply trigger a repeat test (negligible harm), or will it facilitate incorrect therapy (serious or critical harm)? A maximum acceptable probability of harm can be derived from the severity of harm category and the risk acceptability matrix.

The predicted probability of patient harm ($P_H$) from an erroneous result for a QC strategy can be computed from the probability of producing erroneous results ($P_E$). The probability of producing erroneous results is the sum of the probability of producing erroneous results when the test method is "in control"[32] and when the test method is "out of control."[29] The predicted probability of patient harm is computed as the product of the probability of producing erroneous results and the conditional probability of an erroneous result harming a patient ($P_{E|H}$), which is shown in equation (1):

$$P_H = P_E \bullet P_{E|H} \quad (1)$$

where

$P_{E|H}$ is estimated from the predicted response of the clinical system to a result that contains measurement error exceeding the total allowable error for the analyte. A conservative estimate for $P_{E|H}$.

$P_{E|H}$ is 1, presuming that all results with measurement error exceeding the total allowable error will cause patient harm. An estimated $P_{E|H}$.

$P_{E|H}$ of 0.2 presumes that one in five results with measurement error exceeding the total allowable error will cause patient harm.[42]

A QC strategy has managed risk if its predicted $P_H$ is less than or equal to the acceptable $P_H$ derived from the severity of harm category.

### 5.3.2 The Risk Management Index of a Quality Control Strategy

The relationship between the predicted $P_H$ and the acceptable $P_H$ can be expressed as a quotient forming the risk management index (RMI).[42] The RMI is shown in equation (2):

$$RMI = \frac{\text{Predicted } P_H}{\text{Acceptable } P_H} \quad (2)$$

The RMI makes it easy to express relative risk for a QC strategy even when there are very different circumstances with respect to the severity of harm categories for measurands and/or analytes, different test method performances, or different failure rates. If the RMI is ≤ 1, the QC strategy has managed risk. If the RMI is ≥ 1, there is unmanaged risk in the QC strategy. An RMI of 2 implies twice the acceptable level of risk.

### 5.3.3 Example of Assessing the Risk of Patient Harm From a Quality Control Strategy

Table 10 conveys the characteristics of this example for a glucose method. The glucose QC strategy is two levels of QC tested after every 50 patient samples are tested and evaluated with a 1:3s 2:2s R:4s rule.

**Table 10. Example Characteristics of a Glucose Method[a]**

| Characteristic | Value |
|---|---|
| CV | 2.5 |
| Total allowable error | ± 10% |
| Mean time between failures (out-of-control conditions) | 90 days |
| Mean number of patient samples per day | 100 |
| Severity of harm category | Minor |
| ($P_{E|H}$) for glucose | 0.5 |

Abbreviation: CV, coefficient of variation.
Symbol: $P_{E|H}$, probability of an erroneous result harming a patient.
[a] Equations for calculating in-control probability of erroneous results[32] and out-of-control probability of erroneous results[29,42] are published in the literature.

Using the risk acceptability matrix, the maximum acceptable probability of harm is occasional, 1/10 000 or 0.0001. Table 11 shows the worked-out probabilities. Because the RMI is ≤ 1, the QC strategy manages the risk of patient harm from erroneous results.

**Table 11. Example of RMI Calculation[a]**

| Predicted Probabilities | Value |
|---|---|
| In-control erroneous results | 0.00007 |
| Out-of-control erroneous results | 0.000042 |
| Erroneous results = the predicted probability of in-control + out-of-control erroneous results | 0.00007 + 0.000042 = 0.000112 |
| Patient harm from erroneous results = the predicted probability of erroneous results multiplied by the probability of harm given erroneous results | 0.000112 • 0.5 = 0.000056 |
| Patient harm divided by the acceptable probability of patient harm = RMI | 0.000056 / 0.0001 = 0.56 |

Abbreviation: RMI, risk management index.
[a] Equations for calculating in-control probability of erroneous results[32] and out-of-control probability of erroneous results[29,42] are published in the literature.

In an alternative process, the risk priority number (RPN) can be considered when the ability to detect failure can be directly estimated. An RPN can be calculated as probability • severity • detection. The RPN is a relative ranking of the identified hazards that pose the greatest risk. Based on the risk evaluation method, the laboratory should determine which risks will be handled first. This can be determined by prioritizing risks between certain levels. For example, risks with an RPN between 500 and 1000 can be handled first when probability of occurrence, severity, and detection methods are evaluated using a 1 to 10 scale for each (or risks between 75 and 125 when occurrence, severity, and detection methods are evaluated using a 1 to 5 scale). Laboratories can be flexible in adopting their own scales and interpretation of risk estimates. When laboratory resources are limited, the RPN highlights the hazards of greatest risk on which to focus efforts. This process is discussed as part of process failure modes and effects analysis in international standards.[2]

## 5.4 Risk Control

Each of the failure modes identified by the RA as presenting unacceptable risk requires QC measures to reduce the residual risk. The laboratory is encouraged to review the failure modes to verify that residual risks have been reduced as far as is practical. The laboratory should evaluate the risk QC measures implemented to cover each failure mode, such as specific mitigations provided by the developer and the QC tools described in Chapter 3, and verify that the evidence supports their effectiveness in mitigating the effects of a failure to a clinically acceptable "risk" level. If the residual risk is not clinically acceptable, the laboratory needs to identify additional QC measures to reduce the residual risk to a clinically acceptable level. This process is repeated for each of the potential failure modes identified in the RA until the overall residual risk of the test has been reduced as low as is practical and is clinically acceptable.

## 5.5 The Laboratory's Quality Control Plan

Once the residual risk is considered acceptable, the laboratory includes the QC measures as a component of the laboratory's QCP. Each QC or user-required action is added to the laboratory RA and QCP table as one element of the laboratory's QCP for the testing process for a specific measurand and/or analyte. There can be duplicative QC elements that mitigate various risks identified in the review process. The individual QC elements from the table can be grouped into a coherent set that constitutes the QCP.

Before implementation, the laboratory should confirm that the QCP meets applicable regulatory and/or accreditation requirements and that the developer's intended IFU are followed. If not, the QCP should be modified accordingly. Once the laboratory has determined that all identified risks have been mitigated to a clinically acceptable level and that the QCP meets minimum regulatory and/or accreditation requirements and fulfills developer's recommended instructions, the laboratory can implement the QCP. The laboratory should consider change management, the challenges of implementing a QCP, and additional hazards when residual risk is evaluated and make these considerations part of the QCP.

The laboratory's RA and QCP table summarizes the decision-making process and/or rationale used in developing the QCP for use in troubleshooting and for responding to health care provider inquiries. Laboratory inspectors can use this information to determine whether the laboratory's QCP is appropriate. In many cases, the QCP developed for a given measurand and/or analyte can apply to a group of measurands and/or analytes performed on a single measuring system or to a group of identical measuring systems used within a health care environment. A single QCP can apply to individual measurands and/or analytes, all measurands and/or analytes assayed using a measuring system, and/or multiple identical measuring systems, provided they have similar RA and worst case is used to develop the QCP.

## 5.6 Examples of Laboratory Risk Assessment

Examples of an RA and a laboratory-specific QCP are provided in the appendixes. The examples illustrate the process of developing a QCP. They are not comprehensive but include several typical aspects to illustrate the RA process and aggregation of QC elements into a QCP. Appendix C provides an example of an RA and QCP for microbiology (CLSI document M22[43]—exempt media). Appendix D is an example of an RA and QCP for Shiga toxin testing using a visually read unit-use test device. Appendix E is an example of an RA and QCP for an instrument-based device for fetal fibronectin testing. This example includes the five major branches of the fishbone diagram (see Figure 5) and encompasses the preexamination, examination, and postexamination phases of testing.

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# Chapter 6

# Postimplementation Monitoring of the Quality Control Plan

# 6 Postimplementation Monitoring of the Quality Control Plan

As part of its QMS, a laboratory should establish a review system for monitoring quality benchmarks (key performance indictors) or the effectiveness of the QCP over time. One quality benchmark that can be monitored is the frequency of a specific error over time to ensure that the QCP effectively reduces the frequency of error occurrence.[44,45] Unacceptable performance could lead to an investigation to identify the root cause and potentially lead to a repeat risk analysis and/or assessment and appropriate modifications to the QCP. This surveillance system should be part of the corrective action process. In addition, identifying opportunities to reduce acceptable risks even more is part of the continual improvement program for the laboratory. Appendix F provides an example form that can assist with the periodic review of a QCP. The laboratory should ensure appropriate communication and implementation of any developer updates, recalls, or field corrections (eg, calibrator value adjustments), as well as an assessment of any effect on reported test results.

## 6.1 Evaluation of the Effectiveness of the Laboratory Quality Control Plan

An effective QCP optimizes the probability of detecting an error while minimizing the probability of false-error detection. Long-term monitoring of the effectiveness of an implemented QCP can include the following steps:

- Evaluate the QCP at an appropriate interval that is effective to detect unacceptable precision or bias. At a minimum, the review should be conducted at a frequency required for compliance with regulatory and/or accreditation requirements.
- Review nonconformities, including complaints from health care providers or medical staff, to ensure that discrepancies between a laboratory's results and a patient's symptoms or diagnosis are documented and investigated as part of the laboratory's QMS policies, practices, and procedures. If the investigation shows that the results were incorrect, an evaluation of the QCP should demonstrate why the failure was not prevented or detected, whether other patient results were affected, whether the risk to patients is still acceptable, and whether changes to the QCP are needed.
- Track the frequency of nonconformities, complaints, and investigations to ensure that failures are recognized and resolved so problems do not recur.

## 6.2 Investigating Unacceptable Performance and Corrective Action

On determination of unacceptable performance (eg, failure of one or more of the components of the QCP), the laboratory should investigate the cause, taking into consideration the path of workflow, ie, preexamination, examination, and postexamination. When unacceptable performance is identified, the effect on patient care should be assessed and documented as part of a review of the original RA. If the risk is unacceptable, the cause of the unacceptable performance should be determined, the corrective action necessary to prevent similar failures in the future should be implemented, the RA should be updated with the new information, and the QCP should be modified as needed to reduce the residual risk from that component of potential failure. Examples of corrective actions are:

- When the problem is a failure of one of the measuring system's built-in QCs, additional preventive maintenance procedures and/or new QC processes might be necessary.
- If the failure is a result of environmental causes, the measuring system might need to be changed, the laboratory setting might need adaptation, or enhanced monitoring of the laboratory environment might need to be implemented.
- When operator errors are traced to gaps in written procedures or incomplete training, it is possible to revise the procedure and eliminate the opportunities for error; otherwise, the training program might need to be altered to ensure that operators are fully trained and aware of the cause of the failure and are competent to perform the test.[46]
- If the failure is caused by the specimen collection process or compromised integrity, a review of the specimen collection and handling procedures and retraining of personnel responsible for these processes might be needed.
- After a specified period, the laboratory should revisit the issue to ensure that the corrective action remains effective. Appendix G provides an example of how a laboratory can begin documenting and modifying a QCP.

Errors caused by device failures that affect patient care should be reported to the developer and to the regional medical device regulatory organization, as appropriate. Many countries have adverse event reporting systems that include both voluntary and mandatory reporting. The responsible agency sends reported events to developers and shares safety information with participants.

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# Chapter 7

# Conclusion

# 7 Conclusion

EP23 provides guidance based on risk-management principles for laboratories to develop QCPs. The testing process is outlined, including preexamination, examination, and postexamination, to identify potential failures that can lead to erroneous test results (hazards). The QCP defines the actions to mitigate risks, improve detection of erroneous results, and reduce patient harm. A laboratory should establish a review system, including corrective actions, for monitoring quality benchmarks (eg, key performance indicators) and evaluating the effectiveness of the QCP over time. Application of risk management strategies provides laboratories with the tools to continually improve the quality of laboratory tests.

# Chapter 8

# Supplemental Information

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# Appendix A. Potential Sources of Error (Failure Mode)

**NOTE:** Table is not all inclusive, and other sources of error must be considered by the laboratory.

| Potential Sources of Error, failure mode | | Applicable? | |
|---|---|---|---|
| | | Yes | No |
| **1. Specimen Collection** | | | |
| 1.1 | Contamination | | |
| 1.1.1 | Alcohol | | |
| 1.1.2 | Other cleansing agent | | |
| 1.1.3 | Anticoagulants in lines | | |
| 1.1.4 | Intravenous fluids | | |
| 1.1.5 | Admixture with other fluids and/or materials | | |
| 1.2 | Inadequate sample | | |
| 1.2.1 | Poor circulation at sample site | | |
| 1.2.2 | Poor vascular access | | |
| 1.2.3 | Insufficient volume drawn | | |
| 1.2.4 | Poor technique | | |
| 1.2.5 | Excess volume drawn | | |
| 1.3 | Hemolysis | | |
| 1.4 | Drawn from incorrect patient | | |
| 1.5 | Inappropriate specimen drawn | | |
| 1.5.1 | Arterial vs venous vs capillary blood | | |
| 1.5.2 | Whole blood vs plasma | | |
| 1.5.3 | Specimen submitted in wrong container or in syringe and/or specimen contains wrong additives | | |
| 1.5.4 | Fasting vs nonfasting | | |
| 1.5.5 | Clotted sample | | |
| 1.5.6 | Inappropriate time of collection | | |
| 1.6 | Patient condition inappropriate for testing method | | |
| 1.6.1 | Hematocrit too high or too low | | |
| 1.6.2 | Oxygen too low or too unstable | | |
| 1.6.3 | Patient medications interfere with testing method | | |
| 1.6.4 | Lipemia | | |
| 1.6.5 | Dilute urine | | |
| 1.6.6 | Dehydration and/or hemodilution | | |
| 1.6.7 | Shock | | |
| 1.7 | Improper patient preparation | | |
| **2. Sample Presentation** | | | |
| 2.1 | Incorrect procedure and/or technique | | |
| 2.1.1 | Contamination | | |
| 2.2 | Incorrect sample presented | | |

## Appendix A. (Continued)

| Potential Sources of Error, failure mode | | Applicable? Yes | Applicable? No |
|---|---|---|---|
| **2. Sample Presentation (Continued)** | | | |
| 2.2.1 | Sample type | | |
| 2.2.2 | Failure to appropriately dilute sample | | |
| 2.2.3 | Failure to remove excess particulate matter | | |
| 2.2.4 | Incorrect sample temperature | | |
| 2.2.5 | Improper handling of stored samples | | |
| 2.3 | Long delay from collection to analysis | | |
| 2.4 | Sample inadequately mixed | | |
| 2.5 | Sample inadequately mixed with reagents | | |
| 2.6 | Inappropriate amount of sample presented | | |
| 2.6.1 | Insufficient volume | | |
| 2.6.2 | Excessive volume | | |
| 2.7 | Introduction of air bubbles | | |
| 2.8 | Incorrect patient ID information entered into measuring instrument | | |
| **3. Instrument and/or Reagents** | | | |
| 3.1 | Adverse environmental conditions | | |
| 3.1.1 | Temperature | | |
| 3.1.2 | Humidity | | |
| 3.1.3 | Shock and/or vibration | | |
| 3.1.4 | Static electricity | | |
| 3.1.5 | Radio frequency interference and/or electromagnetic interference | | |
| 3.1.6 | Light intensity | | |
| 3.1.7 | Barometric pressure and/or altitude | | |
| 3.1.8 | Inadequate warm-up time | | |
| 3.1.9 | Low power | | |
| 3.2 | Outdated reagents | | |
| 3.3 | Improper reagent shipment | | |
| 3.4 | Improper reagent storage | | |
| 3.5 | Incorrectly prepared reagents | | |
| 3.6 | Incorrect use of reagents | | |
| 3.7 | Reagent contamination | | |
| 3.8 | Deterioration of reagent lots over time | | |
| 3.9 | Lot-to-lot variability | | |
| 3.10 | Sample-related reagent failure | | |
| 3.10.1 | Interfering substances | | |
| 3.10.2 | Excessive analyte concentrate (hook or prozone effects) | | |

## Appendix A. (Continued)

| Potential Sources of Error, failure mode | | Applicable? Yes | Applicable? No |
|---|---|---|---|
| **3. Instrument and/or Reagents (Continued)** | | | |
| 3.10.3 | Unusual pH | | |
| 3.10.4 | Unusual viscosity | | |
| 3.10.5 | Unusual particulate load | | |
| 3.11 | Electronic simulator malfunction | | |
| 3.12 | Improper QC shipment | | |
| 3.13 | Improper QC storage | | |
| 3.14 | Inadequate mixing of QC | | |
| 3.15 | Improper calibration | | |
| 3.16 | Poor precision | | |
| 3.17 | Poor trueness and/or correlation with laboratory method | | |
| 3.17.1 | Bias | | |
| 3.17.2 | Interferences | | |
| 3.18 | Incorrect analysis mode | | |
| 3.18.1 | QC vs patient samples | | |
| 3.18.2 | Incorrect analyte selected | | |
| 3.18.3 | Incorrect programming parameters | | |
| 3.19 | Sample carryover | | |
| 3.20 | Instrument error | | |
| 3.21 | Instrument failure | | |
| 3.21.1 | Software computation | | |
| 3.21.2 | Drift between calibration and analysis | | |
| 3.21.3 | Loss of calibration | | |
| 3.21.4 | Electronic instability | | |
| 3.21.5 | Readout device error | | |
| 3.21.6 | Loss and/or corruption of data | | |
| 3.22 | Instrument and/or reagent performance not verified before use | | |
| 3.22.1 | Initial instrument implementation | | |
| 3.22.2 | Instrument repair and/or maintenance | | |
| 3.22.3 | Battery changes | | |
| 3.22.4 | Reagent lot changes | | |
| 3.22.5 | Routine use | | |
| 3.23 | Improperly functioning instrument not removed from service | | |
| 3.24 | Inadequate instrument maintenance and/or handling | | |
| 3.24.1 | Dirty optics | | |
| 3.24.2 | Scratched lens | | |

## Appendix A. (Continued)

| Potential Sources of Error, failure mode | | Applicable? Yes | Applicable? No |
|---|---|---|---|
| **3. Instrument and/or Reagents (Continued)** | | | |
| 3.24.3 | Fogging | | |
| 3.24.4 | Instrument trauma | | |
| 3.25 | Patient's personal protective equipment used | | |
| 3.26 | Complicated procedure | | |
| 3.27 | Incorrect technique | | |
| **4. Results, Readout, and/or Raw Data** | | | |
| 4.1 | Visual misinterpretation | | |
| 4.1.1 | Color | | |
| 4.1.2 | Number | | |
| 4.2 | Incorrect setting for units of measure | | |
| 4.3 | Incorrect mode setting | | |
| 4.3.1 | Neonatal blood vs whole blood vs plasma | | |
| 4.3.2 | QC vs patient sample | | |
| 4.3.3 | Incorrect programming | | |
| 4.4 | Accidental loss of data | | |
| 4.5 | Calculation required | | |
| **5. Preliminary Review** | | | |
| 5.1 | Improper interpretation of QC results | | |
| 5.2 | Outlier and/or nonsense result not recognized | | |
| 5.3 | Result outside of linear interval not recognized | | |
| 5.4 | Critical value not recognized | | |
| 5.5 | Need for confirmatory sample not recognized | | |
| 5.6 | Effect of preexamination variables not recognized | | |
| 5.7 | Instrument malfunction not recognized | | |
| 5.8 | Interference not recognized | | |
| **6. Test Results Integration and/or Report Into Patient Chart** | | | |
| 6.1 | No result recorded | | |
| 6.2 | Result recorded in incorrect patient chart | | |
| 6.3 | Incorrect information recorded | | |
| 6.3.1 | Data | | |
| 6.3.2 | Time | | |
| 6.3.3 | Result | | |
| 6.4 | Information unreadable | | |
| 6.5 | No aids for clinical interpretation | | |
| 6.5.1 | Reference interval | | |

## Appendix A. (Continued)

| Potential Sources of Error, failure mode | | Applicable? Yes | Applicable? No |
|---|---|---|---|
| **6. Test Results Integration and/or Report Into Patient Chart (Continued)** | | | |
| 6.5.2 | Alert limits | | |
| 6.5.3 | Previous patient results | | |
| 6.6 | Inconsistent location of reporting and/or result difficult to find in patient chart | | |
| 6.7 | Result temporarily unavailable because of reporting mechanism (computer delay) | | |

Abbreviations: ID, identification; pH, negative logarithm of hydrogen ion concentration; QC, quality control.

# Appendix B. Example Checklist for Establishing a Quality Control Plan Based on Risk Management

## Abbreviations for Appendix B

**QC** quality control

**QCP** quality control plan

Recent advances in technology have significantly enhanced the accuracy and reliability of some measuring systems. In recognition of these advances, regulatory and accreditation organizations have provided opportunities for laboratories to establish a quality control plan (QCP) based on risk management. Appropriate site-specific QCPs can be established by systematically analyzing and evaluating factors that can adversely affect the quality of test results and by using an assortment of QC tools to mitigate patient risk. The combination of measuring system, laboratory, or test site environment and clinical application should be considered when a QCP is established. Some of the factors considered by the laboratory are shown in the following checklist. This checklist provides a useful overview of a laboratory's complete QCP. CLSI document EP18[1] and other individualized quality control plan documents[2] should be reviewed for more information. Items in this checklist are not intended to be all-inclusive, but rather, they are intended to provide guidance for establishing a QCP based on risk management and good laboratory practice.

| Quality Control Plan Checklist[3] | |
|---|---|
| **A. Information Gathering** | |
| **Instructions:** Gather and review the following items and information. | |
| • Requirements for IQCP eligibility determination (refer to your regulatory and accreditation organizations) | |
| • Regulatory and accreditation requirements or classifications | |
| • Measuring system information | |
| – Manufacturer's package inserts and IFU | |
| – Manufacturer's performance specifications and limitations | |
| – Manufacturer's information for scope and effectiveness of built-in QCs and recommended QC procedures | |
| – Manufacturer's maintenance recommendations | |
| – Reporting structure (manual vs interfaced results) | |
| – Supplies and inventory management (eg, consumables, standing orders) | |
| – Testing process flow charts or maps | |
| • Organizational information | |
| – Validation, verification, and correlation studies | |
| – Historical QC and PT data | |
| – Maintenance records consistent with manufacturer's IFU | |
| – Testing environments (multiple instruments) | |
| • Recalls, regulatory alerts, product notifications related to measuring system | |
| • Complaints or issuance of corrected reports | |
| • Health care– or organization-specific factors, such as consequences of incorrect, delayed, or unavailable results, consideration of life-threatening results and/or those indicating imminent patient danger, and the need to immediately notify health care providers | |
| • Scientific publications and reports from laboratory peers | |
| • Software, middleware, and/or hardware requirements | |
| • Testing personnel and qualifications | |

## Appendix B. (Continued)

| Quality Control Plan Checklist[3] (Continued) | |
|---|---|
| **B. Risk Assessment** | |
| **Instructions:**<br>**1.** Analyze all items and information gathered.<br>**2.** Review preexamination, examination, and postexamination phases of testing.<br>**3.** Divide each phase into steps to identify risks, potential failures, and errors in all phases of testing as they relate to the measuring system, sample, reagent, environment, and testing personnel.<br>**4.** Identify QC activities that can be implemented to reduce each identified potential failure and error. | |
| **Preexamination** | |
| • Regulatory and/or accreditation requirements | |
| – Consider any regulatory and accreditation requirements. | |
| – Consider any requirements related to measuring system classifications or complexity (waived, moderate, high). | |
| – Review any recalls and product or vendor notifications. | |
| • Measuring system information | |
| – Obtain adequate instructions from the manufacturer for using its methodology with its packaged measuring system. | |
| – Obtain manufacturer's information regarding the scope and effectiveness of built-in QCs. | |
| – Obtain manufacturer's recommendations for QC procedures and appropriate QC materials. | |
| – Obtain manufacturer's stated performance specifications and limitations. | |
| – Obtain manufacturer's stated maintenance and required schedules. | |
| **Preexamination and Examination**<br>**Preexamination – Measuring System Information** | |
| Factors that affect the test method or measuring system: | |
| • Specimen | |
| – Specimen type, volume, quality, and storage | |
| – Specimen collection and/or handling, containers, and preservatives | |
| – Acceptability criteria | |
| – Centrifugation requirements | |
| – Specimen referral | |
| • Reagent | |
| – Shipment, storage, and interchange of reagents between kits | |
| – Availability (multiple lots, standing orders, supply chain concerns) | |
| – Inventory and supply chain management, tracking lot numbers | |
| – Expiration dates recorded, changes documented when modifying, and reagents with no expiration date recorded | |
| – Implementation of procedures to ensure reagent lots are used within the expiration date | |

## Appendix B. (Continued)

| Quality Control Plan Checklist[3] (Continued) | |
|---|---|
| **B. Risk Assessment (Continued)** | |
| **Preexamination and Examination<br>Preexamination – Measuring System Information (Continued)** | |
| • Operator considerations | |
| – Training testing personnel | |
| – Periodic competence monitoring | |
| – Performing QC and PT | |
| – Maintaining adequate staffing and qualified testing personnel | |
| – Preventing operator fatigue | |
| – Continuing education | |
| • Physical and/or environmental considerations | |
| – Room temperature, humidity, and light levels | |
| – Location, altitude, level of work surface, and vibration | |
| – Controlling environmental parameters for mobile, bedside, and/or near-patient testing | |
| – Adequate equipment and/or room ventilation | |
| – Water quality | |
| – Sources of power | |
| – Cleanliness and absence of clutter | |
| – Occupational hazards; handling hazardous material | |
| **Preexamination and Examination<br>Examination – Measuring System Information** | |
| • Stable calibration over time that spans reportable interval | |
| • Mechanical or electronic errors | |
| • Built-in procedural and electronic controls | |
| • Detection procedures for optical systems, pipettes, and bar coding | |
| • QC (assayed and unassayed) | |
| • Negligible sample carryover between tests | |
| • Minimizing visual misinterpretation of test results through training and competence assessment | |
| • Including time to warm-up machines or conduct an analysis during the procedure | |
| • Avoiding risk of introducing air bubbles or by using low- or high-volume samples, clotted samples, wrong calibration code, or incorrect reagent | |
| • Hardware, software, timer, power source, and mechanical systems | |
| • Protecting equipment from exposure to radio frequency or electromagnetic interferences | |
| • Documenting procedures for relocating instruments | |
| • Documenting corrective actions | |

## Appendix B. (Continued)

| Quality Control Plan Checklist[3] (Continued) | |
|---|---|
| **B. Risk Assessment (Continued)** | |
| **Postexamination** | |
| • Reporting format | |
| • Complaints from health care providers | |
| • Number of corrected reports | |
| • Computer fatigue alert | |
| • Transmitting results (manual or interfaced) | |
| • Other factors considered: | |
| • Health care–specific factors | |
| – QCP considers the consequences of an incorrect, delayed, or unavailable result; whether results are acted on immediately; and whether the result is used for screening, diagnosis, and/or patient management. | |
| **Risk Assessment and Control** | |
| • Hazard identification | |
| – The laboratory uses the manufacturer's recommendations and laboratory-specific information to identify potential weaknesses in the examination process that present a risk to patients. | |
| – The laboratory critically assesses the information to determine whether it is appropriate for the conditions that exist in the laboratory or test setting. | |
| – The laboratory reviews the process flow chart and identifies hazards. | |
| – Hazard identification is documented in the following laboratory records: | |
| **C. Risk Estimation, Risk Evaluation, and Risk Control** | |
| **Instructions:** Estimate the probability and severity of harm and the function of measuring system QC processes to determine whether the risk is clinically acceptable. | |
| • Risk estimation | |
| – For each source of error or potential failure, assign probability, severity, and ability to detect the hazard and prevent the error. | |
| • Risk evaluation | |
| – For each risk estimated, compare with clinically acceptable risk. | |
| • Risk control | |
| – For each source of error or potential failure, implement control measures, identify any residual risks, and revise risk control measures or procedures until an acceptable risk level is obtained. | |
| • Risk assessment is documented in the following laboratory records: | |
| • Risk assessment summary | |
| – Determine whether risk assessment covers all phases of testing. | |
| • Ensure the following 5 components are covered in this checklist: | |
| – Specimen | |
| – Measuring system | |
| – Reagent | |
| – Environment | |
| – Testing personnel | |

## Appendix B. (Continued)

| Quality Control Plan Checklist[3] (Continued) | |
|---|---|
| **C. Risk Estimation, Risk Evaluation, and Risk Control (Continued)** | |
| • Determine whether current practices are sufficient to detect sources of error or failure in the measuring system. | |
| • Determine the frequency of identified risks that need to be monitored or controlled. | |
| **D. Laboratory Control Plan** | |
| **Instructions:** Determine whether the QC activities identified in the Risk Assessment and Control section meet the following criteria: | |
| • Provide for immediate detection of errors for each phase of the testing process (ie, preexamination, examination, postexamination) for the test. | |
| • Specify the number, type, and frequency of testing QC materials. | |
| • Contain criteria to determine acceptable QC results. | |
| • Require the laboratory to perform QC as specified by the manufacturer's IFU and not less. | |
| • Indicate that the laboratory director has reviewed, signed, and dated the QC document. | |
| • Risk mitigation is documented in the following laboratory records: | |
| **E. Quality Assessment** | |
| **Instructions:** The following QA activities should ensure that: | |
| • All reports, manufacturer's IFU, and procedure manuals monitor: | |
| – Accuracy and clarity of results reporting | |
| – Appropriateness of specimen, specimen collection, specimen handling, and transportation | |
| – Assay accuracy and precision | |
| – TAT | |
| – Compliance with policy and procedures | |
| • A written procedure or manufacturer's IFU is readily accessible to testing personnel for each assay performed. | |
| • A log of known errors and sources of errors encountered over time is maintained for: | |
| – Specimen collection | |
| – Temperature variations | |
| – Reagent and QC performance | |
| – Personnel errors | |
| • All personnel meet the minimum qualifications necessary for performing testing. | |
| • A formal training period exists for all new personnel, and refresher training is instituted for existing personnel. | |
| • Procedures are in place to document: | |
| – Corrective actions taken | |
| – Records reviews | |
| – Data entry errors | |
| – Laboratory investigations of failures and errors, to include actions taken to prevent future occurrences | |
| – Personnel training and competence assessment | |
| – Complaints received and actions taken to resolve | |
| – QC results for shifts and trends | |
| • All personnel participate in performing PT. | |
| • Laboratory conditions that can adversely affect patient testing are monitored. | |

## Appendix B. (Continued)

| Quality Control Plan Checklist[3] (Continued) | |
|---|---|
| **E. Quality Assessment (Continued)** | |
| • The QA covers the following topics: | |
| – QC practices for the laboratory are outlined. | |
| – QC practices are continually monitored for effectiveness. | |
| – Policies and procedures are revised as necessary to prevent recurrence of problems. | |
| – QA reviews are discussed with appropriate staff. | |
| – All QA activities are documented. | |
| • Modifications to the QCP are documented in the following laboratory records: | |

Abbreviations: IFU, instructions for use; IQCP, individualized quality control plan; PT, proficiency testing; QA, quality assurance; QC, quality control; QCP, quality control plan; TAT, turnaround time.

## References for Appendix B


1 CLSI. *Risk Management Techniques to Identify and Control Laboratory Error Sources; Approved Guideline—Second Edition*. CLSI document EP18-A2. Clinical and Laboratory Standards Institute; 2009.

2 US Department of Health and Human Services. *Guidance for Industry: Q9 Quality Risk Management*. Accessed 3 May 2023. https://www.fda.gov/media/71543/download

3 US Department of Health and Human Services. *IQCP Individualized Quality Control Plan: Developing an IQCP a Step-by-Step Guide*. Accessed 3 May 2023. https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/IQCP-Workbook.pdf

# Appendix C. Example Quality Control Plan: CLSI Document M22[1]–Exempt Microbiology Media

Appendix C is included in this guideline as an example of a quality control plan for a hypothetical hospital. It is not meant to be comprehensive guidance for all health care facilities, and it is not meant to cover all possible scenarios.

| Quality Control Plan<br>Exempt Microbiology Media |
|---|
| **Measuring System** |
| Commercially prepared CLSI document M22[1]–exempt microbiological media used in this laboratory include:<br>• 5% blood agar<br>• Anaerobic transport media<br>• BBE/LK<br>• Blood agar/EMB biplate (eg, urine cultures)<br>• Brain heart infusion broth (eg, QC for organism growth)<br>• Brucella agar (eg, anaerobes)<br>• Chopped meat glucose broth (eg, anaerobe recovery from sterile site)<br>• Levine eosin methylene blue agar (EMB for gram-negative organisms)<br>• Hektoen enteric agar (eg, *Salmonella* and *Shigella* spp.)<br>• Lim broth (eg, group B streptococci)<br>• PEA<br>• Rose agar (CNA and PEA for gram-positive organisms)<br>• Sabouraud's dextrose agar or slant (eg, fungal isolates)<br>• Selective agar for group A *Streptococcus*<br>• Thioglycollate broth[a]<br>• Tryptic soy agar slant (eg, saving organisms of interest)<br>• Tryptic soy broth (eg, used with ertapenem disk added for CRE screen; QC is performed each day of patient testing)<br>• Urea slant/urease agar[b]<br>• Commercially prepared blood culture bottles include blood bottles with trypticase soy broth<br>Remaining media is used for culturing primary specimens and cultivated organisms. |
| **Measuring System Primary SOPs** |
| • 5009 – QC in the Microbiology Laboratory[c]<br>• 5100 – Blood Culture System[c]<br>• 5017 – Inoculation[c]<br>• *General Instructions for Use of the Medical Laboratory* (formerly *Physicians and Nurses Guide to the Laboratory*[d]) |

## Appendix C. (Continued)

| Historical Quality Review |
|---|
| Previously, CLIA interpretive guidelines[2] recognized use of CLSI document M22,[1] which indicates that user retesting of commercially prepared microbiological culture media with QC strains is unnecessary for media that are proven acceptable. CLSI document M22[1] lists media that fall into this category and labels them "exempt." For these media, the user needs only to examine them for obvious defects, which include:<br>• Change in expected color of media<br>• Cracked or damaged plates<br>• Agar detached from the plates<br>• Excessive bubbles or rough surfaces<br>• Frozen or melted agar<br>• Excessive moisture or dehydration<br>• Unequal filling of plates<br>• Obvious contamination[e]<br>• Insufficient agar in the plates (< 3 mm)<br>• Presence of precipitates<br>• Hemolysis of blood containing media<br>This laboratory has been following CLSI document M22[1] for more than 25 years without any significant exempt media QC problems. Any problem related to media performance has involved:<br>• Random and infrequent physical defect (listed above) in a single unit of media<br>• Random and infrequent contamination of a single unit of media<br>Processes to mitigate patient reporting errors based on use of unacceptable exempt media are discussed in this QCP. |
| **Information Used to Conduct Risk Assessment[3]<br>Regulatory and Accreditation Requirements** |
| **Checklist From Accrediting Agency** |
| Checklists obtained from College of American Pathologists:<br>• *All Common Checklist*[4] (COM checklists)<br>• *Microbiology Checklist*[5] (MIC checklists) |
| **Method Verification** |
| Commercial media has been used in this laboratory since the early 1990s. Documentation of the packing slips for new shipments or lots of these media are retained for at least 3 years by microbiology department staff. |
| **Personnel Training** |
| Completion of training on initial hire and/or assignment to the microbiology department is documented in the individual personnel files. |
| **Competence Assessment** |
| Competence assessment records are filed in the individual personnel files. |
| **PT** |
| Rotate personnel and all personnel review results. PT records filed in the Laboratory Operations Manager's office. |

## Appendix C. (Continued)

**QC**

- CLIA specifies:

  "(4) Before, or concurrent with the initial use— (i) Check each batch of media for sterility if sterility is required for testing; (ii) Check each batch of media for its ability to support growth and, as appropriate, select or inhibit specific organisms or produce a biochemical response; and (iii) Document the physical characteristics of the media when compromised and report any deterioration in the media to the manufacturer. (5) Follow the manufacturer's specifications for using reagents, media, and supplies and be responsible for results."[3]
- Alternatively, an IQCP can be developed to modify the QC procedures for exempt media.
- CMS recognition of this option documented here:

- FAQs for IQCP,[6] revised August 2016, Question 50, states in part:

  "For example, laboratory documentation showing visual quality checks of media are acceptable in-house data. The laboratory may also include manufacturer's quality certificates as part of the information considered in its risk assessment."

**Measuring System Information**

**Manufacturer**

- Package inserts indicate that QC testing of exempt media includes use of QC strains and procedures recommended in CLSI document M22[1] and does not indicate that the user must perform additional testing with QC strains.
- CoQs are provided with each lot and/or shipment of exempt media, which indicates that the specific lot of media has met performance specifications described in CLSI document M22.[1]
- Manufacturer informs users of any problems with exempt media that are identified after release of the media with product alerts.
- Manufacturer has hotline available for reporting problems with defective media.
- Package inserts, CoQs, and product alerts are documented in the microbiology department.

**Summary of In-House Data for QC of Exempt Media**

Exempt media were inspected on receipt. Additional media quality checks included the following actions:

- Examined each unit of media for physical defects or contamination as described in the list above under "Historical Quality Review" immediately before inoculation with patient specimens or organisms
- Examined each unit of media that has been inoculated and/or incubated for possible contamination or other defect by observing for:
  - Growth outside the primary streak (ie, plated media)
  - Growth on only 1 unit of media inconsistent with growth on other units when multiple units are inoculated with the same specimen
  - Unexplainable results (ie, fungus growing on the same lot of blood agar plates from several patients' CSF specimens)

## Appendix C. (Continued)

**Summary of In-House Data for QC of Exempt Media (Continued)**

- Reviewed QC records, incidence reports, and staff feedback obtained over the past 12 months, which involved approximately 50 shipments and at least 10 000 units of exempt media that demonstrated:
  - < 0.01% occurrence of defective media (eg, physically damaged primarily resulting from cracked Petri plates)
  - < 0.01% occurrence of contaminated media
- Occurrences of physically defective media were random and not lot specific. Physically defective media were not used for patient specimen testing and were discarded. No patient reports were affected as a result of any physically defective or contaminated media. The records documenting media receipt are in the microbiology department.

**NOTE:** The cutoff for an acceptable failure rate detailed in CLSI document M22[1] is 0.5%. This means 5 of 1000 units of a specific exempt medium might demonstrate a random defect.

**Summary of Corrected Reports and Health Care Provider Complaints**

There were no incidents of corrected reports or health care provider complaints due to defective exempt media.

**Risk Assessment and Determination of Risk Level**

**Frequency of Occurrence**

- Unlikely (once every 2 to 3 years)
- Occasional (once per year)
- Probable (once per month)
- Frequent (once a week)

**Severity of Harm to Patient**

- Negligible (temporary discomfort)
- Minor (temporary injury not requiring medical intervention)
- Serious (impairment requiring medical intervention)
- Critical (life-threatening consequences)

**Risk Level**

- Risk level for any risk factor that is "unacceptable" **must** be covered in the QCP.
- Risk level for any risk factor that is "acceptable" may be included in the QCP at the discretion of the laboratory director.

**NOTE:** Patient response and AST results play a significant role in guiding antimicrobial therapy and provide a limited safeguard for preventing harm to patients for which erroneous AST results are reported or results are delayed.

**Risk Acceptability Matrix**

| Probability of Harm | Negligible | Minor | Serious | Critical |
|---|---|---|---|---|
| Frequent | Unacceptable | Unacceptable | Unacceptable | Unacceptable |
| Probable | Acceptable | Unacceptable | Unacceptable | Unacceptable |
| Occasional | Acceptable | Acceptable | Acceptable | Unacceptable |
| Unlikely | Acceptable | Acceptable | Acceptable | Acceptable |

## Appendix C. (Continued)

| Risk Acceptability Assignment | | | |
|---|---|---|---|
| **Risk Factor, possible sources of error** | **Frequency of Occurrence** | **Severity of Harm to Patient** | **Risk Level** |
| **Preexamination** | | | |
| **Specimen (Primary)** | | | |
| Patient ID | Probable | Minor | Unacceptable |
| Collection, container, and/or volume | Frequent | Negligible | Unacceptable |
| Integrity | Frequent | Negligible | Unacceptable |
| Transport | Frequent | Negligible | Unacceptable |
| Storage | Probable | Negligible | Acceptable |
| **Specimen (Organism)** | | | |
| Colony age, viability, and/or sampling | Unlikely | Minor | Acceptable |
| Media type | Unlikely | Minor | Acceptable |
| Pure isolate | Unlikely | Minor | Acceptable |
| **Examination** | | | |
| **Testing Personnel** | | | |
| Training | Probable | Negligible | Acceptable |
| Competence | Occasional | Negligible | Acceptable |
| Experience | Occasional | Negligible | Acceptable |
| PT | Occasional | Negligible | Acceptable |
| Staffing | Occasional | Negligible | Acceptable |
| **Reagents** | | | |
| Shipping, receiving, and/or storage | Probable | Negligible | Acceptable |
| Expiration dates | Probable | Negligible | Acceptable |
| Batch sterility | Probable | Negligible | Acceptable |
| Visual inspections | Frequent | Negligible | Acceptable |
| **Environment** | | | |
| Temperature, airflow, humidity, and/or ventilation | Occasional | Negligible | Acceptable |
| Utilities | Occasional | Negligible | Acceptable |
| **Measuring System (Media)** | | | |
| Contamination | Probable | Minor | Acceptable |
| Organism growth | Occasional | Minor | Acceptable |

## Appendix C. (Continued)

| Risk Acceptability Assignment (Continued) | | | |
|---|---|---|---|
| **Risk Factor, possible sources of error** | **Frequency of Occurrence** | **Severity of Harm to Patient** | **Risk Level** |
| **Postexamination** | | | |
| **Test Results** | | | |
| Organism growth correlations | Occasional | Serious | Acceptable |
| Review reported results | Unlikely | Minor | Unacceptable |
| Clinician feedback | Unlikely | Critical | Unacceptable |

| Risk Assessment | | |
|---|---|---|
| **Possible Sources of Error** | | **How Can Identified Sources of Error Be Reduced?** |
| **Risk Factor** | **Possible Error** | |
| **Preexamination** | | |
| **Specimen (Primary)** | | |
| • Patient ID<br>• Collection, container, and/or volume<br>• Integrity<br>• Transport<br>• Storage | Improper specimen procurement, handling, and or processing | • Adhere to procedures for handling patient ID and specimen collection, labeling, transport, storage, and remedial actions to control improperly handled specimens or delayed specimens.<br>• Review significant specimen processing errors in real time with all staff involved with patient specimens.<br>• Review internal occurrence reports for mishandled specimens.<br>• During initial training and competence assessment, emphasize:<br>– Proper specimen handling and processing is the most critical part of any test.<br>– Each unit of media must be inspected for contamination and any physical defects before use for inoculating primary specimens.<br>– Failure to inoculate and streak correctly (no isolated colonies) and delayed incubation can result in delayed microbiology reports. |

## Appendix C. (Continued)

| Risk Assessment (Continued) | | |
|---|---|---|
| Possible Sources of Error | | How Can Identified Sources of Error Be Reduced? |
| Risk Factor | Possible Error | |
| **Preexamination (Continued)** | | |
| **Specimen (Organism)** | | |
| Colony age, viability, and/or sampling | Organism is nonviable. | During initial training and competence assessment, emphasize lengths of time various organisms generally remain viable in various specimens and/or media. |
| Media type | • Media appropriate for the organism are used.<br>• Media fails to support growth of test organism.<br>• Media are contaminated. | During initial training and competence assessment, emphasize:<br>• Appropriate media and incubation conditions for various organisms<br>• Recognition of contaminated media |
| Pure isolate | Mixed inoculum | During initial training and competence assessment, emphasize:<br>• Selection of pure cultures for subculture<br>• Potential sources of contamination during testing process |
| **Examination** | | |
| **Testing Personnel** | | |
| • Training<br>• Competence<br>• Experience | | • During initial training and competence assessment, emphasize key aspects of media use and assessment of media quality, including those described in this QCP.<br>• Review and sign 2-week standardized introductory process of new or revised protocols for all relevant staff. |
| PT | | • All appropriate staff review and sign off on PT sample critiques.<br>• Supervisor shares any pertinent information from PT surveys with staff, as appropriate. |
| Staffing | Inadequate to perform testing without errors | Supervisor annually reviews staffing to support evaluation of media on receipt and before use. |

## Appendix C. (Continued)

| Risk Assessment (Continued) | | |
|---|---|---|
| Possible Sources of Error | | How Can Identified Sources of Error Be Reduced? |
| Risk Factor | Possible Error | |
| **Examination (Continued)** | | |
| **Reagents (Media)** | | |
| • Training<br>• Competence<br>• Experience<br>• Expiration dates | | During initial training and competence assessment, emphasize standard rules to always:<br>• Take responsibility for using media appropriately.<br>• Maintain media at proper storage conditions.<br>• Check expiration dates.<br>• Incubate and check representative sample of media for sterility.<br>• Inspect each unit of media for physical defects and random contamination before use as described in this QCP. |
| Receiving and/or storage | • Incorrect ordering<br>• Damaged packaging | Designated staff member(s) are assigned to inventory (eg, order and/or receipt) media to ensure media supply is properly maintained and handled appropriately on receipt. |
| Visual inspection | | • See above (Training, Competence, Experience, Expiration dates).<br>• Implement and maintain log of contaminated media. |
| **Environment** | | |
| • Training<br>• Competence<br>• Experience<br>• Temperature, airflow, humidity, and/or ventilation<br>• Utilities | | During initial training and competence assessment, emphasize standard rules for:<br>• Taking responsibility for any possible instrument and/or environmental problem<br>• Maintaining equipment<br>• Recording temperature<br>• Protecting equipment from electrical surges and using generator as an alternative power supply during power outage |
| **Measuring System (Media)** | | |
| • Training<br>• Competence<br>• Experience | | During initial training and competence assessment, emphasize standard rules for:<br>• Taking responsibility for any out-of-the-ordinary observation with any media<br>• Inspecting each unit of media for contamination and any physical defects before use |
| Contamination | Random contamination on individual unit of media not recognized | During initial training and competence assessment, emphasize standard rules for:<br>• Inspecting each unit of media for contamination before use<br>• Implementing and maintaining a log of contaminated media |

## Appendix C. (Continued)

| Risk Assessment (Continued) | | |
|---|---|---|
| Possible Sources of Error | | How Can Identified Sources of Error Be Reduced? |
| Risk Factor | Possible Error | |
| **Examination (Continued)** | | |
| **Measuring System (Media) (Continued)** | | |
| Organism growth | Media "unexpectedly" fails to support the growth of a microorganism. | • Review manufacturer's CoA to ensure QC was successful as described in CLSI document M22.[1]<br>• Check for inconsistencies in organism growth on all media types.<br>• Check for inconsistencies in organism growth vs Gram stain. |
| **Postexamination** | | |
| **Test Results** | | |
| Review reported results. | | Supervisor maintains records of reporting errors and corrected reports, as well as corrective action to handle any potential exempt media issues. |
| Review health care provider feedback. | Complaints or suggestions regarding potential erroneous results caused by exempt media quality | • See above (Review reported results).<br>• Incorporate suggestions into QA plan, as appropriate. |

**Final Quality Control Plan for Antimicrobial Susceptibility Testing**

Based on our risk assessment and QA, the QCP for exempt media consists of following the instructions that are provided in explicit detail in policy and procedure 5009 – QC in the Microbiology Laboratory[c]:

- Review manufacturer's CoAs provided with each batch, lot, and/or shipment of media on receipt of shipment.
- Visually inspect representative units of exempt media for any physical defects or contamination on receipt.
- Document any issues in the media log.
- Visually inspect all units of exempt media for any physical defects or contamination immediately before inoculation with primary specimen or cultivated microorganism.
- Document any issues in the media log.
- Maintain logs to record media received, any defects observed, and any interactions with manufacturer about defective media. Also, record any instances in which defective media were used for patient specimens and any resultant reporting errors. Supervisor to review these logs monthly for any trends warranting attention.
- Inform manufacturer of any defective media beyond random occurrences.
- Continually monitor storage environment for media.
- Review manufacturer's IFU and media alerts as received.
- During initial training and competence assessment, instruct all staff regarding:
  - Media storage conditions
  - The need to continually look for any defects, contamination, or inconsistencies in growth on exempt media and inform supervisor of such occurrences immediately
- Whenever a problem or potential problem is identified with exempt media, inform staff about it.

## Appendix C. (Continued)

| Quality Assessment: Ongoing Monitoring for Quality Control Plan Effectiveness (performed by supervisor and/or section head) |
|---|
| • Reasons for QC failures, PT failures, and patient isolate reporting errors will be examined and managed as needed in a new or updated risk assessment:<br>**1.** Has a new risk factor been identified?<br>**2.** Does this change the frequency of risk?<br>**3.** Does the risk factor change the potential severity of harm to the patient?<br>• Periodically review patient results for reporting errors and clinician complaints. Take corrective action and revise QCP as needed.<br>• Review manufacturer's package inserts, CoAs, and media alerts as received, and revise QCP as needed.<br>• Perform annual review of *Quality Control of Media and Reagents* protocol[d] and revise as needed.<br>• Perform periodic review of PT results after each report is received from sponsor of PT program. Take corrective action and revise QCP, if necessary, when PT results are unacceptable.<br>• Perform monthly review of all equipment maintenance and monitoring logs according to laboratory protocols. Take corrective action and revise QCP as needed.<br>• Perform periodic training and competence assessment according to standard laboratory protocols. Modify training and revise QCP as needed.<br>• Continually participate in this institution's quality program covering specimen handling and erroneous specimen labeling. Take corrective action and revise QCP as needed. |
| **This QCP has been reviewed and is approved by the laboratory director (as named on the CLIA license).**<br><br>**Signature/Date:** |

Abbreviations: AST, antimicrobial susceptibility testing; BBE/LK, bacteroides bile esculin and laked blood kanamycin biplate vancomycin; CLIA, Clinical Laboratory Improvement Amendments; CMS, Centers for Medicare & Medicaid Services; CoA, certificate of analysis; CoQ, certificate of quality; CNA, Columbia nalidixic acid; CRE, carbapenem-resistant Enterobacterales; CSF, cerebrospinal fluid; EMB, eosin methylene blue agar; FAQ, frequently asked question; ID, identification; IFU, instructions for use; IQCP, individualized quality control plan; PEA, phenylethyl alcohol agar; PT, proficiency testing; QA, quality assurance; QC, quality control; QCP, quality control plan; SOP, standard operating procedure.
[a] Used for primary specimens only.
[b] Used for cultivated organisms only.
[c] Hypothetical SOP included as an example.
[d] Hypothetical protocol included as an example.
[e] Ten plates or tubes of a specific medium from each batch/lot/shipment should be examined on receipt, and all plates or tubes should be examined immediately before inoculation with patient specimens.

## References for Appendix C


1 CLSI. *Quality Control for Commercially Prepared Microbiological Culture Media; Approved Standard—Third Edition.* CLSI document M22-A3. Clinical and Laboratory Standards Institute; 2004.

2 Centers for Medicare & Medicaid Services. *State Operations Manual, Appendix C: Survey Procedures and Interpretive Guidelines for Laboratories and Laboratory Services.* Updated 3 March 2017. Accessed 3 May 2023. https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/som107ap_c_lab.pdf

3 Centers for Medicare & Medicaid Services, US Department of Health and Human Services. *Part 493—Laboratory Requirements: Clinical Laboratory Improvement Amendments of 1988* (Codified at 42 CFR §493). Office of the Federal Register; published annually.

## Appendix C. (Continued)


4 CAP. *All Common Checklist*. College of American Pathologists; 2020.

5 CAP. *Microbiology Checklist*. College of American Pathologists; 2020.

6 Centers for Medicare & Medicaid Services. FAQs for IQCP. Updated August 2016. Accessed 3 May 2023. https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/FAQs-IQCP.pdf

# Appendix D. Example Quality Control Plan: Noninstrumented Unit-Use Device – Shiga Toxin

Appendix D is included in this guideline as an example of a quality control plan for a hypothetical hospital. It is not meant to be comprehensive guidance for all health care facilities, and it is not meant to cover all possible scenarios.

| Quality Control Plan |
|---|
| **Measuring System Primary Procedures** |
| • Processing microbiological specimens<br>• Shiga toxin procedure |
| **Historical Quality Review** |
| • CLIA requires testing of positive and negative QC after establishing and validating procedure.[1] This laboratory has been performing external QC once a week, per lot number and per shipment, without any significant QC problems. It is rare to obtain an invalid QC that indicates a measuring system problem. Nearly all testing errors or delays in reporting occur with individual patient isolates, and these errors are unrelated to testing QC strains or a problem with testing reagents or equipment.<br>• Processes to mitigate patient reporting errors and delayed reports are discussed in this QCP. |
| **Information Used to Conduct Risk Assessment<br>Regulatory and Accreditation Requirements** |
| **Checklist From Accrediting Agency** |
| • Checklists obtained from:<br>– CLIA<br>– CLSI<br>– CAP |
| **Method Verification** |
| Measuring system verification completed in 2016. Documentation filed in microbiology department. |
| **Personnel Training** |
| Completion of training documented in individual personnel file. |
| **Competence Assessment** |
| Checklist completed at new staff orientation and annually thereafter. Documentation in individual personnel file. |
| **PT** |
| Rotate personnel; all personnel review results. PT records filed in microbiology department. |
| **QC** |
| CLIA and accrediting agency require testing of QC strains daily (or each day patient tests are performed) for rapid kits. Alternatively, an IQCP can be developed to modify frequency of testing QC strains. |
| **Measuring System Information** |
| **Manufacturer** |
| Manufacturer IFU contain system performance data and describe testing principle and procedure, QC recommendations, and limitations. IFU are located with the kit. |

## Appendix D. (Continued)

| Measuring System Information (Continued) |
|---|
| **Summary of In-House Data From Routine Testing of QC Strains** |
| QC testing was performed according to procedure. Review of QC records for the past 12 months that contained approximately 25 results demonstrated 0.00% occurrence (zero incidents) of potential system QC errors that required corrective action. |
| **Summary of Corrected Reports and Health Care Provider Complaints** |
| Review of reporting errors identified before report release, corrected reports, physician complaints, and significantly delayed reports (> 5 days after specimen collection) for the past 12 months revealed there were no corrected reports.<br>**NOTE:** During this review of corrected reports and physician complaints, none of the errors could have been avoided by any changes in protocol for testing of QC strains, including testing frequency. |
| **Risk Assessment and Determination of Risk Level** |
| **Frequency of Occurrence** |
| • Unlikely (once every 2 to 3 years)<br>• Occasional (once per year)<br>• Probable (once per month)<br>• Frequent (once a week) |
| **Severity of Harm to Patient** |
| • Negligible (temporary discomfort)<br>• Minor (temporary injury not requiring medical intervention)<br>• Serious (impairment requiring medical intervention)<br>• Critical (life-threatening consequences) |
| **Risk Level** |
| • Risk level for any risk factor that is "unacceptable" must be discussed in the QCP.<br>• Risk level for any risk factor that is "acceptable" may be included in the QCP at the discretion of the laboratory director. |

**Risk Acceptability Matrix**

| Probability of Harm | Negligible | Minor | Serious | Critical |
|---|---|---|---|---|
| Frequent | Unacceptable | Unacceptable | Unacceptable | Unacceptable |
| Probable | Acceptable | Unacceptable | Unacceptable | Unacceptable |
| Occasional | Acceptable | Acceptable | Acceptable | Unacceptable |
| Unlikely | Acceptable | Acceptable | Acceptable | Acceptable |

## Appendix D. (Continued)

| Risk Acceptability Assignment | | | |
|---|---|---|---|
| **Risk Factor, possible sources of error** | **Frequency of Occurrence** | **Severity of Harm to Patient** | **Risk Level** |
| **Preexamination** | | | |
| **Specimen (Primary)** | | | |
| Patient ID and/or specimen | Probable | Minor | Unacceptable |
| Collection, container, and/or volume | Occasional | Negligible | Unacceptable |
| Transport | Probable | Minor | Acceptable |
| Storage | Occasional | Minor | Acceptable |
| Clinically relevant | Probable | Minor | Unacceptable |
| Integrity | Frequent | Minor | Unacceptable |
| Contamination with urine | Unlikely | Minor | Acceptable |
| Preservative used | Unlikely | Minor | Unacceptable |
| **Examination** | | | |
| **Testing Personnel** | | | |
| Training | Occasional | Serious | Unacceptable |
| Competence | Occasional | Serious | Unacceptable |
| Experience | Unlikely | Serious | Unacceptable |
| PT | Unlikely | Negligible | Acceptable |
| Staffing | Occasional | Minor | Acceptable |
| **Reagents** | | | |
| Shipping, receiving, and/or storage | Occasional | Minor | Acceptable |
| Expiration dates | Unlikely | Minor | Acceptable |
| Preparation and use | Unlikely | Minor | Acceptable |
| QC | Occasional | Negligible | Acceptable |
| **Environment** | | | |
| Temperature, airflow, humidity, and/or ventilation | Unlikely | Negligible | Acceptable |
| Utilities | Occasional | Minor | Acceptable |
| Space | Unlikely | Negligible | Acceptable |
| Noise or vibration | Unlikely | Negligible | Acceptable |
| **Measuring System** | | | |
| Transmission of results to LIS | Unlikely | Minor | Acceptable |

## Appendix D. (Continued)

| Risk Acceptability Assignment (Continued) | | | |
|---|---|---|---|
| **Risk Factor, possible sources of error** | **Frequency of Occurrence** | **Severity of Harm to Patient** | **Risk Level** |
| **Postexamination** | | | |
| **Test Results** | | | |
| Results reported within 3 days | Unlikely | Minor | Acceptable |
| Transmission of results to EHR | Occasional | Minor | Acceptable |
| Review reported results | Unlikely | Negligible | Acceptable |
| Clinician feedback | Unlikely | Minor | Acceptable |

| Risk Assessment | | |
|---|---|---|
| **Possible Sources of Error** | | **How Can Identified Sources of Error Be Reduced?** |
| **Risk Factor** | **Possible Error** | |
| **Preexamination** | | |
| **Specimen (Primary)** | | |
| Specimen (Primary) | Improper specimen procurement, handling, and/or processing | • Adhere to procedures that cover patient ID and specimen collection, labeling, transport, storage, and remedial actions to control improperly handled specimens or delayed specimens.<br>• Annually review representative specimen processing errors (N = 10 to 15) with all staff involved with patient specimens.<br>• During initial training and competence assessment, emphasize that proper specimen handling and processing is the most critical part of any test. |
| Patient and/or specimen ID | | See above (Specimen [Primary]). |
| Collection, container, and/or volume | QNS | See above (Specimen [Primary]). |
| Integrity | Reject formed stool | See above (Specimen [Primary]). |
| Transport | Not promptly submitted to the laboratory | See above (Specimen [Primary]). |
| Storage | Not refrigerated within hours | See above (Specimen [Primary]). |
| **Specimen (Organism)** | | |
| Clinically relevant | Clinically irrelevant need tested | • Physicians can request additional testing for select patients.<br>• Supervisor or director discusses with requesting physician those requests that might be inappropriate. |
| Species appropriate | Testing of system | During initial training and competence assessment, emphasize how to manage indeterminate results. |

## Appendix D. (Continued)

| Risk Assessment (Continued) | | |
|---|---|---|
| Possible Sources of Error | | How Can Identified Sources of Error Be Reduced? |
| Risk Factor | Possible Error | |
| **Examination** | | |
| **Testing Personnel** | | |
| • Training<br>• Competence | Incompletely trained | During initial training and competence assessment:<br>• Emphasize acceptable specimens described in this QCP.<br>• Schedule monthly review meetings with supervisor. |
| Experience | | Supervisor reviews reports generated by new staff before release of test results for the first 2 months of their employment. |
| PT | | All staff review and sign off on PT sample critiques. |
| Staffing | Inadequate to perform testing without errors | Supervisor annually reviews appropriate staffing needs to schedule staff accordingly. |
| **Reagents** | | |
| • Training<br>• Competence | | During initial training and competence assessment, emphasize standard rules to always:<br>• Take responsibility for reagents and supplies.<br>• Maintain reagents at proper storage conditions.<br>• Check expiration dates.<br>• Perform required QC. |
| Receiving and storage | • Incorrect ordering<br>• Depleted reagent supply<br>• Reagent integrity compromised | Designated staff member(s) assigned to inventory (eg, order and/or receipt) ensures inventory is properly maintained and testing materials are handled appropriately on receipt. |
| Expiration dates | | See above (Training, Competence). |
| **Environment** | | |
| Environment | Results not reported (eg, ancillary equipment failure, such as incubator malfunction) | Temperature recording |
| Temperature, airflow, humidity, and/or ventilation | | See above (Environment). |
| Utilities | | See above (Environment). |
| Space | | N/A (sufficient space available) |
| Noise and/or vibration | | Install shielding or acoustical sound-deadening enclosures and place refrigerators, incubators, and centrifuges away from primary work areas. Also, move instruments away from those that can generate vibration, such as centrifuges. |

## Appendix D. (Continued)

| Risk Assessment (Continued) | | |
|---|---|---|
| Possible Sources of Error | | How Can Identified Sources of Error Be Reduced? |
| Risk Factor | Possible Error | |
| **Examination (Continued)** | | |
| **Measuring System** | | |
| • Training<br>• Competence | | During initial training and competence assessment, emphasize standard rules for taking responsibility for any possible instrument and/or measuring system problem (out-of-the-ordinary observation). |
| Transmission of results to LIS | • Incorrect transmission of results<br>• Delay in transmission of results | • Supervisor (or supervisor designee) reviews reported results daily.<br>• Supervisor performs annual checks of measuring system and LIS computer interface.<br>• Supervisor monitors QA to measure time from receipt to reporting results. |
| **Postexamination** | | |
| **Test Results** | | |
| Test results | | • Supervisor maintains summary of incorrect results released and meets with laboratory director to review this summary.<br>• Supervisor conducts QA monitoring of indeterminate results. |
| Results reported within 3 days | Results delayed beyond that expected | See above (Test results). |
| Transmission of results to EHR | • Incorrect transmission of results<br>• Delay in transmission of results | See above (Test results). |
| Review reported results | Report missing comments or those inappropriate for the test | See above (Measuring System, Test results).<br>**NOTE:** Results are checked at multiple steps by the laboratorian and then by the supervisor. |
| Clinician feedback | Complaints or suggestions regarding delayed and potential erroneous results | • See above (Test results).<br>• Incorporate suggestions into QA plan, as appropriate. |
| **Final Quality Control Plan for Shiga Toxin Kit** | | |
| • Based on our risk assessment and QA, the QCP consists of following the instructions that are provided in explicit detail in the Quality Control Section for Performance and are summarized here.<br>• QC testing is done once per each new lot and/or shipment before or concurrently with placing these materials into use for testing patient specimens.<br>• Record and evaluate QC results according to QC acceptability criteria as defined in the SOP. Any out-of-interval result is immediately investigated and corrective action is taken before releasing any patient results. | | |

## Appendix D. (Continued)

| Quality Assessment: Ongoing Monitoring for Quality Control Plan Effectiveness (performed by supervisor and/or section head) |
|---|
| • Reasons for QC failures, PT failures, and patient isolate reporting errors will be examined and discussed as needed in a new or updated risk assessment:<br>**1.** Has a new risk factor been identified?<br>**2.** Does the risk factor change the frequency of the risk?<br>**3.** Does the risk factor change the potential severity of harm to patients?<br>• Conduct daily review of patient results for reporting errors and clinician complaints. Take corrective action and revise QCP as needed.<br>• Conduct monthly review of QC results. Take corrective action and revise QCP when unexpected QC failures indicate adjustment to the QCP is needed.<br>• Conduct monthly review of length of time from specimen collection to results reporting to determine incidence of reports delayed beyond 2 days. Take corrective action and revise QCP when number of delayed reports exceeds acceptable limit as established by the laboratory director.<br>• Conduct regular review of PT results. Take corrective action and revise QCP, if necessary, when PT results are unacceptable.<br>• Offer periodic training and competence assessment according to standard laboratory protocols. Modify training and revise QCP as needed.<br>• Continually participate in this institution's quality program that covers specimen handling and labeling. Take corrective action and revise QCP as needed. |
| **This QCP has been reviewed and is approved by the laboratory director (as named on the CLIA license).**<br><br>**Signature/Date:** |

Abbreviations: CAP, College of American Pathologists; CLIA, Clinical Laboratory Improvement Amendments; CLSI, Clinical and Laboratory Standards Institute; EHR, electronic health record; ID, identification; IFU, instructions for use; IQCP, individualized quality control plan; LIS, laboratory information system; N/A, not applicable; PT, proficiency testing; QA, quality assurance; QC, quality control; QCP, quality control plan; QNS, quantity not sufficient; SOP, standard operating procedure.

## Reference for Appendix D

1 Centers for Medicare & Medicaid Services, US Department of Health and Human Services. *Part 493—Laboratory Requirements: Clinical Laboratory Improvement Amendments of 1988* (Codified at 42 CFR §493). Office of the Federal Register; published annually.

# Appendix E. Example Quality Control Plan: Instrumented Unit-Use System – Fetal Fibronectin

Appendix E is included in this guideline as an example of a quality control plan for a hypothetical hospital. It is not meant to be comprehensive guidance for all health care facilities, and it is not meant to cover all possible scenarios.

**Laboratory:** Ideal Labs

**Measuring system:** Fetal fibronectin (fFN) analyzer

| Quality Control Plan<br>Fetal Fibronectin Analyzer<br>Risk Assessment<br>Preexamination Phase | | | | |
|---|---|---|---|---|
| **Risk Factor** | **Can Risk Be Reduced?** | **Measures to Control Risk** | **Relevant Documentation** | **Comments** |
| **Specimen** | | | | |
| Incorrect specimen collection | Yes | • Training<br>• Competence<br>• Laboratory test directory (resource)<br>• Manufacturer-specific collection kit IFU | • Procedures<br>• Training<br>• Competence records<br>• Rapid fFN specimen collection kit<br>• Rapid fFN cassette kit<br>• Rapid fFN analyzer user manual | Specific collection instructions, including specimen type, are available in the rapid fFN specimen collection kit IFU, as well as in the rapid fFN cassette kit used by collection staff. |
| Specimen type | Yes | | | |
| **Specimen Integrity** | | | | |
| Interfering substances | Yes | • Training<br>• Competence<br>• Rapid fFN procedure<br>• Rapid fFN specimen collection kit IFU | • Procedures<br>• Training<br>• Competence records<br>• Rapid fFN specimen collection kit<br>• Rapid fFN cassette kit<br>• Rapid fFN analyzer user manual | The fFN analyzer displays an invalid message if the test does not meet internal acceptance criteria for a valid test. Interfering substances are noted in the rapid fFN specimen collection kit IFU used by collection staff and health care provider. Clinical conditions that could affect results include:<br>• Premature rupture of membranes<br>• Pelvic examination performed before specimen collection<br>• Blood<br>• Patient had sexual intercourse within 24 hours of collection<br>• Patients with reproductive tract cancer |
| Thick or viscous specimens | Yes | • Training<br>• Competence<br>• fFN procedure | | The fFN analyzer displays an invalid message if the test does not meet internal acceptance criteria for a valid test. |

## Appendix E. (Continued)

| Quality Control Plan<br>Fetal Fibronectin Analyzer<br>Risk Assessment<br>Preexamination Phase (Continued) | | | | |
|---|---|---|---|---|
| **Risk Factor** | **Can Risk Be Reduced?** | **Measures to Control Risk** | **Relevant Documentation** | **Comments** |
| **Specimen Integrity (continued)** | | | | |
| Patient ID | Yes | • Training<br>• Competence<br>• Patient ID policy | • Procedures<br>• Training<br>• Competence records<br>• Rapid fFN specimen collection kit IFU | • Clinical staff follow patient ID policy.<br>• Laboratory staff monitor specimen labeling and notifies clinical staff of mislabeled specimens.<br>• The rapid fFN specimen collection kit IFU specifically indicates that patient ID information be placed on the specimen collection tube. |
| Specimen labeling (Core Laboratory and Collecting Department) | Yes | • Training<br>• Competence<br>• Policy for labeling laboratory specimens | | |
| **Other** | | | | |
| | | | | |

| Quality Control Plan<br>Fetal Fibronectin Analyzer<br>Risk Assessment<br>Examination Phase | | | | |
|---|---|---|---|---|
| **Risk Factor** | **Can Risk Be Reduced?** | **Measures to Control Risk** | **Relevant Documentation** | **Comments** |
| **Testing Personnel** | | | | |
| Specimen labeling | Yes | • Training<br>• Competence<br>• Policy for labeling laboratory specimens | • Procedures<br>• Training<br>• Competence records<br>• Rapid fFN collection kit IFU | The rapid fFN collection kit IFU specifically indicates that patient ID information be placed on the specimen collection tube. |
| Sample preparation | Yes | • Training<br>• Competence<br>• fFN procedure | | • Specific collection instructions, including sample preparation, specimen type, and interfering substances, are available in the rapid fFN collection kit IFU used by collection staff.<br>• Laboratory policy and staff training and/or competence specifies that laboratory staff alert collecting staff of possible specimen issues resulting from sample preparation. |

## Appendix E. (Continued)

| Quality Control Plan<br>Fetal Fibronectin Analyzer<br>Risk Assessment<br>Examination Phase (Continued) | | | | |
|---|---|---|---|---|
| **Risk Factor** | **Can Risk Be Reduced?** | **Measures to Control Risk** | **Relevant Documentation** | **Comments** |
| **Testing Personnel (Continued)** | | | | |
| Procedure not followed | Yes | • Training<br>• Competence<br>• fFN procedure<br>• Disciplinary action | • Procedures<br>• Training<br>• Competence records<br>• Rapid fFN specimen collection kit IFU<br>• Rapid fFN cassette kit IFU<br>• Rapid fFN analyzer user manual | |
| **Measuring System** | | | | |
| Delay in testing | Yes | • Training<br>• Competence<br>• fFN procedure | • Procedures<br>• Training<br>• Competence records<br>• Rapid fFN specimen collection kit IFU | • As specified in the collection instructions, specimens not tested within 8 hours are to be stored at 2 to 8°C and assayed within 3 days, or frozen and tested within 3 months.<br>• Sample stability, preparation, specimen type, and interfering substances are available in the rapid fFN collection kit IFU used by collection staff. Laboratory policy training and/or competence specifies that laboratory staff alert collecting staff of possible specimen issues. |
| Inadequate sample volume | Yes | The fFN analyzer shows an invalid message if the test does not meet internal acceptance criteria for a valid test. | Troubleshooting section of the fFN analyzer user manual | The troubleshooting section of the fFN analyzer user manual lists viscous samples as a possible problem. |

## Appendix E. (Continued)

| Quality Control Plan<br>Fetal Fibronectin Analyzer<br>Risk Assessment<br>Examination Phase (Continued) | | | | |
|---|---|---|---|---|
| **Risk Factor** | **Can Risk Be Reduced?** | **Measures to Control Risk** | **Relevant Documentation** | **Comments** |
| **Instrument Failure** | | | | |
| Software failure | Yes | The fFN analyzer displays an error code to alert operators of issues. | Troubleshooting section of the fFN analyzer user manual | • Electrostatic discharge and electrical failures will display an error code.<br>• The troubleshooting section of the fFN analyzer user manual lists physical and software issues that can give error codes. |
| Analyzer failure | Yes | QC device used to verify that the analyzer performs in accordance with specifications. Three different levels of response are measured with the QC device: high, low, and negative. | | |
| **Reagents** | | | | |
| Reagent degradation (shipping, storage, or use beyond expiration date) | Yes | • If an fFN cassette is beyond its expiration date, it is not accepted for patient testing.<br>• Each fFN cassette has an internal QC that is initiated automatically every time a patient sample is tested. This checks for a threshold level of signal and the procedural control position, proper sample flow across the cassette, absence of conjugate aggregation, and proper function of analyzer hardware. | The fFN analyzer user manual | • Cassette lot number is entered in the analyzer.<br>• The expiration of the cassette is verified each time by the user. |

## Appendix E. (Continued)

| Quality Control Plan<br>Fetal Fibronectin Analyzer<br>Risk Assessment<br>Examination Phase (Continued) | | | | |
|---|---|---|---|---|
| **Risk Factor** | **Can Risk Be Reduced?** | **Measures to Control Risk** | **Relevant Documentation** | **Comments** |
| **Reagents (Continued)** | | | | |
| Reagent degradation (shipping, storage, or use beyond expiration date) | Yes | Liquid QCs, with separate positive and negative QCs, are tested:<br>• When new lots and/or shipments are received<br>• When there is uncertainty about fFN cassette performance<br>• At a minimum of once a month | • Rapid fFN specimen collection kit<br>• Rapid fFN cassette kit<br>• Rapid fFN analyzer user manual | |
| QC material degradation (shipping, storage, or use beyond expiration date) | Yes | • If QC degradation occurs and the test does not meet internal acceptance criteria for a valid test, an invalid message is given.<br>• If QC material is past its expiration date, the QC material is not accepted. | Rapid fFN control kit directional insert | Laboratorians check for QC expiration with each use. |
| Performance (cartridge lot variability) | Yes | Liquid QCs, with separate positive and negative QCs, are tested:<br>• When new lots and/or shipments are received<br>• When there is uncertainty about fFN cassette performance<br>• At a minimum of once a month | fFN QC log | |

## Appendix E. (Continued)

| Quality Control Plan<br>Fetal Fibronectin Analyzer<br>Risk Assessment<br>Examination Phase (Continued) | | | | |
|---|---|---|---|---|
| **Risk Factor** | **Can Risk Be Reduced?** | **Measures to Control Risk** | **Relevant Documentation** | **Comments** |
| **Environment** | | | | |
| Power loss or surge | No | fFN analyzer displays error codes depending on the type of electrical issue (eg, electrostatic discharge, power loss). | • Records from generator checks and power outages<br>• Troubleshooting section of the fFN analyzer user manual | |
| Room temperature | Yes | Maintain appropriate environmental temperature as specified in the fFN analyzer user manual. | • Temperature logs<br>• fFN analyzer user manual | The fFN analyzer should not be placed where it will be subjected to extreme temperature variations (eg, near open windows, ovens, hot plates, radiators, or direct sunlight). |
| Humidity | Yes | Maintain appropriate environmental humidity free from vibration as specified in the fFn analyzer user manual. | • fFN analyzer humidity log<br>• User manual | The fFN analyzer should not be placed where it will be subjected to extreme temperature variations (eg, near open windows, ovens, hot plates, radiators, or direct sunlight) or near centrifuges or devices that cause vibration or generate humidity, such as sinks. |
| **Other** | | | | |
| | | | | |

| Quality Control Plan<br>Fetal Fibronectin Analyzer<br>Risk Assessment<br>Postexamination Phase | | | | |
|---|---|---|---|---|
| **Risk Factor** | **Can Risk Be Reduced?** | **Measures to Control Risk** | **Relevant Documentation** | **Comments** |
| **Test Results** | | | | |
| Manual result entry | Yes | Review pending list to ensure result is entered and/or verified. | Pending logs | A 2-step results verification process is in place to help prevent erroneous results from being released. This process will allow the result to be:<br>• Placed in a performed status<br>• Released to a verified status, allowing laboratorian to view the results a second time before releasing to a completed status |
| **Other** | | | | |
| | | | | |

## Appendix E. (Continued)

| Quality Control Plan<br>Fetal Fibronectin Analyzer<br>Risk Control Plan<br>Preexamination Phase | | | | | |
|---|---|---|---|---|---|
| **Risk Factor** | **Quality/Risk Control** | **QC Frequency** | **Criteria for Acceptability** | **Manufacturer Requirements** | **Comments** |
| **Specimen** | | | | | |
| Incorrect specimen collection | • Training<br>• Competence<br>• Laboratory test directory (resource) | • Initial training<br>• Annual competence assessment | Use of correct specimen collection kit with sample collected during a speculum examination | Manufacturer states that the rapid fFN specimen collection kit is to be used to collect specimens during a speculum examination before any examination or manipulation of the cervix or the vaginal tract. | • Staff training and competence are reviewed for the laboratorians performing testing.<br>• Laboratorians are available as a resource for hospital staff. |
| Specimen type (cervicovaginal secretions only) | • Training<br>• Competence | • Initial training<br>• Annual competence assessment | Cervicovaginal secretions tested | Manufacturer states that the rapid fFN specimen collection kit is the only acceptable specimen collection system that can be used to collect specimens for this assay. | • Staff training and competence are reviewed for the laboratorians performing testing.<br>• Laboratorians are available as a resource for hospital staff.<br>• Any specimen integrity issues are noted, logged in the testing section problem log, and reviewed.<br>• Any issues seen with collection are sent by the Quality Department to appropriate hospitals in the area to assist in proper collection practice. |

## Appendix E. (Continued)

| Quality Control Plan<br>Fetal Fibronectin Analyzer<br>Risk Control Plan<br>Preexamination Phase (Continued) | | | | | |
|---|---|---|---|---|---|
| **Risk Factor** | **Quality/Risk Control** | **QC Frequency** | **Criteria for Acceptability** | **Manufacturer Requirements** | **Comments** |
| **Specimen Integrity** | | | | | |
| Interfering substances | • Training<br>• Competence<br>• fFN procedure<br>• Each fFN cassette has an internal QC that is initiated automatically every time a patient sample is tested. This comment warns health care providers to refer to kit collection instruction for specific conditions that can cause test results to be invalid and is appended to the test result. | • Initial training<br>• Annual competence assessment | The fFn analyzer gives an invalid message if the test does not meet internal acceptance criteria for a valid test. | Manufacturer requires that internal acceptance criteria are met for the instrument to report a valid test result. | • Internal QCs check for interfering substances such as high viscosity, as well as cassette imperfections.<br>• Error codes are displayed to alert the operator. |
| Patient ID | • Training<br>• Competence | • Initial training<br>• Annual competence assessment | Correct patient ID is consistent with patient ID policy. | Patient ID policy is followed by all staff. | • Patient ID policy is implemented on a hospital-wide basis.<br>• Discrepancies in labeling are directed to the appropriate clinical department for correction and retraining. |

## Appendix E. (Continued)

| Quality Control Plan<br>Fetal Fibronectin Analyzer<br>Risk Control Plan<br>Preexamination Phase (Continued) | | | | | |
|---|---|---|---|---|---|
| **Risk Factor** | **Quality/Risk Control** | **QC Frequency** | **Criteria for Acceptability** | **Manufacturer Requirements** | **Comments** |
| **Specimen Integrity (Continued)** | | | | | |
| Interfering substances | • Training<br>• Competence<br>• fFN procedure<br>• Each fFN cassette has an internal QC that is initiated automatically every time a patient sample is tested. This comment warns health care providers to refer to kit collection instruction for specific conditions that can cause test results to be invalid and is appended to the test result. | • Initial training<br>• Annual competence assessment | The fFn analyzer displays an invalid message if the test does not meet internal acceptance criteria for a valid test. | Manufacturer requires that internal acceptance criteria be met for the instrument to report a valid test result. | • Internal QCs check for interfering substances, such as high viscosity, as well as cassette imperfections.<br>• Error codes are displayed to alert the operator. |
| **Other** | | | | | |
| | | | | | |

## Appendix E. (Continued)

| Quality Control Plan<br>Fetal Fibronectin Analyzer<br>Risk Control Plan<br>Examination Phase | | | | | |
|---|---|---|---|---|---|
| **Risk Factor** | **Quality/Risk Control** | **QC Frequency** | **Criteria for Acceptability** | **Manufacturer Requirements** | **Comments** |
| **Testing Personnel** | | | | | |
| Sample preparation | • Training<br>• Competence<br>• fFN procedure | • Initial training<br>• Annual competence assessment | The specimen transport tube is to be gently mixed before removing the swab. As much liquid as possible should be expressed from the swab by rolling the tip against the inside of the tube before disposing of the swab. | Manufacturer requires the specimen transport tube to be gently mixed before removing the swab. Then, as much liquid as possible is to be expressed from the swab by rolling the tip against the inside of the tube before disposing of the swab. | Staff undergoes training and competence assessment for specimen preparation and transfer to cassette. |
| Failure to follow procedure | • Training<br>• Competence<br>• fFN procedure<br>• Disciplinary action, if appropriate | • Initial training<br>• Annual competence assessment<br>• Disciplinary action consistent with hospital policy | Staff follows fFN procedure. | Laboratory fFN procedure reflects the requirements of the manufacturer. | Staff undergoes training and competence assessment for specimen preparation and transfer to cassette. |
| **Measuring System** | | | | | |
| Inadequate sample volume | • Training<br>• Competence<br>• fFN procedure<br>• Each fFN cassette has an internal QC that is initiated automatically every time a patient sample is tested. | Internal QCs monitor all components of the fFN analyzer and are performed automatically with every test. | Sample-specific errors cause an invalid result to be reported by the instrument. | Manufacturer programs the fFN analyzer to display an "invalid" message if the test does not meet internal acceptance criteria for a valid test. | Interfering substances are noted in rapid fFN cassette kit IFU as well as in the rapid fFN specimen collection kit used by collection staff and physicians. |

## Appendix E. (Continued)

| Quality Control Plan<br>Fetal Fibronectin Analyzer<br>Risk Control Plan<br>Examination Phase (Continued) | | | | | |
|---|---|---|---|---|---|
| **Risk Factor** | **Quality/Risk Control** | **QC Frequency** | **Criteria for Acceptability** | **Manufacturer Requirements** | **Comments** |
| **Instrument Failure** | | | | | |
| Software failure | fFN analyzer displays an error code to alert operators of issues. | The fFN analyzer automatically performs electronic checks. | Sample-specific errors cause an invalid result to be reported by the instrument. | Manufacturer programs the fFN analyzer to display an "invalid" message if the test does not meet internal acceptance criteria for a valid test. | The troubleshooting section of the fFN analyzer uses manual lists codes for specific issues:<br>• Printer<br>• Software<br>• Optics |
| fFN analyzer failure | • QC device that is used to verify that the fFN analyzer performs in accordance with specifications.<br>• Three different levels of response are measured with the QC device: high, low, and negative. | Daily | The QC device is scanned by the analyzer optics, and the result is interpreted as system "pass" or "fail." | Manufacturer specifies that an acceptable result must be obtained from the QC device before patient samples are tested. | Errors received during QC device testing, daily setup, or patient testing should result in the following actions:<br>• Error during QC device or daily setup: run positive and negative liquid QC<br>• Errors during patient testing: repeat patient specimen; if result obtained with no error, run positive and negative liquid QC before reporting patient result |

## Appendix E. (Continued)

| Quality Control Plan<br>Fetal Fibronectin Analyzer<br>Risk Control Plan<br>Examination Phase (Continued) | | | | | |
|---|---|---|---|---|---|
| **Risk Factor** | **Quality/Risk Control** | **QC Frequency** | **Criteria for Acceptability** | **Manufacturer Requirements** | **Comments** |
| **Reagents** | | | | | |
| Reagent degradation (use of expired reagents) | • If an fFN cassette is beyond its expiration, it is not accepted for patient testing.<br>• Each fFN cassette has an internal QC that is initiated automatically every time a patient sample is tested. This checks for a threshold level of signal and the procedural control position, proper sample flow across the cassette, absence of conjugate aggregation, and proper function of analyzer hardware. | With each new fFN cassette | The fFn analyzer displays an "invalid" message if the test does not meet internal acceptance criteria for a valid test. | Manufacturer programs the fFN analyzer to display an "invalid" message if the internal acceptance criteria for a valid test is not met. | • Laboratorians enter cassette lot number in the fFN analyzer.<br>• Cassette expiration must be manually documented by the fFN analyzer operator. |

## Appendix E. (Continued)

| Quality Control Plan<br>Fetal Fibronectin Analyzer<br>Risk Control Plan<br>Examination Phase (Continued) | | | | | |
|---|---|---|---|---|---|
| **Risk Factor** | **Quality/Risk Control** | **QC Frequency** | **Criteria for Acceptability** | **Manufacturer Requirements** | **Comments** |
| **Reagents (Continued)** | | | | | |
| Reagent degradation during shipping or storage | • Positive and negative liquid QCs are used in monitoring the performance of the fFN cassette.<br>• Liquid QC is performed monthly and on receipt of each shipment at minimum. | The controls are tested once each time a new lot or a new shipment of cassettes is received, or whenever there is uncertainty about the storage of the fFN cassettes. | • Acceptable results for the rapid fFN positive and negative controls will be displayed on the fFn analyzer as "pass."<br>• Unacceptable results will be displayed as "fail" or "invalid." | Manufacturer specifies that an acceptable result must be obtained from the liquid controls before patient samples are tested. | |
| QC material degradation during shipping or storage, or use beyond expiration | • If QC degradation occurs and the test does not meet internal acceptance criteria for a valid test, the fFN analyzer will display an "invalid" message.<br>• If QC material is past its expiration, it will not be accepted.<br>• Liquid QC is performed monthly at minimum. | | | | An "invalid" message caused by internal QC failure is separate from liquid QC providing interval results and should be investigated according to the troubleshooting section of the fFN analyzer user manual. |

## Appendix E. (Continued)

| Quality Control Plan<br>Fetal Fibronectin Analyzer<br>Risk Control Plan<br>Examination Phase (Continued) | | | | | |
|---|---|---|---|---|---|
| **Risk Factor** | **Quality/Risk Control** | **QC Frequency** | **Criteria for Acceptability** | **Manufacturer Requirements** | **Comments** |
| **Reagents (Continued)** | | | | | |
| Performance (cartridge lot variability) | • Positive and negative liquid QCs are used in monitoring the performance of the fFN cassette.<br>• Liquid QC will be performed, at a minimum, monthly and on receipt of each shipment. | The QCs are tested once each time a new lot or a new shipment of cassettes is received or whenever there is uncertainty about the fFN cassettes. | • Acceptable results for the rapid fFN positive and negative controls will be displayed on the fFn analyzer as "pass."<br>• Unacceptable results will be displayed as "fail" or "invalid." | Manufacturer specifies that an acceptable result must be obtained from the liquid controls before patient samples are tested. | |
| Reagent and QC material degradation | Temperature monitoring | Checked and documented daily | Temperature is within acceptable limits. | Manufacturer states that fFN cassettes are to be stored at room temperature (15 to 30°C) and liquid controls are to be stored at 2 to 8°C. | |
| **Environment** | | | | | |
| Power loss or surge | Instrument cannot be operated during power interruption. | When power loss or surge occurs | Continuous instrument operation | Manufacturer states instrument cannot be operated with power interruption. | Analyzer is connected to uninterrupted line, and an error code appears during power interruption. |

## Appendix E. (Continued)

| Quality Control Plan<br>Fetal Fibronectin Analyzer<br>Risk Control Plan<br>Examination Phase (Continued) | | | | | |
|---|---|---|---|---|---|
| **Risk Factor** | **Quality/Risk Control** | **QC Frequency** | **Criteria for Acceptability** | **Manufacturer Requirements** | **Comments** |
| **Environment (Continued)** | | | | | |
| Room temperature | Temperature monitoring | Checked and documented daily | Temperature is within acceptable limits. | • Manufacturer states that prolonged exposure to high temperature should be avoided.<br>• The optimum operating temperature of device is 18 to 30°C and should be held relatively constant.<br>• The instrument should not be subjected to extreme temperature variations (eg, near open windows, ovens, hot plates, radiators, or direct sunlight) or vibration. | Analyzer is placed near the center of the laboratory, away from windows, sunlight, and other sources of extreme or fluctuating temperatures, on a bench away from other instruments that can generate vibration, such as centrifuges. |
| Humidity | Humidity monitoring | | Humidity is within acceptable limits. | • Manufacturer states that prolonged exposure to high humidity should be avoided.<br>• Maximum relative humidity of 80% for temperatures up to 31°C, decreasing linearly to 50% relative humidity at 40°C. | Analyzer is placed near the center of the laboratory, away from windows, sunlight, and other sources of extreme or fluctuating temperatures, on a bench away from other instruments that can generate vibration, such as centrifuges, and protected from sinks and sources of water. |
| **Other** | | | | | |
| | | | | | |

## Appendix E. (Continued)

| Quality Control Plan<br>Fetal Fibronectin Analyzer<br>Risk Control Plan<br>Postexamination Phase | | | | | |
|---|---|---|---|---|---|
| **Risk Factor** | **Quality/Risk Control** | **QC Frequency** | **Criteria for Acceptability** | **Manufacturer Requirements** | **Comments** |
| **Test Results** | | | | | |
| Manual result entry | The pending log is checked. | Checked periodically during each shift | • No pending results<br>• Results entered correctly | | A 2-step result verification process is in place to help prevent erroneous results from being released. This process will allow the result to be:<br>• Placed in a performed status<br>• Released to a verified status, allowing laboratorian to view the results a second time before releasing to a completed status |
| **Other** | | | | | |
| | | | | | |

| Quality Control Plan<br>Fetal Fibronectin Analyzer<br>Quality Assessment<br>Preexamination Phase | | | | |
|---|---|---|---|---|
| **Quality Assessment Activity** | **Frequency** | **Assessment of Monitor** | **Corrective Action, if needed** | **Comments** |
| **Specimen** | | | | |
| Problem log | Monthly | • A record of issues, either with testing equipment or specimens, is kept in the testing area.<br>• The problem log monitors common sources of error, such as inappropriate sample handling, and is reviewed monthly by the laboratory manager and director. | • Corrective action is taken and depends on error identified.<br>• Trends are reviewed and appropriate follow-up taken. | |

## Appendix E. (Continued)

| Quality Control Plan<br>Fetal Fibronectin Analyzer<br>Quality Assessment<br>Preexamination Phase (Continued) | | | | |
|---|---|---|---|---|
| **Quality Assessment Activity** | **Frequency** | **Assessment of Monitor** | **Corrective Action, if needed** | **Comments** |
| **Specimen (Continued)** | | | | |
| Staff complaints | Daily | Reviewed in daily operations meetings | Corrective action is taken and depends on issue identified. | Complaints can reflect any type of problem in the preexamination, examination, or postexamination phases of testing. |
| **Testing Personnel** | | | | |
| Staff complaints | Daily | Reviewed in daily operations meetings | Corrective action is taken and depends on issue identified. | Complaints can reflect any type of problem in the preexamination, examination, or postexamination phases of testing. |
| Competence assessments | 6 months for new activity; annually otherwise | Assessments are performed by designated laboratory staff, monitored for acceptable competence, and revised as procedures or processes change. | Corrective action is taken and depends on issue identified. Retraining occurs if a deficiency is documented. | Competence and training records for laboratory staff provide documentation. |
| **Other** | | | | |
| | | | | |

| Quality Control Plan<br>Fetal Fibronectin Analyzer<br>Quality Assessment<br>Examination Phase | | | | |
|---|---|---|---|---|
| **Quality Assessment Activity** | **Frequency** | **Assessment of Monitor** | **Corrective Action, if needed** | **Comments** |
| **Test Results** | | | | |
| TAT reports, if applicable | | TAT reports are used to determine whether fFN testing meets defined TAT. | Corrective action is taken and depends on reason for delay. | |
| Service and maintenance records | Monthly | Service records are reviewed as part of the laboratory monthly documentation review. | Corrective action is taken and depends on issue identified. | • No routine maintenance for the fFN analyzer is required by the manufacturer.<br>• If the fFN analyzer does not operate within defined parameters, the vendor replaces it and revalidation is required. |

## Appendix E. (Continued)

| Quality Control Plan<br>Fetal Fibronectin Analyzer<br>Quality Assessment<br>Examination Phase (Continued) | | | | |
|---|---|---|---|---|
| **Quality Assessment Activity** | **Frequency** | **Assessment of Monitor** | **Corrective Action, if needed** | **Comments** |
| **Reagents** | | | | |
| External QC review | Monthly | Log is reviewed by designated laboratory staff. | Corrective is taken and depends on issue identified. | |
| Lot shipments and liquid QC records are logged. | Daily if needed; otherwise, monthly | | | Lot numbers for each shipment are recorded on receipt and results of liquid QC documented before patient testing. |
| **Environment** | | | | |
| Room temperature | Daily | Temperature is checked and recorded daily by assigned laboratory staff. | Corrective action is taken when needed and depends on issue identified. | Calibrated thermometers are used until the certificate expires and then are discarded. |
| Humidity | Daily | Humidity is checked and recorded daily by assigned laboratory staff. | | Hospital facilities and plant operations check and calibrate humidity devices for the hospital. |

| Quality Control Plan<br>Fetal Fibronectin Analyzer<br>Quality Assessment<br>Postexamination Phase | | | | |
|---|---|---|---|---|
| **Quality Assessment Activity** | **Frequency** | **Assessment of Monitor** | **Corrective Action, if needed** | **Comments** |
| **Test Results** | | | | |
| Manual result entry | Daily | Pending log is checked by assigned laboratory staff. | Corrective action is taken and depends on the issue identified. | A 2-step result verification process is in place to help prevent erroneous results from being released. This process will allow the result to be:<br>• Placed in a performed status<br>• Released to a verified status, allowing laboratorian to view the results a second time before releasing to a completed status |

## Appendix E. (Continued)

| Quality Control Plan<br>Fetal Fibronectin Analyzer<br>Quality Assessment<br>Postexamination Phase (Continued) | | | | |
|---|---|---|---|---|
| **Quality Assessment Activity** | **Frequency** | **Assessment of Monitor** | **Corrective Action, if needed** | **Comments** |
| **Other** | | | | |
| PT results or quality cross-check results | 2 to 3 times per year | • PT results and quality cross-checks are used to compare laboratory results with results from other laboratories that use the fFN analyzer.<br>• PT samples are treated the same as patient samples and can also provide a measure of staff competence. | Corrective action is taken and depends on the issue identified. | |
| Clinician inquiries | Daily | Reviewed in daily operations meetings | Corrective action is taken and depends on the issue identified. | Clinical inquiries can reflect any type of problem in the preexamination, examination, or postexamination phases of testing. |
| Approved by: | | | | |
| Laboratory Medical Director: | | | | |
| Signature: | | | | |
| Date: | | | | |

Abbreviations: fFN, fetal fibronectin; ID, identification; IFU, instructions for use; PT, proficiency testing; QC, quality control; TAT, turnaround time.

# Appendix F. Example Quality Assurance Review and Quality Control Plan Assessment Form

Appendix F is included in this guideline as an example of a quality assurance review and quality control plan assessment form. It is not meant to be comprehensive guidance for all health care facilities, and it is not meant to cover all possible scenarios.

| Assessment of Quality Assurance Review and Quality Control Plan | | | |
|---|---|---|---|
| **Measuring System or Quality Process** | | | |
| | | | |
| **Location** | | | |
| | | | |
| **Type of Review** | | | |
| | Routine | | |
| | Review of identified problem | | |
| | Corrective action or follow-up review | | |
| **Assessment** | | | |
| **1.** Determine whether problems were identified in the following QA monitors and/or processes and check the appropriate boxes. | | | |
| QC | Yes | No | N/A |
| Function checks | Yes | No | N/A |
| Environment | Yes | No | N/A |
| Measuring system | Yes | No | N/A |
| Reagents | Yes | No | N/A |
| QA documentation | Yes | No | N/A |
| Testing personnel training and/or competence | Yes | No | N/A |
| Measuring system and equipment maintenance | Yes | No | N/A |
| PT | Yes | No | N/A |
| **2.** If you marked "yes" to any of the QA items above, evaluate and describe the problems or errors relating to the preexamination, examination, and postexamination phases of testing. | | | |
| Preexamination phase: | | | |
| Examination phase: | | | |
| Postexamination phase: | | | |
| **3.** Were patient results reviewed? | Yes | No | N/A |
| If yes, how many? | | | |
| **4.** Were quality metrics and performance indicators reviewed and effected? | Yes | No | N/A |
| If yes, describe them. | | | |

## Appendix F. (Continued)

| Assessment of Quality Assurance Review and Quality Control Plan (Continued) | | | |
|---|---|---|---|
| **Assessment (Continued)** | | | |
| **5.** Were complaints from clinicians and/or other health care providers regarding the quality of testing received and reviewed? | Yes | No | N/A |
| If yes, how many complaints were received? | | | |
| If complaints were received and problems were identified, describe and evaluate corrective actions. | | | |
| **6.** Did QCP mitigate potential risks for the measuring system? | Yes | No | N/A |
| If the QCP did not mitigate potential risk, list additional investigation activities and proposed modifications to the QCP. | | | |
| **7.** Is the current QCP acceptable for this test? | Yes | No | N/A |
| **8.** Should any modifications be made to the QCP? | Yes | No | N/A |
| Date modifications implemented: | | | |
| Date of follow-up review: | | | |
| Date of medical director modification approval: | | | |
| Date of last annual review: | | | |
| Supporting data attached? | Yes | No | N/A |
| QCP review staff acknowledgment: | | | |
| Form completed by: | | | |
| Form reviewed by: | | | |
| Date: | | | |

Abbreviations: N/A, not applicable; PT, proficiency testing; QA, quality assurance; QC, quality control; QCP, quality control plan.

# Appendix G. Example of Failure Investigation and Corrective Action for Glucose Measurement on an Automated Measuring System

## Scenario

A 10-member health care provider group practice has an automated glucose measuring system in an office laboratory. Medical assistants perform glucose testing. This health care provider's office is using the following quality control plan.

| Quality Control Plan ABC Health Group Glucose Measuring System |
|---|
| **Electronic Controls** |
| Electronic controls perform automatically every 24 hours. |
| **Quality Control Samples** |
| • Analyze 2 levels of QC samples that were not in the same shipment as the reagents on receipt of new reagents.<br>• Ensure QC sample acceptance criteria are appropriate for the clinical setting.<br>• Analyze 2 levels of QC samples before and after each calibration and major maintenance, and once at least every 3 days that testing is performed.<br>• During the initial 3 months of implementation, analyze 2 levels of QC samples daily in the outpatient clinic and once every 3 days in the hospital laboratory. |
| **External Quality Assessment or Proficiency Testing** |
| Participate in external quality assessment or proficiency testing program to assess overall system performance and compare against other peer laboratories. |
| **Calibration** |
| • Perform after major maintenance.<br>• Perform weekly or with reagent lot changes. |
| **Maintenance** |
| • Follow manufacturer's schedule (emphasize checking probe cleaning and lamp intensities).<br>• Monitor refrigerator temperature daily (implement continuous temperature monitoring for outpatient clinic).<br>• Monitor temperature and humidity at all laboratory locations (install continuous temperature and humidity monitoring with alarm at outpatient clinic).<br>• Install UPS or surge protector at the outpatient clinic laboratory and monitor UPS battery function. |
| **Personnel Training** |
| • Monitor refrigerator temperature daily.<br>• Check condition of the cold packs on receipt of new shipments of reagents.<br>• Double-check manual data entries and emphasize consequences of incorrect data entry.<br>• Check for low-volume sample and clots before testing and monitor frequency of measuring system error messages, which can indicate the need for staff counseling.<br>• Following a sample with glucose > 480 mg/dL (26.7 mmol/L), repeat the next sample to check for sample carryover (until sufficient data are collected to demonstrate the effectiveness of probe washing in reducing the potential risk from carryover).<br>• Check open dating and emphasize consequences of using degraded or expired reagents, QC samples, or calibrators.<br>• Change measuring system passwords periodically, and do not share them. |

## Appendix G. (Continued)

| Quality Control Plan ABC Health Group Glucose Measuring System (Continued) |
|---|
| **Clinical Example** |
| A 45-year-old woman with diabetes visits the clinic because she has had nausea, night sweats, thirst, and increased frequency of urination. A glucose test performed in the office laboratory has a result of 220 mg/dL (12.2 mmol/L). On the way to her car, the woman collapses in the garage; her partner summons an ambulance, and she is brought to the emergency department. On admission, her glucose level measured in the hospital's medical laboratory is 420 mg/dL (23.3 mmol/L). The patient's partner calls the health care providers in the outpatient clinic to let them know the patient has been admitted to the hospital. The patient's primary health care provider investigates the discrepancy between the glucose results. |
| **Investigation** |
| Routine QC sample results were within acceptable limits over the past 6 months, and no measuring system error messages necessitating operator intervention were obtained. Review of the QCP identified that the office laboratory was using 2 concentrations of QC samples at 70 mg/dL (3.9 mmol/L) (with a product insert acceptance interval of 56 to 84 mg/dL [3.1 to 4.6 mmol/L], 10% CV), and 250 mg/dL (13.8 mmol/L) (with a product insert acceptable interval of 200 to 300 mg/dL [11.1 to 16.7 mmol/L], 10% CV). QC samples were analyzed as recommended, before and after calibration and after every 3 days of patient testing. The outpatient clinic verified performance within QC package insert acceptance intervals with each shipment of reagents, choosing to use package insert QC limits as the laboratory's acceptance limits for each lot.<br><br>The original patient sample was retested with a result of 215 mg/dL (11.8 mmol/L). The QC samples were also retested, with results of 72 mg/dL (4.0 mmol/L) and 201 mg/dL (11.1 mmol/L). The original patient sample was sent to a different laboratory for testing, and a result of 421 mg/dL (23.2 mmol/L) was obtained.<br><br>This confirmed discrepancy prompted a review of the QC sample data for the past 6 months. This review revealed a mean value of 73 mg/dL (4.0 mmol/L), 4% CV, and mean value of 253 mg/dL (13.9 mmol/L), 4% CV. The QC sample limits based on the product insert were too wide. Use of the manufacturer's criteria compromised the ability to detect reagent degradation and/or calibration deterioration. The laboratory reexamined the historical QC sample data using the 4% CV and observed that a trend had occurred over the past 6 weeks in which all values were below the mean, with the last 4 observations exceeding an acceptable QC sample limit based on a 4% CV. Because the QC sample limits provided in the product insert were wide, use of the manufacturer's QC sample intervals might have compromised the laboratory's ability to detect reagent degradation, calibration deterioration, or other measuring system failure, resulting in the release of incorrect patient test results. The physician's office did not follow its own QCP to ensure that the QC sample interval criteria were appropriate for the clinical setting. |
| **Possible Causes of Measurement Errors** |
| Possible causes of measurement errors include incorrect calibration or incorrect calibrator value if a recalibration had occurred, calibration drift, reagent deterioration, and measuring system failure. |
| **Additional Investigation** |
| The measuring system was recalibrated with fresh reagents from the same lot and same vial of calibrator that had been used for the past 2 weeks, and acceptable QC sample results based on 4% CV acceptance criteria were obtained. Had the calibrator values been incorrect, the correct QC sample values would not have been recovered. Consequently, the reagent in use at the time of the erroneous result was suspected to have deteriorated prematurely after its container was opened. However, other possible causes are not excluded without additional investigation. Temperature monitoring records indicated the reagent was stored within the manufacturer recommendations and was used within the expiration date and open-bottle stability specification. |

## Appendix G. (Continued)

| Quality Control Plan ABC Health Group Glucose Measuring System (Continued) |
|---|
| **Investigation Conclusions** |
| • The automated built-in reagent monitoring system failed to detect the reagent deterioration.<br>– Cause: to be determined by the manufacturer<br>– Contributing cause: the laboratory failed to verify that the control sample interval criteria were appropriate for the clinical setting.<br>• QC testing at 2 levels of glucose using the package insert acceptable intervals failed to detect reagent deterioration that caused a shift of –200 mg/dL (11.0 mmol/L) at 420 mg/dL (23.2 mmol/L).<br>– Immediate cause: the laboratory failed to implement appropriate acceptance limits (ie, laboratory-specific limits determined statistically from QC sample results), which caused the outpatient laboratory to fail to recognize a clinically significant change in glucose performance at higher concentrations before the release of the incorrect patient test results.<br>– Root causes: the laboratory's QCP failed to require implementation of appropriately determined control limits and to verify that the glucose control limits were adequate for the medical use of the test results. |
| **Corrective Actions** |
| • QC sample acceptance criteria based on measuring system performance using laboratory-specific QC limits were initiated to improve the ability to detect reagent deterioration or other measurement issues.<br>• Weekly correlation testing of 5 patient samples with the main laboratory was initiated. |

Abbreviations: CV, coefficient of variation; QC, quality control; QCP, quality control plan; UPS, uninterruptible power supply.

## Appendix G. (Continued)

Table G1 describes the potential risk of reagent deterioration during shipment, the laboratory's actions to manage validation of reagents on receipt, and QC strategies to manage storage within the manufacturer's specifications.

**Table G1. Risk Assessment for Reagent Receipt and Storage**

| Targeted Failure Mode, hazard | Measuring System Feature or Recommended Action | Known Limitations of Feature or Recommended Action | QC Process Effective? | QCP Actions Necessary to Handle Known Limitations | Residual Risk Acceptable? (Yes/No) |
|---|---|---|---|---|---|
| Incorrect results caused by use of deteriorated reagents | Test QC samples that were not in the same shipment as the reagent on receipt of new shipment. | Deterioration of QC sample could cause assay integrity to be incorrectly assessed. | • N/A[a]<br>• No automated QC process to detect reagent stability during shipment | Follow manufacturer's recommendations:<br>• Test QC samples that were not in the same shipment as the reagent on receipt of new shipment.<br>• Store QC samples as indicated in the manufacturer's instructions for use.<br>Laboratory-implemented QC processes:<br>• Implement continuous temperature monitoring for outpatient clinics.<br>• Ensure QC samples are within the expiration date and within the open-vial stability claim.<br>• Check the condition of the cold packs on receipt of reagent shipment.<br>• Ensure QC sample interval criteria are appropriate for the clinical setting. | Yes |

Abbreviations: N/A, not applicable; QC, quality control; QCP, quality control plan.
[a] The risk analysis was not modified.

## Appendix G. (Continued)

Table G2 refers to the automated QC that detects reagent deterioration based on the reagent blank absorbance and the laboratory's actions to manage open-bottle stability.

**Table G2. Risk Assessment for Reagent Deterioration**

| Targeted Failure Mode, hazard | Measuring System Feature or Recommended Action | Known Limitations of Feature or Recommended Action | QC Process Effective? | QCP Actions Necessary to Handle Known Limitations | Residual Risk Acceptable? (Yes/No) |
|---|---|---|---|---|---|
| Incorrect results caused by use of deteriorated reagents | • Discoloration of reagent occurs with deterioration and is detected by measurement of the absorbance of the reagent blank.<br>• Periodic QC sample measurement verifies system performance. | Does not detect reagent storage or expiration | • Partial[a]<br>• Requires additional QC processes to monitor reagent storage and expiration | Manufacturer recommendation:<br>Automated reagent blank measurement<br>Laboratory-implemented QC processes:<br>• Monitor bar-coded reagent expiration dates and open-bottle stability.<br>• Evaluate reagent performance on receipt of shipments.<br>• Monitor storage conditions or use continuous temperature monitoring.<br>• Analyze QC samples daily in outpatient clinic and once every 3 days in hospital laboratory (for first 3 months of system use). | Yes |

Abbreviations: QC, quality control; QCP, quality control plan.
[a] The risk analysis was partially modified.

## Appendix G. (Continued)

The investigation showed that the automated QC, a blank absorbance monitor, was insufficient to detect reagent deterioration and prevent incorrect results from being reported before clinical action. In addition, the QC intervals were not adequate to detect a trend in measuring system reagent performance. Therefore, the risk analysis was modified, as shown in Table G3.

**Table G3. Risk Assessment Modification for Reagent Deterioration**

| Targeted Failure Mode, hazard | Measuring System Feature or Recommended Action | Known Limitations of Feature or Recommended Action | QC Process Effective? | QCP Actions Necessary to Handle Known Limitations | Residual Risk Acceptable? (Yes/No) |
|---|---|---|---|---|---|
| Incorrect results caused by reagent deterioration during shipment | Test QC samples that were not in the same shipment as the reagent, on receipt of new shipment. | Deterioration of QC sample could cause assay integrity to be incorrectly assessed. | • N/A[a]<br>• No automated QC process to detect reagent stability during shipment | • Ensure QC sample interval criteria are appropriate for the clinical setting.<br>• Ensure that QCP is followed in all laboratory settings and that site-specific QC sample limits are developed instead of using package insert criteria. | Yes |
| Incorrect results caused by use of deteriorated reagents | • Discoloration of reagent occurs with deterioration and is detected by measurement of the absorbance of the reagent blank.<br>• Periodic QC sample measurement verifies system performance. | Does not detect reagent storage or expiration | • Partial[b]<br>• Requires additional QC processes to monitor reagent storage and expiration | • Analyze QC samples daily in outpatient clinic and once every 3 days in hospital laboratory (for first 3 months of system use).<br>• Correlate 5 patient samples weekly between the clinic and central hospital laboratory. | Yes |

Abbreviations: N/A, not applicable; QC, quality control; QCP, quality control plan.
[a] The risk analysis was not modified.
[b] The risk analysis was partially modified.

# The Quality Management System Approach

Clinical and Laboratory Standards Institute (CLSI) subscribes to a quality management system (QMS) approach in the development of standards and guidelines that facilitates project management, defines a document structure using a template, and provides a process to identify needed documents. The QMS approach applies a core set of "quality system essentials" (QSEs), basic to any organization, to all operations in any health care service's path of workflow (ie, operational aspects that define how a particular product or service is provided). The QSEs provide the framework for delivery of any type of product or service, serving as a manager's guide. The QSEs are:

- Organization and Leadership
- Customer Focus
- Facilities and Safety Management
- Personnel Management
- Supplier and Inventory Management
- Equipment Management
- Process Management
- Documents and Records Management
- Information Management
- Nonconforming Event Management
- Assessments
- Continual Improvement

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